Evidence Based Management of Cancers in India

Peri-Operative Care: Improving Outcomes After Surgery

PART A

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Guidelines for Peri-Operative Care: Improving Outcomes After Surgery

Guidelines for Imaging in Oncology

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Dedicated to
all our patients at
The Tata Memorial Hospital
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This year marks the 12th “Evidence-Based Management” meeting at Tata Memorial Centre. Evidence-based medicine (EBM) has been defined as the use of current best evidence to make informed clinical decisions for individual patients. The Tata Memorial Centre has pioneered the concept of EBM in oncology in India and has been conducting the annual meeting on EBM in common cancers for the past 11 years.

The focus of this year’s meeting is on “Peri-operative Care: Improving Outcomes After Surgery”. With advances in medicine and technology, we are now performing increasingly complex surgeries on patients with multiple risk factors. There is growing evidence that outcomes after surgery are influenced not only by the actual surgical technique but also by a host of other peri-operative factors. Several studies have demonstrated the impact of pre-operative investigations and optimisation, peri-operative anaesthetic and analgesic techniques, fluid therapy, ventilation strategies and post-operative management on morbidity and mortality. It has been shown that modification of these factors can significantly improve patient outcomes.

This book highlights the important guidelines and issues in peri-operative care and summates the best available
evidence to answer clinically important questions for the management of patients undergoing surgery. Abstracts of key papers on each topic have been included along with a list of references for further reading. This should be a useful guide for all clinicians dealing with patients in the peri-operative period.

February 2014
R A Badwe
Director,
Mumbai Tata Memorial Centre
Section-1:
Guidelines for Peri-operative Care
Preoperative Fasting Guidelines

Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. American Society of Anesthesiologists Committee.

Anesthesiology 2011; 114: 495-511

Introduction
Preoperative fasting is defined as a prescribed period of time before a procedure when patients are not allowed the oral intake of liquids or solids. Withholding solids and liquids for specified times before surgery is important to ensure gastric emptying and to prevent pulmonary aspiration of gastric contents. However, excessive fasting can result in dehydration, hypoglycaemia and patient discomfort. The American Society of Anaesthesiologists has laid down recommendations for preoperative fasting
as well as recommendations regarding the administration of pharmacologic agents to modify the volume and acidity of gastric contents during procedures in which upper airway protective reflexes may be impaired. The intended patient population for these guidelines is limited to healthy patients of all ages undergoing elective procedures. These guidelines do not apply to patients who undergo procedures with no anesthesia or only local anesthesia when upper airway protective reflexes are not impaired, and when no risk factors for pulmonary aspiration are apparent. These guidelines are also not intended for women in labor. These guidelines may not apply to, or may need to be modified for (1) patients with coexisting diseases or conditions that can affect gastric emptying or fluid volume (e.g., pregnancy, obesity, diabetes, hiatal hernia, gastroesophageal reflux disease, ileus or bowel obstruction, emergency care, enteral tube feeding) and (2) patients in whom airway management might be difficult.

**Recommendations for Preoperative Assessment**
A review of pertinent medical records, a physical examination, and patient survey or interview should be performed as part of preoperative evaluation. The history, examination, and interview should include pertinent assessment of gastroesophageal reflux disease, dysphagia symptoms, or other gastrointestinal motility disorders, potential for difficult airway management, and metabolic disorders (e.g., diabetes mellitus) that may increase the risk of regurgitation and pulmonary aspiration. Patients should be informed of fasting requirements and the reasons for them, sufficiently in
advance of their procedures. Verification of patient compliance with fasting requirements should be assessed at the time of the procedures. When the fasting recommendations in these guidelines are not followed, the practitioner should compare the risks and benefits of proceeding, with consideration given to the amount and type of liquids or solids ingested.

Summary of Fasting Recommendations

<table>
<thead>
<tr>
<th>Ingested Material</th>
<th>Minimum Fasting Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear liquids</td>
<td>2 h</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4 h</td>
</tr>
<tr>
<td>Infant formula</td>
<td>6 h</td>
</tr>
<tr>
<td>Nonhuman milk</td>
<td>6 h</td>
</tr>
<tr>
<td>Light meal</td>
<td>6 h</td>
</tr>
</tbody>
</table>

Following the guidelines does not guarantee complete gastric emptying. The fasting periods noted above apply to patients of all ages.

Examples of clear liquids include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. Because nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.

A light meal typically consists of toast and clear liquids.

Meals that include fried or fatty foods or meat may prolong gastric emptying time. Additional fasting time (e.g., 8 h or more) may be needed in these cases. Both
the amount and type of food ingested must be considered when determining an appropriate fasting period.

**Pharmacologic Recommendations**

There is no role for routine use of any of the following pharmacological agents either singly or in combination: gastrointestinal stimulants (metoclopramide), gastric acid secretion blockers (H2 receptor blockers or proton pump inhibitors), antacids (sodium citrate, sodium bicarbonate, magnesium trisilicate), antiemetics (droperidol, ondansetron), anticholinergics (atropine, scopolamine, glycopyrrolate).
Evaluation of the Cardiac Patient for Non cardiac Surgery


Class of Recommendation

- **Class I**
  Benefit >>> Risk.
  Procedure /treatment Should be performed

- **Class II a**
  Benefit >> Risk. Additional Studies with focused objectives required
  It is reasonable for Procedure /treatment to be performed

- **Class II b**
  Benefit >/= Risk.
Additional Studies with broad objectives required.
Addtional registry data will be useful
Procedure /treatment may be considered

- **Class III**
  Risk \( \geq \) Benefit
  No additional studies needed
  Procedure /treatment Should Not be performed since it is not helpful and may be harmful

**Levels of Evidence**
A. Multiple (3-5) population risk strata evaluated.
   General consistency of direction and magnitude of effect
   Evidence from multiple randomized controlled trials
B. Limited (2-3) population risk strata evaluated
   Evidence from single randomized controlled trial or nonrandomized studies
C. Very limited (1-2) population risk strata evaluated
   Expert opinion, case studies or standard -of -care

**Active Cardiac Conditions for which the Patient should Undergo Evaluation and Treatment before Noncardiac Surgery (Class I, Level of Evidence : B)**
### Condition Examples

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable coronary syndromes</td>
<td>Unstable or severe angina* (CCS class III or IV) + Recent MI ++</td>
</tr>
<tr>
<td>Decompensated HF (NYHA functional class IV; worsening or new-onset HF)</td>
<td>High-grade atioventricular block Mobitz II atioventricular block Third-degree atioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR greater than 100 bpm at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia</td>
</tr>
<tr>
<td>Significant arrhythmias</td>
<td>Severe aortic stenosis (mean pressure gradient greater than 40 mm Hg, aortic valve area less than 1.0cm$^2$ or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)</td>
</tr>
<tr>
<td>Severe valvular disease</td>
<td></td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society; HF, heart failure; HR, heart rate; MI, myocardial infarction; NYHA, New York Heart Association.

*According to Campeau. 10

+ May include “stable” angina in patients who are unusually sedentary

++ The American College of Cardiology National Database Library defines recent MI as more than 7 days but less than or equal to 1 month (within 30 days).
Figure 1. Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or greater. *See Table 2 for active clinical conditions. † See Class III recommendations in Section 5.2.3. Noninvasive Stress Testing. ‡ See Table 3 for estimated MET level equivalent. § Noninvasive testing may be considered before surgery in specific patients with risk factors if it will change management. ¶ Clinical risk factors include ischemic heart disease, compensated or prior heart failure, history of compensated or prior heart failure, diabetes mellitus, and renal insufficiency. ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate; LCE, level of evidence; and MET, metabolic equivalent.
Indications for cardiac tests and medications

Preoperative Resting 12-Lead ECG

Class I
- At least 1 clinical risk factor - Vascular surgical procedures. (B )
- Patients with known coronary heart disease, peripheral arterial disease or cerebrovascular disease - Intermediate-risk procedures. (C )

Class IIa
- No clinical risk factors - Vascular surgical procedures. (B )

Class IIb
- At least 1 clinical risk factor - intermediate-risk procedures. (B )

Class III
- Asymptomatic persons - Low-risk procedures

Preoperative Noninvasive Evaluation of Left Ventricular Function

Class IIa
- Dyspnea of unknown origin (C )
- Current or prior heart failure with worsening dyspnea or other change in clinical status if not performed within 12 months. (C )
**Class IIb**
- Reassessment of LV function in clinically stable patients with previously documented cardiomyopathy (C)

**Class III**
- Routine perioperative evaluation of LV function in patients is not recommended. (B)

**Noninvasive stress testing before noncardiac surgery**

**Class I**
- Patients with active cardiac conditions (B)

**Class IIa**
- 3 or more clinical risk factors and poor functional capacity (less than 4 metabolic equivalents [METs]) for Vascular surgery - if it will change management. (B)

**Class IIb**
- At least 1 to 2 clinical risk factors and poor functional capacity - Intermediate-risk noncardiac surgery- if it will change Mx. (B)
- At least 1 to 2 clinical risk factors and good functional capacity (greater than or equal to 4 METs) for vascular surgery. (B)

**Class III**
- Not useful for patients with no clinical risk factors undergoing intermediate-risk noncardiac surgery. (C)
- Not useful for patients undergoing low-risk noncardiac surgery. (C)

Preoperative coronary revascularization CABG / PCI

Class I

- Stable angina with left main coronary artery stenosis. (A)
- Stable angina with 3-vessel disease. (A)
- Stable angina with 2-vessel disease with significant proximal LAD stenosis and either EF < 0.50 or demonstrable ischemia on noninvasive testing. (A)
- High-risk unstable angina or non–ST-segment elevation myocardial infarction (MI). (A)
- Acute ST elevation MI. (A)

Class IIa

- Mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare metal stent placement followed by 4 to 6 weeks of dual-antiplatelet therapy is probably indicated. (B)
- In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. (C)
**Class IIb**

- Not well established in high-risk ischemic patients (eg, abnormal dobutamine stress echocardiogram with at least 5 segments of wall-motion abnormalities). (C)

- Not well established for low-risk ischemic patients with an abnormal dobutamine stress echocardiogram (segments 1 to 4). (B)

**Class III**

- Stable coronary artery disease (CAD) for noncardiac surgery. (B)

- Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy or aspirin and thienopyridine therapy will need to be discontinued perioperatively. (B)

- Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. (B)

**Recommendations for Beta-Blocker medical therapy**

**Class I**

- Continued in patients undergoing surgery who are receiving beta blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications. (C)
- Patients undergoing vascular surgery who are at high cardiac risk owing to the finding of ischemia on preoperative testing. (B)

**Class IIa**
- Vascular surgery or Intermediate-risk surgery in pt with coronary heart disease or in pt at high cardiac risk, defined by the presence of more than 1 clinical risk factor (B)

**Class IIb**
- Above with a single clinical risk factor. (C)
- Vascular surgery with no clinical risk factors, not on beta blockers (B)

**Class III**
- Pts with absolute contraindications to beta blockade. (C)

**Recommendations for statin therapy**

**Class I**
- Currently taking statins and scheduled for noncardiac surgery (B)

**Class IIa**
- Vascular surgery with or without clinical risk factors (B)

**Class IIb**
- Intermediate-risk procedures - At least 1 clinical risk factor (C)
Recommendations for alpha-2 agonists

**Class IIb**
- Perioperative control of hypertension in pts with CAD or at least 1 clinical risk factor (B)

**Class III**
- Patients who have contraindications (C)

Recommendations for use of volatile anesthetic agents

**Class IIa**
- It can be beneficial to use volatile anesthetic agents for maintenance of anesthesia in hemodynamically stable patients at risk for myocardial ischemia. (B)

Recommendation for prophylactic intraoperative nitroglycerin

**Class IIb**
- The usefulness of intraoperative nitroglycerin as a prophylactic agent to prevent myocardial ischemia and cardiac morbidity is unclear for high-risk patients undergoing noncardiac surgery, particularly those who have required nitrate therapy to control angina.

Disease-Specific Approaches

Patients with known coronary artery disease
Given recent evidence regarding the limited value of coronary revascularization before noncardiac surgery, the indication for preoperative testing is limited to the group in whom coronary revascularization may be beneficial independent of noncardiac surgery.
**Hypertension**

Numerous studies have shown that stage 1 or stage 2 hypertension (systolic blood pressure below 180 mm Hg and diastolic blood pressure below 110 mm Hg) is not an independent risk factor for perioperative cardiovascular complications.

Patients with preoperative hypertension appear more likely to develop intraoperative hypotension than nonhypertensive persons; this is particularly true for patients taking ACE inhibitors or angiotensin II receptor antagonists. Several authors have suggested withholding ACE inhibitors and angiotensin receptor antagonists the morning of surgery. Consideration should be given to restarting ACE inhibitors in the postoperative period only after the patient is euvoletic, to decrease the risk of perioperative renal dysfunction.

**Prognostic Gradient of Ischemic Responses during an ECG-Monitored Exercise Test in Patients with Suspected or Proven CAD**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Ischemic Response Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Ischemia induced by low-level exercise* (less than 4 METs or heart rate less than 100 bpm or less than 70% of age-predicted heart rate) manifested by 1 or more of the following: Horizontal or downsloping ST depression greater than 0.1 mV ST-segment elevation greater than 0.1 mV in noninfarct lead Five or more abnormal leads Persistent ischemic response &gt; 3 minutes after exertion Typical angina</td>
</tr>
<tr>
<td>Risk Level</td>
<td>Ischemic Response Gradient</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Exercise-induced decrease in systolic blood pressure by 10 mm Hg</td>
</tr>
<tr>
<td>Low</td>
<td>No ischemia or ischemia induced at high-level exercise† (greater than 7 METs or heart rate greater than 130 bpm i.e. greater than 85% of age-predicted heart rate) manifested by: Horizontal or downsloping ST depression &gt; 0.1 mV One or 2 abnormal leads</td>
</tr>
</tbody>
</table>

bpm indicates beats per min; CAD, coronary artery disease; and MET, metabolic equivalent.

*Workload and heart rate estimates for risk severity require adjustment for patient age. Maximum target heart rates for 40- and 80-year-old subjects taking no cardioactive medication are 180 and 140 bpm, respectively.61–68 †Based on Weiner et al,61 Morris et al,62 Chaitman,63 Gianrossi et al,64 Detrano et al,65 Mark et al,66 Mark et al,67 and Gibbons et al.68
Evaluation of the Lung Cancer Patient for Pulmonary Resection

Introduction

Surgical resection is the only curative treatment modality for patients with lung cancer; however, this is associated with a reduction in the amount of functioning lung tissue. The post-operative preservation of respiratory function has been shown to be proportional to the amount of functioning lung parenchyma preserved. Pre-operative prediction of post-operative lung function is important for risk stratification and to identify and exclude patients who may end up as respiratory cripples after lung resection. In addition, since patients with lung cancer are more likely to be long-term smokers, they may present with pre-existing cardio-pulmonary disorders which further increases their peri-operative risk.

The following evidence-based clinical practice guidelines have been developed by the American College of Chest Physicians for evaluation of the patient with lung cancer being considered for lung resection surgery to identify
patients at increased risk of both peri-operative complications and long-term disability.

**Figure-1: Physiologic Evaluation Cardiac Algorithm**

ThRCRI (Thoracic Revised Cardiac Risk Index)
- Pneumonectomy: 1.5 points
- Previous ischemic heart disease: 1.5 points
- Previous stroke or TIA: 1.5 points
- Creatinine > 2 mg/dl: 1 point

ACC= American College of Cardiology
AHA= American Heart Association
CABG=Coronary Artery Bypass Graft surgery
CPET=CardioPulmonary Exercise Testing
PCI=Percutaneous Coronary Intervention
Figure-2: Physiologic Evaluation Resection Algorithm

Actual risks affected by parameters defined here and
- Patient factors: Co-morbidities, age
- Structural aspects: Centre (Volume, Specialization)
- Process factors: Management of complications
- Surgical access: Thoracotomy versus minimally invasive

Reference
Peri-operative Management of Anti-platelet Therapy

Introduction
Platelets play a central role in atherosclerotic plaque disruption and subsequent thrombus formation. Aspirin is recommended as a lifelong therapy that should never be interrupted for patients with cardiovascular disease. The risk of surgical hemorrhage is increased approximately 20 percent by aspirin or clopidogrel alone and 50 percent by dual antiplatelet therapy (i.e. aspirin and clopidogrel).[1] However, the present clinical data suggest that the risk of a cardiovascular event when stopping antiplatelet agents preoperatively is higher than the risk of surgical bleeding when continuing these drugs, except during surgery in a closed space (e.g. intracranial, posterior chamber of eye) or surgeries associated with massive bleeding and difficult hemostasis.[1]
Peri-operative anticoagulation

- To eliminate effect of antithrombotic therapy before surgery, treatment should be stopped before surgery (~5 days for warfarin, 7-10 days for antiplatelet drug) to minimize bleeding risk.

- Giving bridging after surgery increases risk for bleeding; this risk depends on anticoagulant dose (therapeutic-dose > low-dose) and proximity to surgery (higher risk if given closer to surgery)

In resuming treatment after surgery, it takes:

- 2-3 days for anticoagulant effect to begin after starting warfarin

- 3-5 h for peak anticoagulant effect after starting low molecular weight heparin (LMWH)
• Minutes for an antiplatelet effect to begin after starting acetyl salicylic acid (ASA)
• 3-7 days for peak inhibition of platelet aggregation after starting a maintenance dose of clopidogrel

**Is interruption of antithrombotic therapy in the perioperative period needed?**

• In patients who are having a major surgical or other major invasive procedure, interruption of antithrombotic therapy is typically required to minimize the risk for perioperative bleeding. Continuation of Vitamin K antagonist therapy or aspirin in the perioperative period confers an increased risk for bleeding.

• In patients who are undergoing minor surgical or invasive procedures (eg, dental, skin, or cataract), interruption of antithrombotic therapy may not be required.

**Surgeries considered to have a high risk of bleeding include:**

• Urologic surgery and procedures consisting of transurethral prostate resection, bladder resection, or tumor ablation; nephrectomy; or kidney biopsy in part due to untreated tissue damage (after prostatectomy) and endogenous urokinase release

• Pacemaker or implantable cardioverter-defibrillator device implantation in which separation of infraclavicular fascial layers and lack of suturing of unopposed tissues within the device pocket may predispose to hematoma development
• Colonic polyp resection, typically of large (i.e., 1-2 cm long) sessile polyps, in which bleeding may occur at the transected stalk following hemostatic plug release

• Surgery and procedures in highly vascular organs, such as the kidney, liver, and spleen

• Bowel resection in which bleeding may occur at the bowel anastomosis site

• Major surgery with extensive tissue injury (e.g., cancer surgery, joint arthroplasty, reconstructive plastic surgery)

• Cardiac, intracranial, or spinal surgery, especially as small pericardial, intracerebral, or epidural bleeds can have serious clinical consequences

**Peri-operative anti-platelet therapy**

• Patients with coronary artery or other cardiovascular disease, who may be considered at moderate to high risk for perioperative adverse cardiovascular events, may benefit from perioperative continuation of ASA

• Moderate- to high-risk patients include those with ischemic heart disease, compensated or prior congestive heart failure, diabetes mellitus, renal insufficiency, or cerebrovascular disease.

• In addition, patients undergoing selected types of surgery associated with an increased risk for perioperative cardiovascular events, such as carotid endarterectomy and peripheral artery bypass surgery may also benefit from perioperative continuation of ASA.
In patients considered at low risk for cardiovascular events in whom there is likely to be fewer potential benefits of perioperative continuation of ASA, interruption of ASA may be reasonable.

**If antithrombotic therapy is interrupted before surgery, is “bridging anticoagulation” needed?**

The need for bridging is driven by patients’ estimated risk for thromboembolism (TE):

- In **high-risk patients**, the need to prevent TE will dominate management irrespective of bleeding risk; the potential consequences of TE may justify bridging
- In **moderate-risk patients**, a single perioperative strategy is not dominant and management will depend on individual patient risk assessment
- In **low-risk patients**, the need to prevent TE will be less dominant and bridging may be avoided
- In **all patients**, judicious use of postoperative bridging is needed to minimizing bleeding that would have the undesired effect of delaying resumption of antithrombotic therapy after surgery.

**What are bridging anticoagulation regimens?**

A “high-dose” (therapeutic-dose) regimen involves giving a dose similar to that used to treat acute VTE or ACS (eg, enoxaparin, 1 mg/kg BID or 1.5 mg/kg QD, dalteparin 100 IU/kg BID or 200 IU/kg QD, tinzaparin 175 IU/kg QD, IV UFH to attain aPTT 1.5- to 2-times the control aPTT).
A “low-dose” (prophylactic-dose) regimen involves giving a dose used, typically, to prevent postoperative VTE (eg, enoxaparin 30 mg BID or 40 mg QD, dalteparin 5000 IU QD, UFH 5000-7500 IU BID).

An “intermediate-dose” regimen has been recently studied for bridging and is intermediate in anticoagulant intensity between a high-dose and low-dose regimen (eg, enoxaparin 40 mg BID).

Recommendations in this chapter, unless otherwise specified, refer to a “therapeutic-dose” regimen because it is most widely studied, it is widely used in clinical practice, and it is the regimen considered most important because of the potential to confer the greatest benefit and harm.

Different bridging regimens may have potential advantages or drawbacks over a “therapeutic-dose” regimen.

Summary

In patients who are receiving acetyl salicylic acid (ASA) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, it is suggested to continue ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure (Grade 2C).

In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, it is suggested to continue ASA around the time of
surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C).

- In patients at low risk for cardiovascular events who are receiving ASA therapy, it is suggested to stop ASA 7 to 10 days before surgery instead of continuation of ASA (Grade 2C).

- In patients who are receiving ASA and require CABG surgery, it is suggested to continue ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C).

- In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, it is suggested to continue ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery instead of continuing dual antiplatelet therapy around the time of surgery.

References
Introduction

Coronary stents are of two types: bare metal stents (BMS) and drug eluting stents (DES). BMS undergo rapid epithelisation and hence do not need long term anti-platelet therapy, but, they carry risk of re-stenosis. DES reduce the risk of re-stenosis; however they need long term anti-platelets to prevent in-stent thrombosis. Patients with coronary stents usually receive dual anti-platelet therapy with aspirin and a thienopyridine (e.g., clopidogrel). Premature discontinuation of dual antiplatelet therapy markedly increases the risk of catastrophic stent thrombosis and death or MI.


Classification of recommendations and levels of evidence
Level A  Multiple (3-5) population risk strata evaluated
Level B  Limited (2-3) population risk strata evaluated
Level C  Very limited (1-2) population risk strata evaluated

<table>
<thead>
<tr>
<th>Class</th>
<th>Benefit vs Risk</th>
<th>Procedure/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>should be performed/administered</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>It is reasonable to perform procedure/administer treatment</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Benefit &gt;= Risk</td>
<td>Procedure/treatment may be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Risk &gt;= Benefit</td>
<td>Procedure/treatment should NOT be performed/administered</td>
</tr>
</tbody>
</table>

**Class IIa recommendations**

1. In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need elective non-cardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare-metal stent placement followed by 4 to 6 weeks of dual anti-platelet therapy is probably indicated. (Level of Evidence: B)

2. In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. (Level of Evidence: C)
**Class III recommendations**

1. Elective non-cardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy, or aspirin and thienopyridine therapy, will need to be discontinued peri-operatively. (Level of Evidence: B)

2. Elective non-cardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. (Level of Evidence: B)


**Background:** It is unclear how to appropriately manage discontinuation and resumption of antiplatelet therapy in patients with coronary stents who need non-cardiac surgery. We undertook a systematic review of the literature to identify practice guideline statements regarding antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery.

**Methods:** We used six search strategies to identify practice guideline statements that comment on perioperative antiplatelet management for patients with coronary stents undergoing non-cardiac surgery. Two independent reviewers assessed study eligibility, abstracted data and completed quality assessment.
Results: We identified 11 practice guidelines that met the eligibility criteria and were included in the review. These guidelines advised that elective non-cardiac surgery be delayed for at least four weeks after bare-metal stent (BMS) implantation and at least six months after drug-eluting stent (DES) implantation. For elective surgery, all guidelines advised continuing ASA therapy whenever possible. If interruption of antiplatelet therapy was required, four guidelines advised to discontinue ASA/clopidogrel at least five days before surgery while two guidelines advised to discontinue 7-10 days before surgery. Five guidelines provided varying guidance for the use of perioperative bridging during antiplatelet therapy interruption.

Conclusion: Most current recommendations are based on expert opinion. This review highlights the need for well-designed prospective studies to identify optimal management strategies in patients with coronary stents on antiplatelet therapy who need non-cardiac surgery.

Summary:
- In patients who are undergoing preparation for percutaneous coronary intervention and are likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a BMS or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.
- Patients with coronary stents should not undergo elective surgery within 4-6 weeks of BMS and within 1 year of DES if thienopyridine therapy, or aspirin
and thienopyridine therapy, will need to be discontinued peri-operatively (some guidelines recommend 6 months after DES).

- For emergency surgeries, the risk of stent thrombosis should be weighed against the risk of bleeding and the management of peri-operative anti-platelet should be planned accordingly. The cardiologist should be consulted to identify patients with high risk for stent thrombosis. Aspirin should preferably be continued.

- The role of bridging therapy in patients with coronary stents who require elective surgery is uncertain.
The incidence of neurological dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is reported to be less than 1 in 150,000 epidurals and 1 in 222,000 anaesthetics. This risk may be increased in patients with abnormalities of the spinal cord or vertebral column, underlying coagulopathy and difficulty in performing the neuraxial procedure. To improve patient safety during regional anesthesia procedures, the American Society of Regional Anesthesia
and Pain Medicine has laid down consensus guidelines, recommendations and suggestions for the anaesthetic management of patients on peri-operative anticoagulant therapy.

**Strength and grade of recommendations**

Grade 1 represents general agreement in the efficacy, Grade 2 notes conflicting evidence or opinion on the usefulness, and Grade 3 suggests that the procedure may not be useful (but possibly harmful).

Level – A: Randomized clinical trials, meta-analyses, well-done observational series yielding very large risk reduction

Level – B: observational and epidemiologic series

Level – C: Recommendations based on the pharmacology of hemostasis-altering drugs, risk of surgical bleeding, and expert opinion

**Anesthetic management of the patient receiving subcutaneous unfractionated heparin**

- Daily review of the patient’s medical record to determine the concurrent use of medications that affect other components of the clotting mechanisms is recommended. These medications include anti-platelet medications, LMWH, and oral anticoagulants (Grade 1B).

- In patients receiving prophylaxis with subcutaneous UFH with dosing regimens of 5000 U twice daily, there is no contraindication to the use of neuraxial techniques. The risk of neuraxial bleeding may be
reduced by delay of the heparin injection until after the block and may be increased in debilitated patients after prolonged therapy (Grade 1C).

- The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. The risk and benefits of thrice-daily UFH should be assessed on an individual basis and techniques to facilitate detection of new/progressive neurodeficits (e.g., enhanced neurologic monitoring and neuraxial solutions to minimize sensory and motor block) should be applied (Grade 2C).

- Because heparin-induced thrombocytopenia may occur during heparin administration, it is recommended that patients receiving heparin for more than 4 days have a platelet count assessed before neuraxial block and catheter removal (Grade 1C).

**Management of the patient receiving intraoperative anticoagulation with heparin**

- Combining neuraxial techniques with intraoperative anticoagulation with heparin during vascular surgery is acceptable with the following recommendations (Grade 1A):
  - Avoid the technique in patients with other coagulopathies.
o Delay heparin administration for 1 hr after needle placement.

o Remove indwelling neuraxial catheters 2 to 4 hrs after the last heparin dose and assess the patient’s coagulation status; re-heparin 1 hr after catheter removal.

o Monitor the patient postoperatively to provide early detection of motor blockade and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma.

- Although the occurrence of a bloody or difficult neuraxial needle placement may increase risk, there are no data to support mandatory cancellation of a case. Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is warranted.

- Currently, insufficient data and experience are available to determine if the risk of neuraxial hematoma is increased when combining neuraxial techniques with the full anticoagulation of cardiac surgery. Postoperative monitoring of neurologic function and selection of neuraxial solutions that minimize sensory and motor block will facilitate detection of new/progressive neurodeficits (Grade 2C).

**Anesthetic management of the patient receiving low-molecular weight heparin**

- The anti-Xa level is not predictive of the risk of bleeding. Routine use of monitoring of the anti-Xa level is not recommended (Grade 1A).
- Antiplatelet or oral anticoagulant medications administered in combination with LMWH increase the risk of spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.

- Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, regardless of LMWH dosing regimen is not recommended (Grade 1A).

- The presence of blood during needle and catheter placement does not necessitate postponement of surgery. It is suggested that initiation of LMWH therapy in this setting should be delayed for 24 hrs postoperatively and that this consideration be discussed with the surgeon (Grade 2C).

**Preoperative LMWH**

- Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement should occur at least 10 to 12 hrs after the LMWH dose (Grade 1C).

- In patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hrs, Enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hrs, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily, delay of at least 24 hrs to ensure normal hemostasis at the time of needle insertion (Grade 1C).

- In patients administered a dose of LMWH 2 hrs preoperatively (general surgery patients), neuraxial
techniques are not recommended because needle placement would occur during peak anticoagulant activity (Grade 1A).

**Postoperative LMWH**

- Patients with postoperative LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule. (Grade 1C).
  - Twice-daily dosing: This dosage regimen is associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hrs postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight, but must be removed before the first dose of LMWH. Administration of LMWH should be delayed for 2 hrs after catheter removal.
  - Single-daily dosing: The first postoperative LMWH dose should be administered 6 to 8 hrs postoperatively. The second postoperative dose should occur no sooner than 24 hrs after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10
to 12 hrs after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hrs after catheter removal. No additional hemostasis-altering medications should be administered due to the additive effects.

Regional anesthetic management of the patient on oral anticoagulants

- Caution should be used when performing neuraxial techniques in patients recently discontinued from long-term warfarin therapy. In the first 1 to 3 days after discontinuation of warfarin therapy, the coagulation status (reflected primarily by factor II and X levels) may not be adequate for hemostasis despite a decrease in the INR (indicating a return of factor VII activity). Adequate levels of II, VII, IX, and X may not be present until the INR is within reference limits. It is recommended that the anticoagulant therapy must be stopped (ideally 4 to 5 days before the planned procedure) and the INR must be normalized before initiation of neuraxial block (Grade 1B).

- The concurrent use of medications that affect other components of the clotting mechanisms and may increase the risk of bleeding complications for patients receiving oral anticoagulants and do so without influencing the INR. These medications include aspirin and other NSAIDs, ticlopidine and clopidogrel, UFH, and LMWH (Grade 1A).

- In patients who are likely to have an enhanced response to the drug, it is recommended that a reduced dose be administered.
- Algorithms have been developed to guide physicians in the appropriate dosing of warfarin based on desired indication, patient factors, and surgical factors. These algorithms may be extremely useful in patients at risk for an enhanced response to warfarin (Grade 1B).

- In patients receiving an initial dose of warfarin before surgery, the INR should be checked before neuraxial block if the first dose was given more than 24 hrs earlier or if a second dose of oral anticoagulant has been administered (Grade 2C).

- In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis (Grade 2C).

- Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurologic evaluation, it is recommended that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (Grade 1C).

- As thromboprophylaxis with warfarin is initiated, neuraxial catheters should be removed when the INR is less than 1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%. It is suggested that neurologic assessment be continued for at least 24 hrs after catheter removal for these patients (Grade 2C).

- In patients with INR greater than 1.5 but less than 3, it is recommended that removal of indwelling
catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not affect the INR (e.g., NSAIDs, ASA, clopidogrel, ticlopidine, UFH, LMWH) (Grade 2C).

- It is also recommended that neurologic status be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level (Grade 1C).

- In patients with an INR greater than 3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (Grade 1A).

- No definitive recommendation can be made regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (Grade 2C).

**Anaesthetic management of the patient on anti-platelet medications**

- Nonsteroidal anti-inflammatory drugs seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. Nonsteroidal anti-inflammatory drugs (including aspirin) do not create a level of risk that will interfere with the performance of neuraxial blocks. In patients receiving these medications, there are no specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative
monitoring, or the timing of neuraxial catheter removal (Grade 1A).

- In patients receiving NSAIDS, the performance of neuraxial techniques is not recommended if the concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, UFH, and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications. Cyclooxygenase-2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation (Grade 2C).

- The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Management is based on labeling precautions and the surgical, interventional cardiology/radiology experience (Grade 1C).

- On the basis of labeling and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. If a neuraxial block is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.

- Platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. After administration, the time to normal platelet aggregation is 24 to 48 hrs for abciximab and 4 to 8 hrs for eptifibatide and tirofiban. Neuraxial techniques should be avoided
until platelet function has recovered. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be administered in the postoperative period (after a neuraxial technique), it is recommended that the patient be carefully monitored neurologically.

**Recommendations for patients scheduled to receive thrombolytic therapy**

- The patient should be queried and medical record reviewed for a recent history of lumbar puncture, spinal or epidural anesthesia, or epidural steroid injection to allow appropriate monitoring. Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs for 10 days after puncture of non-compressible vessels (Grade 1A).

**Recommendations for neuraxial blocks in patients who have received fibrinolytic and thrombolytic drugs**

- Performance of spinal or epidural anesthetics should be avoided except in highly unusual circumstances (Grade 1A).
- Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.
- In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, neurological monitoring should be continued for an appropriate interval. It may be that the interval of monitoring should not be more
than 2 hrs between neurologic checks. If neuraxial blocks have been combined with fibrinolytic and thrombolytic therapy and ongoing epidural catheter infusion, the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurologic function (Grade 1C).

- There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. The measurement of fibrinogen level (one of the last clotting factors to recover) should be used to evaluate the presence of residual thrombolytic effect and appropriate timing of catheter removal (Grade 2C).

**Anaesthetic management of the patient on herbal medications**

- The use of herbal medications does not create a level of risk that will interfere with the performance of neuraxial block. Mandatory discontinuation of these medications or avoidance of regional anesthetic techniques in patients in whom these medications have been administered is not recommended (Grade 1C).

**Anesthetic management of patients receiving thrombin inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)**

- In patients receiving thrombin inhibitors, the performance of neuraxial techniques is not recommended (Grade 2C).
Anesthetic management of patients receiving fondaparinux

- Until further clinical experience is available, performance of neuraxial techniques should occur under conditions used in clinical trials (single-needle pass, atraumatic needle placement, avoidance of in-dwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered.

The obstetric patient

- In the absence of a large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment of VTE, it is suggested that the ASRA guidelines (derived from mainly from surgical patients) be applied to parturients (Grade 2C). This also applies to patients undergoing deep plexus or peripheral nerve block (Grade 1C)
Peri-operative Fluid Therapy in the Paediatric Patient

Introduction
Paediatric surgical patients, especially those who undergo extensive bowel resections and emergency laparotomies, may have acute alterations in volume status and in the composition of intracellular and extracellular fluids. Precise perioperative management of fluids and electrolytes is a fundamental part of the patient’s overall surgical treatment, which can have a significant effect on perioperative morbidity and mortality. The primary goal of fluid administration is to restore the effective circulating blood volume and maintain a desirable equilibrium between the various fluid compartments within the body.

Pre-operative fasting
- Children can safely be allowed clear fluids 2 hours before surgery without increasing the risk of aspiration.
- Food should normally be withheld for 6 hours prior to surgery in children aged 6 months or older.
- In children under 6 months of age it is probably safe to allow breast milk feed up to 4 hours before surgery.

Fluid management
A fluid management plan for any child should address 3 key issues:

i. Any fluid deficit which is present
ii. Maintenance fluid requirements
iii. Any losses due to surgery e.g. Blood loss, 3rd space losses

Assessment and correction of fluid deficit
- Dehydration without signs of hypovolaemia should be corrected slowly.
- The fluid used to replace this deficit should be isotonic – such as 0.9% sodium chloride or Ringer lactate/Hartmann’s solution.
- Hypovolaemia should be corrected rapidly to maintain cardiac output and organ perfusion with an initial fluid bolus of 10-20ml/kg of an isotonic fluid or colloid, repeated as necessary.
- In the child, a fall in blood pressure is a late sign of hypovolaemia.
Maintenance fluid requirements in children

Maintenance fluids should be calculated using the formula of Holliday and Segar

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Daily fluid requirement</th>
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<tbody>
<tr>
<td>0-10kg</td>
<td>4ml/kg/hr</td>
</tr>
<tr>
<td>10-20kg</td>
<td>40ml/hr + 2ml/kg/hr above 10kg</td>
</tr>
<tr>
<td>&gt;20kg</td>
<td>60ml/hr + 1ml/kg/hr above 20kg</td>
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</tbody>
</table>

Choice of fluid

- In term neonates during the first 48 hours of life 10% dextrose should be given at a rate of 2-3ml/kg/hr or 40-80ml/kg/day.
- From day 3 onwards, it is recommended that the maintenance fluid should be 0.18% saline in 10% dextrose given at a rate of 4ml/kg/hr or 100-120ml/kg/day.
- For children over 1 month, isotonic fluids should be administered such as sodium chloride 0.9% with dextrose 5%, sodium chloride 0.9% or Hartmann’s solution / Ringer Lactate solution.
- The majority of children over 1 month of age will maintain a normal blood sugar if given non-dextrose containing fluid during surgery. However, blood glucose should be monitored if no dextrose is given.

Glycemic control

Children at risk of hypoglycaemia if non-dextrose containing fluid is given are
- Those on parenteral nutrition or a dextrose containing solution prior to theatre
- Children of low body weight (<3rd centile)
- Children having surgery of more than 3 hours duration
- Children having extensive regional anaesthesia

These children at risk should be given dextrose containing solutions (1 – 2.5% dextrose) or have their blood glucose monitored during surgery.

Management of other losses
- All losses during surgery should be replaced with an isotonic fluid such as 0.9% sodium chloride, Ringer lactate/Hartmann’s solution, a colloid or a blood product, depending on the child’s haematocrit.
- Third space loss is difficult to quantify and normally an estimate is made with 1-2ml/kg/hr given for superficial surgery, 4-7ml/kg/hr given for thoracotomy and 5-10ml/kg/hr given for abdominal surgery.
- Blood loss during surgery should be replaced initially with crystalloid or colloid, and then with blood once the haematocrit has fallen to 25%.
- Children with cyanotic congenital heart disease and neonates may need a higher haematocrit to maintain oxygenation.

Post-operative fluid therapy
- Fluid therapy should be monitored by daily electrolyte estimation, use of a fluid input/output chart and daily weighing if feasible.
• Hypotonic fluids should not be used for postoperative maintenance as this may cause hyponatraemia

• Ongoing losses from drains or nasogastric tubes should be replaced with an isotonic fluid such as 0.9% sodium chloride with or without added KCl.
Peri-operative Deep Vein Thrombosis Prophylaxis:


Prevention of Venous thrombo embolism (VTE) in Nonorthopedic Surgical Patients
Patients Undergoing General, Gastro intestinal, Urological, Gynecologic, Bariatric, Vascular, Plastic, or Reconstructive Surgery

- For general and abdominal-pelvic surgery patients at very low risk for Venous Thrombo Embolism (VTE) ( < 0.5%; Rogers score, < 7; Caprini score, 0), - No specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation.

- For general and abdominal-pelvic surgery patients at low risk for VTE ( ~1.5%; Rogers score, 7-10;
Caprini score, 1-2), - Mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C).

- For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications,
  - LMWH (Grade 2B), LDUH (Grade 2B), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

- For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, > 10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, - Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C).

- For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, >/= 5) who are not at high risk for major bleeding complications, - Pharmacologic prophylaxis with LMWH (Grade 1B) or LDUH (Grade 1B) over no prophylaxis. Mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis (Grade 2C).

- For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, Extended-duration pharmacologic prophylaxis
(4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B).

- For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, - Use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

- For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, >/= 5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, - Low-dose aspirin (Grade 2C), fondaparinux (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

- For general and abdominal-pelvic surgery patients, - An inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C).

- For general and abdominal-pelvic surgery patients, - Periodic surveillance with venous compression ultrasound should not be performed (Grade 2C).

**Patients undergoing cardiac surgery**

- For cardiac surgery patients with an uncomplicated postoperative course, - Mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C).
For cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications, -Add pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis (Grade 2C).

Patients undergoing thoracic surgery

- For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, - LDUH (Grade 2B), LMWH (Grade 2B), or mechanical prophylaxis with optimally applied IPC (Grade 2C) over no prophylaxis.

- For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, - LDUH (Grade 1B) or LMWH (Grade 1B) over no prophylaxis. In addition, mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis (Grade 2C).

- For thoracic surgery patients who are at high risk for major bleeding, - Mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

Patients undergoing craniotomy

- For craniotomy patients, - Mechanical prophylaxis, preferably with IPC, be used over no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C).

- For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant
disease), - Add Pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C).

**Patients undergoing spinal surgery**

- For patients undergoing spinal surgery, -Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C), unfractionated heparin (Grade 2C), or LMWH (Grade 2C).

- For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), -Add pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C).

**Patients with major trauma:**

Traumatic Brain Injury, Acute Spinal Injury, and Traumatic Spine Injury

- For major trauma patients, - LDUH (Grade 2C), LMWH (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

- For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), -Add mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) when not contraindicated by lower extremity injury.
• For major trauma patients in whom LMWH and LDUH are contraindicated, - Mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) when not contraindicated by lower-extremity injury. Add pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves (Grade 2C).

• For major trauma patients, - IVC filter should not be used for primary VTE prevention (Grade 2C).

• For major trauma patients, - Periodic surveillance with venous compression ultrasound should not be performed (Grade 2C).

**Prevention of VTE in orthopedic surgery patients**

Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS)

• In patients undergoing THA or TKA, - Use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C).

• In patients undergoing HFS, - Use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C).
• For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, -Start either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B).

• In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, - LMWH in preference to the other agents we are recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C).

• In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, use of LMWH in preference to the other agents recommended as alternatives: fondaparinux, LDUH (Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C).

• For patients undergoing major orthopedic surgery, -Extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (Grade 2B).

• In patients undergoing major orthopedic surgery, - Use dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C).

• In patients undergoing major orthopedic surgery and increased risk of bleeding, - Use IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C).
- In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, use apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B).
- In patients undergoing major orthopedic surgery, suggestion against using IVC filter placement for primary prevention over no thromboprophylaxis in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C).
- For asymptomatic patients following major orthopedic surgery, recommendation against Doppler (or duplex) ultrasound screening before hospital discharge (Grade 1B).

**Patients with isolated lower-leg injuries distal to the knee**
- No prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C).

**Patients undergoing knee arthroscopy**
- For patients undergoing knee arthroscopy without a history of prior VTE, no thromboprophylaxis rather than prophylaxis (Grade 2B).

**Abbreviations**
LMWH : Low Molecular Weight Heparin  
LDVH : Low Dose Unfractionated Heparin  
VKA : Vitamin K Antagonists  
IPC : Intermittent Pneumatic Compression  
GCS : Graduated Compression Stockings
## Strength of the Recommendations Grading System

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit vs Risk and Burdens</th>
<th>Methodological Strength of Supporting Evidence</th>
<th>Implications</th>
</tr>
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<tbody>
<tr>
<td>Strong recommendation, high-quality evidence (1A)</td>
<td>Benefits clearly outweigh Risk and burdens or vice versa.</td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.</td>
<td>Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Strong recommendation, low- or very-low-quality evidence (1C)</td>
<td>Benefits clearly outweigh risk burdens or vice versa.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence</td>
<td>Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
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<td>Weak recommendation, high–quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden.</td>
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<td>The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.</td>
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<td>Weak recommendation, moderate-quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden.</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.</td>
<td>Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Weak recommendation, low-or very-low-quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risk, and burden; benefits, risk, and burden may be closely balanced.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.</td>
<td>Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
</tr>
</tbody>
</table>
## Rogers score

Venous Thromboembolic Event Complication Risk Index for General and Vascular Surgery Patients

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk score points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation type other than endocrine</td>
<td></td>
</tr>
<tr>
<td>Respiratory and hemic</td>
<td>9</td>
</tr>
<tr>
<td>Thoracoabdominal aneurysm, embolectomy / thrombectomy, venous reconstruction, and endovascular repair</td>
<td>7</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>4</td>
</tr>
<tr>
<td>Mouth, palate</td>
<td>4</td>
</tr>
<tr>
<td>Stomach, intestines</td>
<td>4</td>
</tr>
<tr>
<td>Integument</td>
<td>3</td>
</tr>
<tr>
<td>Hernia</td>
<td>2</td>
</tr>
<tr>
<td>ASA physical status classification</td>
<td></td>
</tr>
<tr>
<td>3, 4 or 5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Work RVU</td>
<td></td>
</tr>
<tr>
<td>&gt;17</td>
<td>3</td>
</tr>
<tr>
<td>10-17</td>
<td>2</td>
</tr>
<tr>
<td>Two points for each of these conditions</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated cancer</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy for malignancy within 30d of operation</td>
<td></td>
</tr>
<tr>
<td>Preoperative serum sodium &gt;145 mmol / L</td>
<td></td>
</tr>
<tr>
<td>Risk factor</td>
<td>Risk score points</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Transfusion &gt; 4u packed RBCs in 72h before operation</td>
<td></td>
</tr>
<tr>
<td>Ventilator - dependent</td>
<td></td>
</tr>
<tr>
<td>One point for each of these conditions</td>
<td>1</td>
</tr>
<tr>
<td>Wound class (clean/contaminated)</td>
<td></td>
</tr>
<tr>
<td>Preoperative hematocrit &lt; 38%</td>
<td></td>
</tr>
<tr>
<td>Preoperative bilirubin &gt; 1.0mg / dl</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt; 3.5 mg / dl</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
</tr>
<tr>
<td>Zero points for each of these conditions</td>
<td>0</td>
</tr>
<tr>
<td>ASA physical status class 1</td>
<td></td>
</tr>
<tr>
<td>Work RVU &lt; 10</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
</tbody>
</table>

ASA, American Society of Anesthesiologists; RBC, red blood cell; RVU, relative value unit
## Caprini Score

### Each Risk Factor Represents 1 Point

- Age 41-60 years
- Swollen legs (current)
- Varicose veins
- Obesity (BMI > 25)
- Minor surgery planned
- Sepsis (<1 month)
- Serious Lung disease including pneumonia (<1 month)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (>3), premature birth with toxemia or growth-restricted infant
- Acute myocardial infarction
- Congestive heart failure (<1 month)
- Medical patient currently at bed rest
- History of inflammatory bowel disease
- History of prior major surgery (<1 month)
- Abnormal pulmonary function (COPD)
- Other risk factors ______________________

Subtotal : ______________________

### Each Risk Factor Represents 5 Points

- Stroke (<1 month)
- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (<1 month)
- Multiple trauma (<1 month)
- Acute Spinal cord injury (paralysis) (< 1 month)

Subtotal : ______________________
<table>
<thead>
<tr>
<th>Each Risk Factor Represents 2 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Age 61-74 years</td>
</tr>
<tr>
<td>➢ Arthroscopic surgery</td>
</tr>
<tr>
<td>➢ Malignancy (present or previous)</td>
</tr>
<tr>
<td>➢ Laparoscopic surgery (&gt;45 minutes)</td>
</tr>
<tr>
<td>➢ Patient confined to bed (&gt;72 hours)</td>
</tr>
<tr>
<td>➢ Immobilizing plaster cast (&lt;1 month)</td>
</tr>
<tr>
<td>➢ Central venous access</td>
</tr>
<tr>
<td>➢ Major surgery (&gt;45 minutes)</td>
</tr>
<tr>
<td>➢ Age 75 years or older</td>
</tr>
<tr>
<td>➢ History of DVT/PE</td>
</tr>
<tr>
<td>➢ Positive Factor V Leiden</td>
</tr>
<tr>
<td>➢ Elevated serum homocysteine</td>
</tr>
<tr>
<td>➢ Heparin-induced thrombocytopenia (HIT)</td>
</tr>
<tr>
<td>(Do not use heparin or any low molecular weight heparin)</td>
</tr>
<tr>
<td>➢ Elevated anticardiollpin antibodies</td>
</tr>
<tr>
<td>➢ Other congenital or acquired thrombophilia if yes : Type ________________</td>
</tr>
<tr>
<td>➢ Family History of thrombosis*</td>
</tr>
<tr>
<td>➢ Positive Prothrombin 20210A</td>
</tr>
<tr>
<td>➢ Positive Lupus anticoagulant</td>
</tr>
</tbody>
</table>

*Most frequently missed risk factor

Subtotal ________________________

**Total Risk Factor Score :**
Enhancing Recovery After Surgery (ERAS) Protocols

The aim of the Enhanced Recovery After Surgery (ERAS) protocol is to attenuate the stress response to surgery and enable rapid recovery using a multimodal approach.

Maintaining metabolic control and homeostasis are key elements of the patient-focused rehabilitation ERAS protocol. The core principles of ERAS are to minimise invasive surgery and optimise pain control, gastrointestinal function and mobilisation. Key components of the protocol are illustrated below. All components of the protocol should be implemented for optimal clinical outcome.
The ERAS Society has published a comprehensive set of recommendations for perioperative care for elective colonic surgery, elective rectal/pelvic surgery and pancreaticoduodenectomy.

**Reference**

Acute Pain Management in the Paediatric Patient

The objective of pain assessment is to ensure that effective procedures and processes are instituted to prevent or minimise pain. Pain is not only a sensory perception but has emotional, cognitive, and behavioural components, which also need to be recognised. Uncontrolled pain can impact health outcomes. Pain is a common complaint among paediatric patients but is often under-diagnosed and inadequately treated. This is mainly because children experience difficulty in expressing their pain in a way that is recognised and clearly understood. It is essential that health care professionals looking after children of all ages are trained to recognise and treat pain.

These recommendations for the assessment and management of acute pain in paediatric patients are based on the following guidelines -
Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias</td>
<td></td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias</td>
<td></td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
<td></td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies e.g., case reports, case series</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>
**Grading of recommendations**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
</tbody>
</table>

**Assessment of pain**

- Children’s self-report of their pain is the preferred approach: Grade B
- No individual measure can be broadly recommended for pain assessment across all children or all contexts: Grade B
- An observational measure should be used in conjunction with self-report with 3–5-year-olds as there is limited evidence for the reliability and validity of self-report measures of pain intensity in this age group: Grade B
Recommended measures for procedural and post-operative pain assessment as a function of the child’s chronological age

<table>
<thead>
<tr>
<th>Child’s age*</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn to 3 years old</td>
<td>COMFORT or FLACC</td>
</tr>
<tr>
<td>4 years old</td>
<td>FPS-R + COMFORT or FLACC</td>
</tr>
<tr>
<td>5 to 7 years old</td>
<td>FPS-R</td>
</tr>
<tr>
<td>7 years old +</td>
<td>VAS or NRS or FPS-R</td>
</tr>
</tbody>
</table>

*With assumed normal cognitive development
COMFORT: 8 behavioural indicators
FLACC scale: Face, Legs, Arms, Cry, and Consolability scale
FPS-R: Faces Pain Scale – Revised
VAS: Visual Analog Scale; NRS: Numerical Rating Scale

**Medical procedures**

**Neonates**

- Breast-feeding should be encouraged during the procedure, if feasible: Grade A
- Non-pharmacological measures such as non-nutritive suckling, swaddling, heel massage can be used for brief procedures: Grade A

For blood sampling (including peripheral venous, arterial and percutaneous central venous catheter insertion)

- Sucrose or other sweet solutions can be used: Grade A
- Topical local anaesthetics can be used for venepuncture pain: Grade B
• Venepuncture by a trained practitioner is preferred to heel lance: Grade A

For lumbar puncture
• Topical local anaesthetic is effective in reducing pain: Grade A

Older children

Blood sampling and intravenous cannulation
• Topical local anaesthesia should be used for intravenous cannulation: Grade A
• Psychological strategies to reduce pain (distraction techniques, hypnosis) should be used: Grade A

Lumbar puncture
• Topical local anaesthetic and local anaesthetic infiltration are useful and do not decrease success rates (Grade B)
• 50% nitrous oxide in oxygen should be offered to children who are willing to co-operate (Grade C)

Post-operative pain

Good practice points
• Post-operative analgesia should be appropriate to developmental age, surgical procedure and clinical setting to provide safe, potent and flexible pain relief.
• Combinations of analgesics should be used unless there are specific contra-indications. For example; local anaesthetics, opioids, NSAIDs, and paracetamol can be given in conjunction, not exceeding maximum recommended dose.
General surgery and Urology (Minor and Intermediate)

Sub-umbilical surgery

- Local anaesthetic should be used when feasible: wound infiltration, transversus abdominis plane block, ilio-inguinal nerve block and caudal analgesia are effective in the early post-operative period: Grade A

General surgery and Urology (Major)

Major intra-abdominal surgery

- Intravenous opioids either as nurse-controlled analgesia or patient controlled analgesia are effective in the early post-operative period: Grade A
- Epidural analgesia with local anaesthetic should be considered for major abdominal surgery. The addition of neuraxial clonidine or opioid may further improve analgesia but side effects may also be increased: Grade B

Laparoscopic surgery – Good practice point

- Infiltration of port sites with local anaesthetic as part of a multimodal analgesic strategy may reduce postoperative pain

Thoracotomy

- Epidural analgesia is effective for post-thoracotomy pain: Grade D
Lower limb surgery

- Peripheral nerve blocks provide superior analgesia and are associated with fewer adverse effects compared with intravenous opioids: Grade B
- Continuous peripheral nerve blocks are feasible, effective and safe, and are associated with lower pain scores: Grade B
- Epidural opioids are effective, reduce the dose requirements of local anaesthetic, and rescue IV opioids but increase the incidence of side effects: Grade B
- Epidural techniques are associated with lower pain scores than intravenous opioid analgesia: Grade C
- Systemic paracetamol and NSAID reduce intravenous opioid requirements: Grade C

Upper limb surgery

- Brachial plexus blocks provide satisfactory analgesia for hand and forearm surgery extending into the post-operative period: Grade B
- Axillary, infra-clavicular, supra-clavicular and interscalene approaches are feasible and effective: Grade B

Analgesia

Local anaesthetics

Bupivacaine, Levo-bupivacaine, Ropivacaine

- Maximum recommended dose for single bolus injection is 2 mg/kg in neonates and 2.5 mg/kg in children.
- Maximum recommended rate for continuous infusion is 0.2 mg/kg/hr in neonates and 0.4 mg/kg/hr in children.

**Lidocaine**
- Plain: Maximum dose should not exceed 3 mg/kg
- With epinephrine: Should not be used near extremities. Maximum dose is 5 mg/kg for lidocaine and 5 mg/kg for epinephrine

**EMLA**
- Can be used in neonates above 37 weeks gestational age.
- Methemoglobin values to be monitored in infants less than 3 months of age
- EMLA should not be used in infants under 1 year who are receiving methemoglobin-inducing drugs

**Opioids**
Opioids remain the most powerful and widely used group of analgesics. They are considered safe, provided accepted dosing regimens are used and appropriate monitoring and staff education are in place. Opioids given as a continuous infusion require higher level of monitoring.
### Morphine

<table>
<thead>
<tr>
<th>Route</th>
<th>Neonate: 80 mcg/kg 4-6 hourly</th>
<th>Child: 200-500 mcg/kg 4 hourly</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV or SC loading dose (titrated to response)</td>
<td>Neonate: 25 mcg/kg increments</td>
<td>Child: 50 mcg/kg increments</td>
</tr>
<tr>
<td>IV or SC infusion</td>
<td>10-40 mcg/kg/hr</td>
<td></td>
</tr>
<tr>
<td>Patient-controlled analgesia</td>
<td>Bolus: 10-20 mcg/kg; Lock-out interval: 5-10 min</td>
<td>Background infusion: 0-4 mcg/kg/hr</td>
</tr>
<tr>
<td>Nurse-controlled analgesia</td>
<td>Bolus: 10-20 mcg/kg; Lock-out interval: 20-30 min</td>
<td>Background infusion: 0-20 mcg/kg/hr (no background if less than 5 kg)</td>
</tr>
</tbody>
</table>

IV = intravenous; SC = sub-cutaneous

### Fentanyl

IV loading dose: 0.5-1.0 mcg/kg titrated to response (decrease dose in neonates)

IV infusion: 0.5-2.5 mcg/kg/hr

Transdermal: 12.5-100 mcg/hr

### Tramadol

Oral, rectal or IV: 1-2 mg/kg every 4-6 hrs
# Paracetamol

**Paracetamol dosing guide: oral and rectal administration**

<table>
<thead>
<tr>
<th>Age</th>
<th>Route</th>
<th>Loading dose (mg/kg)</th>
<th>Maintenance dose (mg/kg)</th>
<th>Interval (hrs)</th>
<th>Maximum daily dose (mg/kg)</th>
<th>Duration at maximum dose (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 – 32 weeks PCA</td>
<td>Oral</td>
<td>20</td>
<td>10 – 15</td>
<td>8 – 12</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 – 52 weeks PCA</td>
<td>Oral</td>
<td>20</td>
<td>10 – 15</td>
<td>6 – 8</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
<td>30</td>
<td>20</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 3 months</td>
<td>Oral</td>
<td>20</td>
<td>15</td>
<td>4</td>
<td>90</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
<td>40</td>
<td>20</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCA = post-conceptual age
**Paracetamol dosing guide:**
*Intravenous administration*

<table>
<thead>
<tr>
<th>Weight (kg) daily dose</th>
<th>Dose (mg/kg)</th>
<th>Interval (hrs)</th>
<th>Maximum daily dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 (term neonate)</td>
<td>7.5</td>
<td>4 - 6</td>
<td>30</td>
</tr>
<tr>
<td>5 - 10</td>
<td>10</td>
<td>4 - 6</td>
<td>40</td>
</tr>
<tr>
<td>10 - 50</td>
<td>15</td>
<td>4 - 6</td>
<td>60</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>1</td>
<td>4 - 6</td>
<td>4</td>
</tr>
</tbody>
</table>

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Dose (mg/kg)</th>
<th>Interval (hrs)</th>
<th>Maximum daily dose (mg/kg/day)</th>
<th>Licensed from age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>5 - 10</td>
<td>6 - 8</td>
<td>30</td>
<td>3 months</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>6 months</td>
</tr>
<tr>
<td>Ketorolac*</td>
<td>0.5</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>7.5</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Piroxicam*</td>
<td>0.5</td>
<td>24</td>
<td>0.5</td>
<td>N/R</td>
</tr>
<tr>
<td>Ketoprofen*</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*high incidence of GI complications. Not licensed for acute pain
Additives to epidural analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single dose (mcg/kg)</th>
<th>Infusion (mcg/kg/hr)</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>1 - 2</td>
<td>0.08 – 0.2</td>
<td>Sedation, dose-related hypotension and bradycardia (5 mcg/kg), delayed respiratory depression and bradycardia in neonates</td>
</tr>
<tr>
<td>Ketamine</td>
<td>250 - 500</td>
<td></td>
<td>Hallucinations at higher doses</td>
</tr>
<tr>
<td>Morphine</td>
<td>15 - 50</td>
<td>0.2 – 0.4</td>
<td>Nausea and vomiting, urinary retention, pruritus, delayed respiratory depression</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5 - 1</td>
<td>0.3 – 0.8</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Tramadol</td>
<td>500 - 2000</td>
<td></td>
<td>Nausea and vomiting</td>
</tr>
</tbody>
</table>

Summary

- Appropriate assessment and management of acute pain in paediatric patients is important to enhance post-operative recovery. For this, recommendations and guidelines are available.
- Monitoring of patients is essential to minimise adverse effects.
Section-2: Issues in Peri-operative Care
Should Pre Operative Investigations be Targeted or Routine?

The aim of preanaesthesia assessment is to detect abnormalities that would lead to change in perioperative management or change in risk stratification. Investigations done as part of preanaesthesia assessment can be classified as either routine investigations or targeted. Routine investigations are those done as screening tests in an asymptomatic patient whereas targeted investigations are those which are ordered on basis of clinical findings. There can be no doubt from the practice guidelines and investigative literature from developed countries that routine investigations done as part of the preanaesthesia assessment for surgical patients in the general population are not recommended, as it adds to patient discomfort and cost of care without improving patient management. However, there is not much evidence whether the same can be applied to special patient groups such as cancer patients. Also the
applicability of the same standards to a country like India with inconsistent primary health care is not known as there are very few studies addressing the issue.


Routine Preoperative Testing

- Preoperative tests should not be ordered routinely.
- Preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management.

Electrocardiogram

- Important clinical characteristics may include cardiocirculatory disease, respiratory disease, and type or invasiveness of surgery.
- The Task Force recognizes that ECG abnormalities may be higher in older patients and in patients with multiple cardiac risk factors.
- An ECG may be indicated for patients with known cardiovascular risk factors or for patients with risk factors identified in the course of a preanesthesia evaluation. Age alone may not be an indication for ECG.

Preanesthesia Chest Radiographs

- Clinical characteristics to consider include smoking, recent upper respiratory infection, COPD, and cardiac disease.
The Task Force recognizes that chest radiographic abnormalities may be higher in such patients but does not believe that extremes of age, smoking, stable COPD, stable cardiac disease, or resolved recent upper respiratory infection should be considered unequivocal indications for chest radiography.

**Preanesthesia Hemoglobin or Hematocrit**
- Routine hemoglobin or hematocrit is not indicated.
- Clinical characteristics to consider as indications for hemoglobin or hematocrit include type and invasiveness of procedure, patients with liver disease, extremes of age, and history of anemia, bleeding, and other hematologic disorders.

**Preanesthesia Coagulation Studies**
- Clinical characteristics to consider for ordering selected coagulation studies include bleeding disorders, renal dys-function, liver dysfunction, and type and invasiveness of procedure.
- The Task Force recognizes that anticoagulant medications and alternative therapies may present an additional perioperative risk.
- The Task Force believes that there were not enough data to comment on the advisability of coagulation tests before regional anesthesia.

**Preanesthesia Serum Chemistries**  
(*i.e.*, Potassium, Glucose, Sodium, Renal and Liver Function Studies)
Clinical characteristics to consider before ordering preanesthesia serum chemistries include likely perioperative therapies, endocrine disorders, risk of renal and liver dysfunction, and use of certain medications or alternative therapies.

The Task Force recognizes that laboratory values may differ from normal values at extremes of age.

**Preanesthesia Urinalysis**

- Urinalysis is not indicated except for specific procedures (e.g., prosthesis implantation, urologic procedures) or when urinary tract symptoms are present.

**Preanesthesia Pregnancy Testing**

- Patients may present for anesthesia with early undetected pregnancy.
- The Task Force believes that the literature is inadequate to inform patients or physicians on whether anesthesia causes harmful effects on early pregnancy.
- Pregnancy testing may be offered to female patients of childbearing age and for whom the result would alter the patient’s management.

**Timing of Preoperative Testing**

- The current literature is not sufficiently rigorous to permit an unambiguous assessment of the clinical benefits or harms of the timing for preoperative tests.
- There is insufficient evidence to identify explicit decision parameters or “rules” for ordering
preoperative tests on the basis of specific patient factors.

- Test results obtained from the medical record within 6 months of surgery generally are acceptable if the patient’s medical history has not changed substantially.

- More recent test results may be desirable when the medical history has changed, or when a test result may play a role in the selection of a specific anesthetic technique (e.g., regional anesthesia in the setting of anticoagulation therapy).

**Summary**

- There is strong evidence that routine investigations have no role in preanaesthesia assessment in low risk surgery in the developed countries.

- There is little data from Indian patients but the available evidence from Asian counties seem to support the recommendations from the developed countries.

- There is insufficient data to decide role of routine investigations in special patient groups such as cancer patients.
Does Cardio-pulmonary Exercise Testing help in Pre-operative Risk Stratification?

Introduction:
Cardiopulmonary exercise testing provides a global assessment of the integrated response to increasing aerobic work involving the cardiovascular, respiratory, neuro-physiological, haematological and skeletal muscle systems, all of which are activated during the neuro-humoral stress response to surgery [1]. It is used to objectively assess the exercise capacity and cardiopulmonary fitness of the patient to withstand the stress during the peri-operative period. Hence, it is increasingly being used for pre-operative evaluation of patients undergoing major surgeries. Anaerobic threshold (AT) and VO2 peak are the most studied variables. Studies have shown a relationship between pre-operative CPET values and mortality [2], postoperative complications and length of hospital stay [3]. CPET helps in prognosticating the patient who can thus take an informed decision.
Abstracts:


Objective: To perform a systematic review of cardiopulmonary exercise testing (CPET) in the preoperative evaluation of patients with abdominal aortic aneurysm or peripheral vascular disease requiring surgery.

Methods: Review methods and reporting were according to the PRISMA guidelines. Studies were eligible if they reported CPET-derived physiological parameters in patients undergoing abdominal aortic aneurysm repair or lower extremity arterial bypass. Data were extracted regarding patient populations and correlation between CPET and surgical outcomes including mortality, morbidity, critical care bed usage and length of hospital stay.

Results: The searches identified 1301 articles. Although 53 abstracts referred to the index vascular procedures, only seven articles met inclusion criteria. There were no data from randomised controlled trials. Data from prospective studies did not comprehensively correlate CPET and surgical outcomes in patients with abdominal aortic aneurysms. There were no studies reporting CPET in patients undergoing lower extremity arterial bypass. Major limitations included small sample sizes, lack of blinding, and an absence of reporting standards.
**Conclusion**: The paucity of robust data precludes routine adoption of CPET in risk stratifying patients undergoing major vascular surgery. The use of CPET should be restricted to clinical trials and experimental registries, reporting to consensus-defined standards.


**Background**: Contemporary liver surgery practice must accurately assess operative risk in increasingly elderly populations with greater co-morbidity. This study evaluated preoperative cardiopulmonary exercise testing (CPET) in high-risk patients undergoing hepatic resection.

**Methods**: In a prospective cohort referred for liver resection, patients aged over 65 years (or younger with co-morbidity) were evaluated by preoperative CPET. Data were collected prospectively on functional status, postoperative complications and survival.

**Results**: Two hundred and four patients were assessed for hepatic resection, of whom 108 had preoperative CPET. An anaerobic threshold (AT) of 9·9 ml O(2) per kg per min predicted in-hospital death and subsequent survival. Below this value, AT was 100 per cent sensitive and 76 per cent specific for in-hospital mortality, with a positive predictive value (PPV) of 19 per cent and a negative predictive value (NPV) of 100 per cent: no deaths occurred above the threshold. Age and respiratory efficiency in the elimination of carbon dioxide
(VE/VCO(2)) at AT were statistically significant predictors of postoperative complications. Receiver operating characteristic (ROC) curve analysis showed that a threshold of 34·5 for VE/VCO(2) at AT provided a specificity of 84 per cent and a sensitivity of 47 per cent, with a PPV of 76 (95 per cent confidence interval (c.i.) 58 to 88) per cent and a NPV of 60 (48 to 72) per cent for postoperative complications. Long-term survival of those with an AT of less than 9·9 ml O(2) per kg per min was significantly worse than that of patients with a higher AT (hazard ratio for mortality 1·81, 95 per cent c.i. 1·04 to 3·17; \(P = 0·036\)).

**Conclusion:** CPET provides a useful prognostic adjunct in the preoperative assessment of patients undergoing hepatic resection.


**Background:** Surgical patients with poor functional capacity, determined by oxygen consumption at anaerobic threshold (AT) during cardiopulmonary exercise testing (CPET), experience longer hospital stays and worse short- and medium-term survival. However, previous studies excluded patients who were unable to perform a CPET or who failed to demonstrate an AT. We hypothesized that such patients are at risk of inferior outcomes after elective surgery.
Methods: All patients undergoing major colorectal surgery attempted CPET to assist in the planning of care. Patients were stratified by their test results into Fit (AT \( \geq 11.0 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1} \)), Unfit (AT < 11.0 ml O\(_2\) kg\(^{-1}\) min\(^{-1}\)), or Unable to CPET groups (failed to pedal or demonstrate an AT). For each group, we determined hospital stay and mortality.

Results: Between March 2009 and April 2010, 269 consecutive patients were screened, and proceeded to bowel resection. Median hospital stay was 8 days (IQR 5.1–13.4) and there were 44 deaths (16%) at 2 yr; 26 (9.7%) patients were categorized as Unable to CPET, 69 (25.7%) Unfit and 174 (64.7%) Fit. There were statistically significant differences between the three groups in hospital stay [median (IQR) 14.0 (10.5–23.8) vs 9.9 (5.5–15) vs 7.1 (4.9–10.8) days, \( P < 0.01 \)] and mortality at 2 yr [11/26 (42%) vs14/69 (20%) vs 19/174 (11%), respectively \( P < 0.01 \)] although the differences between Unable and Unfit were not statistically different.

Conclusions: Patients’ inability to perform CPET is associated with inferior outcomes after major colorectal surgery. Future studies evaluating CPET in risk assessment for major surgery should report outcomes for this subgroup.

**Background:** Cardiopulmonary exercise testing (CPET) provides an objective assessment of functional capacity. The aim of this study was to assess whether preoperative CPET identifies patients at risk of early death following elective open and endovascular abdominal aortic aneurysm (AAA) repair.

**Methods:** Prospective data were collected from a pilot study between September 2005 and February 2007, and from all patients who underwent CPET before elective AAA repair at two vascular centres between February 2007 and November 2011. Symptom-limited, maximal CPET was performed on each patient. Univariable and multivariable analyses were used to identify risk factors for 30- and 90-day mortality.

**Results:** Some 415 patients underwent CPET before elective AAA repair. Anaerobic threshold (AT), peak oxygen consumption (peak VO(2)) and ventilatory equivalents for carbon dioxide were associated with 30- and 90-day mortality on univariable analysis. On multivariable analysis, open repair (odds ratio (OR) 4.92, 95 per cent confidence interval 1.55 to 17.00; P = 0.008), AT below 10.2 ml per kg per min (OR 6.35, 1.84 to 29.80; P = 0.007), anaemia (OR 3.27, 1.04 to 10.50; P = 0.041) and inducible cardiac ischaemia (OR 6.16, 1.48 to 23.07; P = 0.008) were associated with 30-day mortality. Anaemia, inducible cardiac ischaemia and peak VO(2) less than 15 ml per kg per min (OR 8.59, 2.33 to 35.75; P = 0.005) were associated with 90-day mortality on multivariable analysis. Patients with two or more subthreshold CPET values were at increased risk of both 30- and 90-day mortality.
**Conclusion:** An AT below $10.2 \text{ ml per kg per min}$, peak $V\text{.O}(2)$ less than $15 \text{ ml per kg per min}$ and at least two subthreshold CPET values identify patients at increased risk of early death following AAA repair.


**Introduction:** An anaerobic threshold (AT) of $<11 \text{ ml/min/kg}$ can identify patients at high risk of cardiopulmonary complications after major surgery. The aim of this study was to assess the value of cardiopulmonary exercise testing (CPET) in predicting cardiopulmonary complications in high risk patients undergoing oesophagogastric cancer resection.

**Methods:** Between March 2008 and October 2010, 108 patients (83 men, 25 women) with a median age of 66 years (range: 38-84 years) underwent CPET before potentially curative resections for oesophagogastric cancers. Measured CPET variables included AT and maximum oxygen uptake at peak exercise (VO2 peak). Outcome measures were length of high dependency unit stay, length of hospital stay, unplanned intensive care unit (ICU) admission, and postoperative morbidity and mortality.

**Results:** The mean AT and VO2 peak were $10.8 \text{ ml/min/kg}$ (standard deviation [SD]: $2.8 \text{ ml/min/kg}$, range: $4.6-19.3 \text{ ml/min/kg}$) and $15.2 \text{ ml/min/kg}$ (SD: $5.3 \text{ ml/min/kg}$, range: $5.4-33.3 \text{ ml/min/kg}$) respectively; 57 patients (55%) had an AT of $<11 \text{ ml/min/kg}$ and 26
(12%) had an AT of <9 ml/min/kg. Postoperative complications occurred in 57 patients (29 cardiopulmonary [28%] and 28 non-cardiopulmonary [27%]). Four patients (4%) died in hospital and 21 (20%) required an unplanned ICU admission. Cardiopulmonary complications occurred in 42% of patients with an AT of <9 ml/min/kg compared with 29% of patients with an AT of <9 ml/min/kg but <11 ml/min/kg and 20% of patients with an AT of <11 ml/min/kg (p = 0.04). There was a trend that those with an AT of <11 ml/min/kg and a low VO2 peak had a higher rate of unplanned ICU admission.

**Conclusions:** This study has shown a correlation between AT and the development of cardiopulmonary complications although the discriminatory ability was low.

**Prentis JM, Trenell MI, Vasdev N et al. Impaired cardiopulmonary reserve in an elderly population is related to postoperative morbidity and length of stay after radical cystectomy. BJU Int. 2013; 112:E13-9.**

**Objective:** To determine the relationship of preoperatively measured cardiorespiratory function, to the development of postoperative complications and length of hospital stay (LOS) in a cohort of patients undergoing radical cystectomy (RC), as RC and conduit formation is curative but is associated with significant postoperative morbidity and mortality.
**Patients And Methods:** Consecutive patients planned to have radical cystectomy underwent cardio-pulmonary exercise testing (CPET) to a standardised protocol. The results of the CPET were ‘blinded’ from the clinicians involved in the care of the patients. Patients were prospectively monitored for the primary outcome of postoperative complications, as defined by a validated classification (Clavien-Dindo). Secondary outcome included LOS and mortality.

**Results:** In all, 82 patients underwent CPET before RC. Eight patients did not subsequently undergo RC and a further five did not exercise sufficiently to allow for appropriate determination of the cardiopulmonary variables of interest. There was a significant difference in LOS between those patients who had a major perioperative complication (Clavien score > 3) and those that did not (16 vs 30 days; P < 0.001; hazard ratio [HR] 3.6, 95% confidence interval [CI] 2.1-6.3). The anaerobic threshold (AT) remained as the only significant independent predictor variable for the presence or absence of major postoperative complications (odds ratio 0.74, 95% CI 0.57-0.97; P = 0.03). When the optimal predictive value of AT of 12 mL/min/kg was used as a fitness marker, there was a significant relationship between fitness and LOS (median LOS: ‘unfit’ 22 days vs ‘fit’ 16 days; HR 0.47, 95% CI 0.28-0.80; P = 0.006)

**Conclusion:** Impaired preoperative cardiopulmonary reserve was related to major morbidity, prolonged LOS and increased use of critical care resource after RC.
This has important health and economic implications for risk assessment, rationalisation of postoperative resource and the potential for therapeutic preoperative intervention with exercise therapy.


Background: Cardiopulmonary exercise testing (CPET) is used to assess perioperative risk in surgical patients. While previous studies have looked at short-term outcomes, this paper explores the ability of CPET to predict 5 yr survival after major surgery.

Methods: Over a period (1996-2009), 1725 patients referred for CPET subsequently underwent major surgery. Breath-by-breath data derived during each patient’s CPET was processed using customized software to extract variables likely to impact on survival. Initial analysis examined the predictive power of single variables. Subsequently, Bayesian model averaging (BMA) was used to construct a multivariate model defining the association between CPET data and 5 yr survival.

Results: Six hundred and sixteen (36%) of the study patients died. Single variables were not significantly associated with 5yr postoperative survival. BMA indicated the following major predictors of 5 yr survival: patient gender; type of surgery, and forced vital capacity. Four variables derived at the patient’s anaerobic threshold were weaker predictors. These were end-tidal
oxygen concentration, respiratory exchange ratio, oxygen consumption per unit body weight, and oxygen consumption per heart beat. The resulting model was then used to divide patients into low-, medium-, or high-risk categories, and 5 yr survival for each category was 87.8; 75.8, and 53.8% respectively. Survival was independent of patient age.

Conclusions: Multivariate analysis and model generation techniques can be applied to CPET data to predict 5 yr survival after major surgery more accurately than is possible with single variable analysis.


This study reviews the predictive value of maximum oxygen consumption (VO2max) and anaerobic threshold, obtained through cardiopulmonary exercise testing, in calculating peri-operative morbidity and mortality in non-cardiopulmonary thoraco-abdominal surgery. A literature review provided nine studies that investigated either one or both of these two variables across a wide range of surgical procedures. Six of the seven studies that reported sufficiently detailed results on peak oxygen consumption and four of the six studies that reported sufficiently detailed results on anaerobic threshold found them to be significant predictors. We conclude that peak oxygen consumption and possibly anaerobic threshold are valid predictors of peri-operative
morbidity and mortality in non-cardiopulmonary thoraco-abdominal surgery. These indicators could potentially provide a means of allocating increased care to high-risk patients.


**Background:** This study assessed whether the minute ventilation-to-carbon dioxide output (VE/VCO2) slope, a measure of ventilatory efficiency routinely measured during cardiopulmonary exercise testing (CPET), is an independent predictor of respiratory complications after major lung resections.

**Methods:** Prospective observational analysis was performed on 225 consecutive candidates after lobectomy (197 patients) or pneumonectomy (28 patients) from 2008 to 2010. Inoperability criteria were peak oxygen consumption (VO2) of less than 10 mL/kg/min in association with predicted postoperative forced expiratory volume in 1 second of less than 30% and diffusion capacity of the lung for carbon monoxide of less than 30%. All patients performed a symptom-limited CPET on cycle ergometer. Respiratory complications (30 days or in-hospital) were prospectively recorded: pneumonia, atelectasis requiring bronchoscopy, respiratory failure on mechanical ventilation exceeding 48 hours, adult respiratory distress
syndrome, pulmonary edema, and pulmonary embolism. Univariable and multivariable regression analyses were used to identify independent predictors of respiratory complications.

**Results:** Cardiopulmonary morbidity and mortality rates were 23% (51 patients) and 2.2% (5 patients). The 25 patients with respiratory complications had a significantly higher VE/VCO2 slope than those without complications (34.8 vs 30.9, p=0.001). Peak VO2 was not associated with respiratory complications. Logistic regression and bootstrap analyses showed that, after adjusting for other baseline and perioperative variables, the strongest predictor of respiratory complications was VE/VCO2 slope (regression coefficient, 0.09; bootstrap frequency, 89%; p=0.004). Patients with a VE/VCO2 slope exceeding 35 had a higher incidence of respiratory complications (22% vs 7.6%, p=0.004) and mortality (7.2% vs. 0.6%, p=0.01).

**Conclusions:** VE/VCO2 slope is a better predictor of respiratory complications than peak VO2. This inexpensive and operator-independent variable should be considered in the clinical practice to refine operability selection criteria.

**Summary:**

- CPET is an important objective tool for risk stratification for a wide spectrum of high risk cases.
- Anaerobic threshold (AT <11ml/kg/min) and peak oxygen consumption (VO2 peak < 15ml/kg/min) have been found to be associated with increased postoperative morbidity and mortality
There is also an increasing interest in the role of ventilator equivalents of CO₂ and O₂ in identifying the high-risk patients. VE/VCO2 slope may be a better predictor of respiratory complications in patients undergoing lung resection surgery.

References:


Should the Cardiac Patient Undergoing non-cardiac surgery receive beta-blockers & statins?

Beta Blockers
Most evidence suggests that perioperative beta blockade reduces the risk of MI and cardiac death. However, enthusiasm for perioperative beta blockade was significantly tempered in 2008 after results of the Perioperative Ischemic Evaluation (POISE) trial were published. Although beta-blocker therapy reduced the risk of nonfatal MI and cardiac death, overall mortality and stroke risk increased, possibly because of drug-induced hypotension. The ACC and AHA thereafter, published an update in which the only class I recommendation for perioperative beta blockade was that it be continued in patients, who were already receiving chronic beta-blocker therapy. Although perioperative beta blockade could still be considered in patients with inducible ischemia, coronary artery disease, or multiple cardiac risk factors, this update emphasized
the mixed evidence and potential hazards of rigorous treatment.


**Classification of recommendations and levels of evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Procedure/Treatment</th>
<th>Class</th>
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<tr>
<td>Level A</td>
<td>Multiple (3-5) population risk strata evaluated</td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Class I</td>
</tr>
<tr>
<td>Level B</td>
<td>Limited (2-3) population risk strata evaluated</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Class IIa</td>
</tr>
<tr>
<td>Level C</td>
<td>Very limited (1-2) population risk strata evaluated</td>
<td>Benefit = Risk</td>
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<tr>
<td></td>
<td></td>
<td>Risk = Benefit</td>
<td>Class III</td>
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</tbody>
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Procedure/treatment should be performed/administered

It is reasonable to perform procedure/administer treatment

Procedure/treatment may be considered

Procedure/treatment should NOT be performed/administered
Recommendations for Perioperative Beta-Blocker Therapy (UPDATED)

Class I

- Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs. (Level of Evidence: C)

Class IIa

- Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. (Level of Evidence: B)

- Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor. (Level of Evidence: C)

- Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor, who are undergoing intermediate-risk surgery. (Level of Evidence: B)
**Class IIb**

- The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease. (Level of Evidence: C)

- The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. (Level of Evidence: B)

**Class III**

- Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. (Level of Evidence: C)

- Routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery. (Level of Evidence: B)


**Objective:** To re-evaluate the effects of perioperative beta-blockade on mortality and major outcomes after surgery.

**Design:** A meta-analysis of parallel randomized, controlled trials published in English.
Participants: Patients undergoing surgery.

Interventions: Two interventions were evaluated: (1) Stopping or continuing a β-blocker in patients on long-term β-blocker therapy; and (2) Adding a β-blocker for the perioperative period.

Measurements and Main Results: Stopping a β-blocker before the surgery did not change the risk of myocardial infarction (3 studies including 97 patients): risk ratio (RR), 1.08 (95% confidence interval 0.30, 3.95); I², 0%. Adding a β-blocker reduced the risk of death at 1 year: RR, 0.56 (0.31, 0.99); I², 0%; p = 0.046; number needed to treat 28 (19, 369) (4 studies with 781 patients). Adding a β-blocker reduced the 0-to-30 day risk of myocardial infarction: RR, 0.65 (0.47, 0.88); I², 12.9%; p = 0.006 (15 studies with 12,224 patients), but increased the risk of a stroke: RR, 2.18 (1.40, 3.38); I², 0%; p = 0.001 (8 studies with 11,737 patients); number needed to harm 177 (512, 88).

Conclusions: β-blockers reduced the 1-year risk of death, and this effect seemed greater than the risk of inducing a stroke.


Introduction: American College of Cardiology and American Heart Association (ACC/AHA) guidelines on perioperative assessment recommend perioperative β blockers for non-cardiac surgery, although results of some clinical trials seem not to support this
recommendation. We aimed to critically review the evidence to assess the use of perioperative β blockers in patients having non-cardiac surgery.

**Methods**: We searched PubMed and Embase for randomised controlled trials investigating the use of β blockers in non-cardiac surgery. We extracted data for 30-day all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, heart failure, and myocardial ischaemia, safety outcomes of perioperative bradycardia, hypotension, and bronchospasm.

**Findings**: 33 trials included 12306 patients. β blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure, but were associated with a decrease (odds ratio [OR] 0.65, 95% CI 0.54–0.79) in non-fatal myocardial infarction (number needed to treat [NNT] 63) and decrease (OR 0.36, 0.26–0.50) in myocardial ischaemia (NNT 16) at the expense of an increase (OR 2.01, 1.27–3.68) in non-fatal strokes (number needed to harm [NNH] 293). The beneficial effects were driven mainly by trials with high risk of bias. For the safety outcomes, β blockers were associated with a high risk of perioperative bradycardia requiring treatment (NNH 22), and perioperative hypotension requiring treatment (NNH 17). We recorded no increased risk of bronchospasm.

**Interpretation**: Evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery.
The ACC/AHA guidelines committee should soften their advocacy for this intervention until conclusive evidence is available.


**Background:** Trials of β blockers in patients undergoing non-cardiac surgery have reported conflicting results. This randomised controlled trial, done in 190 hospitals in 23 countries, was designed to investigate the effects of perioperative β blockers.

**Methods:** We randomly assigned 8351 patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery to receive extended-release metoprolol succinate (n=4174) or placebo (n=4177), by a computerised randomisation phone service. Study treatment was started 2–4 h before surgery and continued for 30 days. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. Analyses were by intention to treat.

**Findings:** All 8351 patients were included in analyses; 8331 (99.8%) patients completed the 30-day follow-up. Fewer patients in the metoprolol group than in the placebo group reached the primary endpoint (244 [5.8%] patients in the metoprolol group vs 290 [6.9%])
in the placebo group; hazard ratio 0.84, 95% CI 0.70–0.99; \( p = 0.0399 \)). Fewer patients in the metoprolol group than in the placebo group had a myocardial infarction (176 [4.2%] vs 239 [5.7%] patients; 0.73, 0.60–0.89; \( p = 0.0017 \)). However, there were more deaths in the metoprolol group than in the placebo group (129 [3.1%] vs 97 [2.3%] patients; 1.33, 1.03–1.74; \( p = 0.0317 \)). More patients in the metoprolol group than in the placebo group had a stroke (41 [1.0%] vs 19 [0.5%] patients; 2.17, 1.26–3.74; \( p = 0.0053 \)).

**Interpretation**: Our results highlight the risk in assuming a perioperative \( \beta \)-blocker regimen has benefit without substantial harm, and the importance and need for large randomised trials in the perioperative setting. Patients are unlikely to accept the risks associated with perioperative extended-release metoprolol.

**Summary**

- The only class I recommendation for perioperative beta blockade is that it be continued in patients who were already receiving chronic beta-blocker therapy
- Acute preoperative beta blockade in a beta-blocker–naive population results in worse cardiac outcomes compared with patients receiving chronic beta-blocker therapy.
- Therapeutic benefit is maximum when beta-blockers are started at least two weeks before surgery.
Statins
Statins are used for primary prevention of cardiovascular events due to surgical stress in the setting of known atherosclerotic disease. Recommendations of perioperative use of statin for non-cardiac surgery are based mainly on considerable evidence from retrospective and observational trials. There is no clearly identifiable time of initiation and duration of statin therapy, statin dose, target or achieved low-density lipoprotein levels.


Recommendations for Statin Therapy

Class I
- For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued. (Level of Evidence: B)

Class IIa
- For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable. (Level of Evidence: B)
Class IIb

- For patients with at least 1 clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered. (Level of Evidence: C)


**Background:** Adverse cardiac events are common after vascular surgery. We hypothesized that perioperative statin therapy would improve postoperative outcomes.

**Methods:** In this double-blind, placebo-controlled trial, we randomly assigned patients who had not previously been treated with a statin to receive, in addition to a beta-blocker, either 80 mg of extended-release fluavastatin or placebo once daily before undergoing vascular surgery. Lipid, interleukin-6, and C-reactive protein levels were measured at the time of randomization and before surgery. The primary end point was the occurrence of myocardial ischemia, defined as transient electrocardiographic abnormalities, release of troponin T, or both, within 30 days after surgery. The secondary end point was the composite of death from cardiovascular causes and myocardial infarction.

**Results:** A total of 250 patients were assigned to fluavastatin, and 247 to placebo, a median of 37 days before vascular surgery. Levels of total cholesterol, low-density lipoprotein cholesterol, interleukin-6, and
C-reactive protein were significantly decreased in the fluvastatin group but were unchanged in the placebo group. Postoperative myocardial ischemia occurred in 27 patients (10.8%) in the fluvastatin group and in 47 (19.0%) in the placebo group (hazard ratio, 0.55; 95% confidence interval [CI], 0.34 to 0.88; P = 0.01). Death from cardiovascular causes or myocardial infarction occurred in 12 patients (4.8%) in the fluvastatin group and 25 patients (10.1%) in the placebo group (hazard ratio, 0.47; 95% CI, 0.24 to 0.94; P = 0.03). Fluvastatin therapy was not associated with a significant increase in the rate of adverse events.

**Conclusions:** In patients undergoing vascular surgery, perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome.

**Summary**

- Statins reduce incidence of death and cardiac events in perioperative period even in non cardiac surgeries. However maximum evidence is from observational trials and retrospective studies. Nevertheless they are safe to use in perioperative period.

- Patients who are already on statins should continue it. Statin therapy is reasonable for vascular surgery patients even without risk factors. Statins may be considered for patients having risk factors and posted for intermediate risk surgery.

- Peri-operative period window may be used as an opportunity to start statins in eligible patients.
Do Preoperative Nutritional Strategies (Carbohydrate Loading and Immuno-nutrition) Improve Outcomes?

From metabolic and nutritional point of view, the key aspects of perioperative care include:

- avoidance of long periods of pre-operative fasting,
- re-establishment of oral feeding as early as possible after surgery,
- integration of nutrition into the overall management of the patient,
- metabolic control, e.g. of blood glucose,
- reduction of factors which exacerbate stress related catabolism or impair GI function

**Grades of recommendation:**

A  Ia Meta-analysis of randomized controlled trials
    Ib At least one randomized controlled trial
B  IIa At least one well-designed controlled trial without randomization
At least one other type of well-designed, quasi-experimental study

Well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies

Expert opinions and/or clinical experience of respected authorities

Carbohydrate Loading

Introduction:
Metabolic and immune responses to surgery are known to result in a catabolic state and insulin resistance, which are known risk factors for postoperative complications. The beneficial effects of reducing insulin resistance can be achieved by preoperative carbohydrate loading. Studies have shown that pre operative administration of carbohydrate containing oral fluid reduces preoperative thirst, hunger, anxiety and post operative insulin resistance. Carbohydrate treatment not only reduces postoperative losses of nitrogen and protein, it also helps to maintain the lean body mass and muscle strength.

Is preoperative metabolic preparation of the elective patient using carbohydrate treatment useful?


ESPEN 2006 guidelines recommend preoperative carbohydrate loading instead of overnight fasting in most
patients undergoing major surgery (B). Recommendations are to give a clear carbohydrate rich drink ie 800ml containing 100 gm carbohydrate orally the night before surgery and 400 ml containing 50 gm carbohydrate 3 hours prior to induction of anaesthesia.


Results:
Twenty-one randomised studies of 1685 patients (733 PCT: 952 control) were included. No overall difference in length of stay was noted for analysis of all studies or subgroups of patients undergoing surgery with an expected hospital stay d”2 days or orthopaedic procedures. However, patients undergoing major abdominal surgery following PCT had reduced length of stay [mean difference, 95% confidence interval: -1.08 (-1.87 to -0.29); I² = 60%, p = 0.007]. PCT reduced postoperative insulin resistance with no effects on in-hospital complications over control (risk ratio, 95% confidence interval, 0.88 (0.50-1.53), I² = 41%; p = 0.640). There was significant heterogeneity amongst studies and, therefore, quality of evidence was low to moderate.

Conclusions:
PCT may be associated with reduced length of stay in patients undergoing major abdominal surgery, however, the included studies were of low to moderate quality.

**Result:** CHO increased the insulin and glucose levels on the first day after surgery higher than those in overnight fasting group (fifteen RCTs) and i.v. glucose infusion group (three RCTs). The pooled results of thirteen RCTs showed greater declines in the insulin level at the induction of anesthesia and a smaller increase in the glucose level at the end of surgery, and fewer decreases in the postoperative insulin sensitivity index in the CHO group were observed as compared to the placebo group. No aspiration was observed in any of the included studies.

**Conclusion:** CHO appears to be safe, and may attenuate postoperative insulin resistance as compared to placebo. However, the quality of most of the published trials has been poor, and the evidence levels for most outcomes were low, so rigorous and larger RCTs are needed in the future.

**Comment:** Carbohydrate loading should be considered in patients undergoing abdominal surgery as it has been shown to reduce the hospital stay, however the quality of the studies are poor and larger RCTs are needed.

**Is early normal food intake or EN (<24 h) following gastrointestinal surgery beneficial?**

Early initiation of normal food intake or enteral feeding is recommended after gastrointestinal surgery (A). When anastomoses of the proximal gastrointestinal tract have
been performed, EN can be delivered via a tube whose tip is placed distal to the anastomosis (B).

Early tube feeding (TF) (within 24 h) is indicated in patients in whom early oral nutrition cannot be initiated, in case of patients:

- undergoing major head and neck or gastrointestinal surgery for cancer (A),
- with severe trauma (A),
- with obvious undernutrition at the time of surgery (A),
- in whom oral intake will be inadequate (<60%) for more than 10 days (C).

The amount of initial oral intake should be adapted to the state of gastrointestinal function and to individual tolerance.

Comment: Several prospective studies have shown the beneficial effects of early normal food or EN with regard to the rate of infectious complications and the length of hospital stay. Early TF was not a risk factor for gastric intolerance and pneumonia. There is limited data available regarding immediate oral nutrition in patients with anastomoses in the proximal gastrointestinal tract, e.g. following gastrectomy, pancreatoduodenectomy or oesophageal resection. Many studies have shown the benefits and feasibility of feeding via a tube either inserted distal to the anastomosis, e.g. jejunostomy, or inserted via the nose with its tip passed distally at the time of operation, e.g. nasojejunal tube (IIb). Another study in patients undergoing total laryngectomy with
primary pharyngeal closure showed that initiation of oral feeding on the first postoperative day was safe (Ib).

**When is perioperative nutritional support indicated?**

The main goals of perioperative nutritional support are to minimize negative protein balance by avoiding starvation, with the purpose of maintaining muscle, immune, and cognitive function and to enhance postoperative recovery. Inadequate oral intake for more than 14 days is associated with a higher mortality (Ib). EN is therefore indicated even in patients without obvious undernutrition, if it is anticipated that the patient will be unable to eat for more than 7 days perioperatively. It is also indicated in patients who cannot maintain oral intake above 60% of recommended intake for more than 10 days. In these situations nutritional support (by the enteral route if possible) should be initiated without delay (C).

The enteral route should always be preferred except for the following contraindications:

- intestinal obstructions or ileus,
- severe shock,
- intestinal ischemia.

Combination with parenteral nutrition should be considered in patients in whom there is an indication for nutritional support and in whom energy needs cannot be met (< 60% of caloric requirement) via the enteral route, e.g. in upper GI fistulae (C).
ESPEN working group reviewed 35 prospective randomised controlled trials focussing on endpoints of outcomes in patients receiving enteral nutrition. Twenty-four of these 35 trials reported significant advantages of EN with particular regard to the reduction of infectious complications, length of hospital stay and costs (Ib). Compared to TPN, early EN decreased postoperative infection rate in undernourished GI cancer patients, but not in those who were well nourished. Two meta analyses of studies, in which EN was compared with PN in both surgery and internal medicine, showed a significantly reduced rate of infections140 (Ia) and a shortened length of hospital stay141 (Ia) in the enterally fed patients.

**When is preoperative EN indicated?**

Patients with severe nutritional risk benefit from nutritional support for 10–14 days prior to major surgery even if surgery has to be delayed (A). Whenever feasible, the enteral route should be preferred (A).

In cancer patients undergoing upper major abdominal surgery preoperative EN preferably with immune modulating substrates (arginine, ω-3 fatty acids and nucleotides) is recommended for 5–7 days independently of their nutritional risk (A).

Preoperative EN should preferably be administered before admission to the hospital (C).

“Severe” nutritional risk is defined by the ESPEN working group as the presence of at least one of the following criteria:
• weight loss >10–15% within 6 months,
• BMI<18.5 kg/m2,
• Subjective Global Assessment (SGA) Grade C, serum albumin<30 g/l (with no evidence of hepatic or renal dysfunction).

Which formulae should be used?

According to 2006 ESPEN guidelines, in most patients a standard whole protein formula is appropriate (C). With special regard to patients with obvious severe nutritional risk, those undergoing major cancer surgery of the neck (laryngectomy, pharyngectomy) and of the abdomen (oesophagectomy, gastrectomy, and pancreatoduodenectomy) as well as after severe trauma benefit from the use of immune modulating formulae (enriched with arginine, omega-3 fatty acids and nucleotides) (A). Whenever possible administration of these supplemented formulae should be started before surgery (A) and continued postoperatively for 5–7 days after uncomplicated surgery (C).
Introduction
Surgery is a hypermetabolic state accompanied by increased oxidative stress and increased protein catabolism.

Specific nutrients like arginine, glutamine, omega-3-fatty acids, ribonucleic acids and antioxidants such as ascorbic acid and selenium have effects on immune system, metabolism and GI structure and function. It has been suggested that addition of immune enhanced diet may improve outcomes in patients undergoing surgery.

The supplementation may be oral or parenteral. It may be given preoperatively; particularly in the malnourished cancer patients; or in the early postoperative period.

Arginine:
Arginine is involved in multiple metabolic pathways and is a source of nitrogen for nitric oxide synthesis. It is an essential precursor for immune cells particularly
lymphocyte function. It stimulates the secretion of anabolic hormones like growth hormone and insulin. These growth factors increase substrates necessary for the synthesis of connective tissue which leads to wound healing. Though arginine is considered a non essential amino acid its availability is reduced in trauma and sepsis. In early post-operative period there is an increase in myeloid derived cells expressing arginase 1 which deplete arginine. Also there is poor intake of arginine. This deficiency can be overcome with arginine supplementation.

Omega 3 fatty acids have potent anti inflammatory properties which suppresses the generalized inflammatory response and subsequent immunosupression and capillary leakage after major surgery. They may also blunt the upregulation of myeloid derived cells and decrease the expression of arginase 1.


Abstract

Results: Twenty-one relevant studies were identified, which included a total of 1918 patients. Immunonutrition significantly reduced the risk of acquired infections, wound complications, and LOS. The mortality rate was 1% in both groups. The treatment effect was similar regardless of the timing of the commencement of the IMD. The benefits of immunonutrition required both arginine and fish oil.
**Conclusions:** An immunomodulating enteral diet containing increased amounts of both arginine and fish oil should be considered in all high-risk patients undergoing major surgery. Although the optimal timing cannot be determined from this study, it is suggested that immunonutrition be initiated preoperatively when feasible.


**Background:** Immune modulating nutrition (IMN) has been shown to reduce complications after major surgery, but strong evidence to recommend its routine use is still lacking.

**Objective:** The aim of this meta-analysis was to evaluate the impact of IMN combinations on postoperative infectious and noninfectious complications, length of hospital stay, and mortality in patients undergoing major open gastrointestinal surgery.

**Methods:** Randomized controlled trials published between January 1980 and February 2011 comparing isocaloric and isonitrogenous enteral IMN combinations with standard diet in patients undergoing major open gastrointestinal surgery were included. The quality of evidence and strength of recommendation for each postoperative outcome were assessed using the GRADE approach and the outcome measures were analyzed with
RevMan 5.1 software (Cochrane Collaboration, Copenhagen, Denmark).

Results: Twenty-six randomized controlled trials enrolling 2496 patients (1252 IMN and 1244 control) were included. The meta-analysis suggests strong evidence in support of decrease in the incidence of postoperative infectious [risk ratio (RR) (95% confidence interval [CI]): 0.64 (0.55, 0.74)] and length of hospital stay [mean difference (95% CI): “1.88 (“2.91, “0.84 days)] in those receiving IMN. Even though significant benefit was observed for noninfectious complications [RR (95% CI): 0.82 (0.71, 0.95)], the quality of evidence was low. There was no statistically significant benefit on mortality [RR (95% CI): 0.83 (0.49, 1.41)].

Conclusions: IMN is beneficial in reducing postoperative infectious and noninfectious complications and shortening hospital stay in patients undergoing major open gastrointestinal surgery.


Abstract
Results: Twenty studies yielding 21 sets of data met inclusion criteria. A total of 2005 patients were represented (pharmaconutrition, n = 1010; control, n = 995), in whom pharmaconutrition was provided
preoperatively \((k = 5)\), perioperatively \((k = 2)\), or postoperatively \((k = 14)\). No differences were seen in postoperative mortality with the provision of pharmaconutrition irrespective of timing of administration. Statistically significant reductions in infectious complications and length of stay were found with perioperative and postoperative administration. Perioperative administration was also associated with a statistically significant reduction in anastomotic dehiscence, whereas a reduction in noninfective complications was demonstrated with postoperative administration. Preoperative pharmaconutrition demonstrated no notable advantage over standard nutrition provision in any of the clinical outcomes assessed. Conclusions: This meta-analysis highlights the importance of timing as a clinical consideration in the provision of pharmaconutrition in elective gastrointestinal surgical patients and identifies areas where further research is required.

Immune modulating formulas enriched with arginine, nucleotides and omega 3 fatty acids

ERAS and ESPEN guidelines 2012:
- In upper GI surgical patients – Yes
- In trauma – Yes (A)
- In burns – no recommendation

ASPEN guidelines 2009
- Should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation
Glutamine:
It is a conditionally essential amino acid. It is the most important carrier of nitrogen from peripheral tissues to splanchnic area. It also regulates nucleoside and nucleotide synthesis which help to maintain gut integrity and cellular immune response. It is a precursor for arginine synthesis, substrate for glutathione synthesis and enhances cell mediated immunity. Glutamine levels are decreased after major surgery and in critical illness. Glutamine supplementation will help to maintain gut integrity and cellular immunity. Parenteral glutamine is preferred to enteral glutamine as it is difficult to achieve high enough plasma and tissue levels of glutamine.


Abstract
Sixteen RCTs with 773 patients were included in this meta-analysis. The results showed a significant decrease in the infectious complication rates of patients undergoing abdominal surgery receiving GLN-PN (risk ratio [RR], 0.48; 95% confidence interval [CI], 0.32 to 0.72; P = 0.0004). The overall effect indicated glutamine significantly reduced the length of hospital stay in the form of alanyl-glutamine (weighted mean difference [WMD], -3.17; 95% CI, -5.51 to -0.82; P = 0.008) and in the form of glycyl-glutamine (WMD, -3.40; 95% CI, -5.82 to -0.97; P = 0.006). A positive effect in improving postoperative cumulative nitrogen balance was observed.
between groups (WMD, 7.40; 95% CI, 3.16 to 11.63; \( P = 0.0006 \)), but no mortality (RR, 1.52; 95% CI, 0.21 to 11.9; \( P = 0.68 \)). Perioperative GLN-PN is effective and safe to shorten the length of hospital stay, reduce the morbidity of postoperative infectious complications, and improve nitrogen balance in patients undergoing abdominal surgery.

**Should enteral nutrition be supplemented with glutamine?**

**ERAS and ESPN 2012**
- Glutamine should be added to a standard enteral formula in burnt patients (A) and trauma patients (A)
- Not sufficient data to support enteral glutamine supplementation in surgical or heterogenous critically ill patients

**ASPEN 2009**
- The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) should be considered in burn, trauma, and mixed ICU patients (Grade B)
- When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine (Grade C).

**Summary**
- As current evidence stands immunonutrition leads to reduction in infectious complications and length of stay. Immune modulating diets containing
arginine and fish oils should be used in high risk patients undergoing major surgery. Timing of pharmaconutrition is important and it should be administered in the perioperative and postoperative period. Parenteral glutamine supplementation should be considered in patients undergoing abdominal surgery. However immunonutrition is not recommended in critically ill patients.
What is the Role of Preoperative Biliary Drainage in Obstructive Jaundice?

Introduction-
Carcinoma of head pancreas or periampullary region cause biliary obstruction and jaundice. Jaundice has been considered as a potential risk factor for poor outcome. Obstructive jaundice can range from mild to severe and the degree of jaundice is associated with coagulation disorders, decreased hepatic function, and development of cholangitis. Pre-operative biliary drainage (PBD) has been proposed as a method of reversing these pathophysiologic disturbances. However routine PBD before these surgeries remains controversial as endoscopic PBD is associated with complications like cholangitis, bleeding, perforation, and pancreatitis. Also there is additional risk of tumor seeding following percutaneous biliary drainage in addition to bleeding and bile leakage.

Introduction: In this review of the literature, we analyze the indications for preoperative drainage in jaundiced patients who are candidates for pancreaticoduodenectomy (PD) or major hepatectomy due to periampullary or proximal bile duct neoplasms.

Objective: The aim of this study is to review the literature and to report on the current management of jaundiced patients with periampullary or proximal bile duct neoplasms who are candidates for PD or major liver resection.

Background: Jaundiced patients represent a major challenge for surgeons. Alterations and functional impairment caused by jaundice increase the risk of surgery; therefore, preoperative biliary decompression has been suggested.

Methods: A literature review was performed in the MEDLINE database to identify studies on the management of jaundice in patients undergoing PD or liver resection. Papers considering palliative drainage in jaundiced patients were excluded.

Results: The first group of papers considered patients affected by middle-distal obstruction from periampullary neoplasms, in which preoperative drainage was applied selectively. The second group of papers evaluated
patients with biliary obstructions from proximal biliary neoplasms. In these cases, Asian authors and a few European authors considered it mandatory to drain the future liver remnant (FLR) in all patients, while American and most European authors indicated preoperative drainage only in selected cases (in malnourished patients and in those with hypoalbuminemia, cholangitis or long-term jaundice; with an FLR < 30% or 40%) given the high risk of complications of drainage (choleperitoneum, cholangitis, bleeding, and seeding). The optimal type of biliary drainage is still a matter of debate; recent studies have indicated that endoscopy is preferable to percutaneous drainage. Although the type of endoscopic biliary drainage has not been clearly established, the choice is made between plastic stents and short, covered, metallic stents, while other authors suggest the use of nasobiliary drainage.

**Conclusions:** A multidisciplinary evaluation (made by a surgeon, biliary endoscopist, gastroenterologist, and radiologist) of jaundiced neoplastic patients should be performed before deciding to perform biliary drainage. Middle-distal obstruction in patients who are candidates for PD does not usually require routine biliary drainage. Proximal obstruction in patients who are candidates for major hepatic resection in the majority of cases requires a drain; however, the type, site, number, and approach must be defined and tailored according to the planned hepatic resection. Recently, the use of preoperative biliary drainage limited to the FLR has been a suggested strategy. However, multicenter, randomized, controlled trials should be conducted to clarify this issue.

**Background**: Patients with obstructive jaundice have various pathophysiological changes that affect the liver, kidney, heart, and the immune system. There is considerable controversy as to whether temporary relief of biliary obstruction prior to major definitive surgery (pre-operative biliary drainage) is of any benefit to the patient.

**Objectives**: To assess the benefits and harms of pre-operative biliary drainage versus no pre-operative biliary drainage (direct surgery) in patients with obstructive jaundice (irrespective of a benign or malignant cause).

**Search Methods**: We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded until February 2012.

Selection Criteria: We included all randomised clinical trials comparing biliary drainage followed by surgery versus direct surgery, performed for obstructive jaundice, irrespective of the sample size, language, and publication status.

**Main Results**: We included six trials with 520 patients comparing pre-operative biliary drainage (265 patients) versus no pre-operative biliary drainage (255 patients). Four trials used percutaneous transhepatic biliary drainage and two trials used endoscopic sphincterotomy and stenting as the method of pre-operative biliary
The risk of bias was high in all trials. The proportion of patients with malignant obstruction varied between 60% and 100%. There was no significant difference in mortality (40/265, weighted proportion 14.9%) in the pre-operative biliary drainage group versus the direct surgery group (34/255, 13.3%) (RR 1.12; 95% CI 0.73 to 1.71; P = 0.60). The overall serious morbidity was higher in the pre-operative biliary drainage group (60 per 100 patients in the pre-operative biliary drainage group versus 26 per 100 patients in the direct surgery group) (RR 1.66; 95% CI 1.28 to 2.16; P = 0.0002). The proportion of patients who developed serious morbidity was significantly higher in the pre-operative biliary drainage group (75/102, 73.5%) versus the direct surgery group (37/94, 37.4%) (P < 0.001). Quality of life was not reported in any of the trials. There was no significant difference in the length of hospital stay (2 trials, 271 patients; MD 4.87 days; 95% CI -1.28 to 11.02; P = 0.12) between the two groups. Trial sequential analysis showed that for mortality only a small proportion of the required information size had been obtained. There seemed to be no significant differences in the subgroup of trials assessing percutaneous compared to endoscopic drainage.

**Authors’ Conclusions**: There is currently not sufficient evidence to support or refute routine pre-operative biliary drainage for patients with obstructive jaundice. Pre-operative biliary drainage may increase the rate of serious adverse events. So, the safety of routine pre-operative biliary drainage has not been established. Pre-operative biliary drainage should not be used in patients
undergoing surgery for obstructive jaundice outside randomised clinical trials.


**Aim:** To evaluate the effect of preoperative biliary drainage (PBD) on obstructive jaundice resulting from malignant tumors.

**Methods:** According to the requirements of Cochrane systematic review, studies in the English language were retrieved from MEDLINE and Embase databases from 1995 to 2009 with the key word “preoperative biliary drainage”. Two reviewers independently screened the eligible studies, evaluated their academic level and extracted the data from the eligible studies confirmed by cross-checking. Data about patients with and without PBD after resection of malignant tumors were processed for meta-analysis using the Stata 9.2 software, including postoperative mortality, incidence of postoperative pancreatic and bile leakage, abdominal abscess, delayed gastric emptying and incision infection.

**Results:** Fourteen retrospective cohort studies involving 1826 patients with malignant obstructive jaundice accorded with our inclusion criteria, and were included in meta-analysis. Their baseline characteristics were comparable in all the studies. No significant difference was found in combined risk ratio (RR) of postoperative mortality and incidence of pancreatic and bile leakage, abdominal abscess, delayed gastric emptying between
patients with and without PBD. However, the combined RR for the incidence of postoperative incision infection was improved better in patients with PBD than in those without PBD ($P < 0.05$).

**Conclusion:** PBD cannot significantly reduce the postoperative mortality and complications of malignant obstructive jaundice, and therefore should not be used as a preoperative routine procedure for malignant obstructive jaundice.


**Background:** The benefits of preoperative biliary drainage, which was introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head, are unclear.

**Method:** In this multicenter, randomized trial, we compared preoperative biliary drainage with surgery alone for patients with cancer of the pancreatic head. Patients with obstructive jaundice and a bilirubin level of 40 to 250 micromol per liter (2.3 to 14.6 mg per deciliter) were randomly assigned to undergo either preoperative biliary drainage for 4 to 6 weeks, followed by surgery, or surgery alone within 1 week after diagnosis. Preoperative biliary drainage was attempted primarily with the placement of an endoprosthesis by means of endoscopic retrograde cholangiopancreatography. The primary outcome was the rate of serious complications within 120 days after randomization.
**Result:** We enrolled 202 patients; 96 were assigned to undergo early surgery and 106 to undergo preoperative biliary drainage; 6 patients were excluded from the analysis. The rates of serious complications were 39% (37 patients) in the early-surgery group and 74% (75 patients) in the biliary-drainage group (relative risk in the early-surgery group, 0.54; 95% confidence interval [CI], 0.41 to 0.71; P<0.001). Preoperative biliary drainage was successful in 96 patients (94%) after one or more attempts, with complications in 47 patients (46%). Surgery-related complications occurred in 35 patients (37%) in the early-surgery group and in 48 patients (47%) in the biliary drainage group (relative risk, 0.79; 95% CI, 0.57 to 1.11; P = 0.14). Mortality and the length of hospital stay did not differ significantly between the two groups.

**Conclusions:** Routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications. (Current Controlled Trials number, ISRCTN31939699.)

**Summary:** Current evidence suggests that preoperative biliary drainage does not confer any benefit and may be associated with adverse outcomes.

**Objectives:** Whilst there are theoretical benefits from pre-operatively draining the biliary tree prior to pancreateoduodenectomy (PD), the current literature does not support this intervention. The aim of this study was to explore the relationship between pre-operative stenting, bactibilia and outcome in a large United Kingdom tertiary referral practice.

**Methods:** Patients undergoing PD were identified from a prospectively maintained database. The presence or absence of a stent prior to PD, and the results of bile cultures taken at PD were related to the subsequent post-operative course and the development of complications.

**Results:** 280 patients underwent PD for periampullary malignancies, all of whom presented with jaundice. 118 patients were stented prior to referral (98 ERCP, 20 PTC). Bile cultures were positive more frequently in the stent group (83% vs. 55%; \(p = 0.000002\)) and bactibilia was more common after ERCP than PTC (83% vs. 56%; \(p = 0.006\)). The overall prevalence of complications was 54% in the stented and 41% in the non-stented group \((p = 0.03)\) with statistical significance achieved for pancreatic leak \((p = 0.013)\) and haemorrhagic complications \((p = 0.03)\). Comparing stent with no stent, there was no difference in the 30-day mortalities \((8.5\% \text{ vs. } 6.8\%; \ p = 0.6)\) or the 1-year mortality rates \((35\% \text{ vs. } 28\%; \ p = 0.21)\). Mortality rates in the infection versus no infection groups were comparable at 30 days \((8.5\% \text{ vs. } 5.5\%; \ p = 0.21)\), and at 1 year \((30.7\% \text{ vs. } 26.4\%; \ p = 0.25)\).
Conclusions: Pre-operative stent insertion prior to PD is associated with increased morbidity but not mortality and this is greatest for stents placed at ERCP.

Summary

- There is no concrete evidence to support use of preoperative biliary drainage to improve surgical outcome in all patients. The need for biliary drainage has to be considered on individual patient basis. For patients undergoing hepatic resection use of preoperative biliary drainage limited to the future liver remnant has been a suggested strategy by many researchers. However in patients with pancreaticobiliary malignancy, preoperative biliary drainage may be associated with more hazards.
Fluid Therapy for Gastrointestinal Surgery – Which fluid and how much should we give?

Introduction:
For optimal cellular & organ function, fluid and electrolyte homeostasis is essential. Any injury including surgery results in alteration of the normal homeostatic mechanism. Peri-operative fluids are required to counter the hypovolemia caused by anaesthesia and surgery.

Intraoperative fluid therapy in gastrointestinal surgery is based on two mutually exclusive and paradoxical concepts developed half a century ago. Moore proposed sodium and water retention as a metabolic response to surgical stress and advised fluid restriction in the perioperative period. Shires proposed the exactly opposite concept of extracellular fluid volume depletion due to third space (redistribution of fluid to a hypothetical space) and advised replacement of the third space losses with crystalloid to maintain adequate plasma volume.
Positive fluid balance in post operative period is common and can be readily calculated by weight gain in the post operative period. Weight gain of more than 10% from preoperative weight is considered as excessive intravascular volume and is associated with 3 fold increase in mortality. In the same study, 20% weight gain was associated with 100 % mortality\(^1\).

Peri-operative fluid therapy is often a subject of great debate but there is increasing evidence that the peri-operative fluid therapy may alter the post-operative outcomes. The traditional practice of large amount of fluid transfusions is now being challenged by data supporting restrictive and goal directed strategies using various newer haemodynamic monitoring techniques available. However, perioperative fluid therapy is still not standardized. This may be due to conflicting data with diverse methodology (with respect to type, amount, timing of fluid therapy and outcome measures).

Another aspect of colonic surgery that affects perioperative fluid requirement is mechanical bowel preparation. Mechanical Bowel Preparation has been administered to patients undergoing colorectal surgery for over a century, and though the methods and agents used for intestinal cleansing have evolved over time, many surgeons still embrace bowel preparation as a necessary, essential regimen. The accepted rationale for bowel preparation includes evacuation of stool to allow visualization of the luminal surfaces as well as to reduce the fecal flora, which is believed to lower risk of infectious and anastomotic complications at surgery. An early
challenge to the dogma of bowel preparation came from Hughes in 1972, who claimed that the risks of sepsis and anastomotic complications were no greater in unprepared bowel and argued against the practice as unnecessary and since then many randomized controlled trials and meta analysis have questioned use of bowel preparation.


**Background**: Intraoperative fluid therapy regimens using oesophageal Doppler monitoring (ODM) to optimize stroke volume (SV) (goal-directed fluid therapy, GDT) have been associated with a reduction in length of stay (LOS) and complication rates after major surgery. We hypothesized that intraoperative GDT would reduce the time to surgical readiness for discharge (RfD) of patients having major elective colorectal surgery but that this effect might be less marked in aerobically fit patients.

**Methods**: In this double-blinded controlled trial, 179 patients undergoing major open or laparoscopic colorectal surgery were characterized as aerobically ‘fit’ (n=123) or ‘unfit’ (n=56) on the basis of their performance during a cardiopulmonary exercise test. Within these fitness strata, patients were randomized to receive a standard fluid regimen with or without ODM-guided intraoperative GDT.
Results: GDT patients received an average of 1360 ml of additional intraoperative colloid. The mean cardiac index and SV at skin closure were significantly higher in the GDT group than in controls. Times to RfD and LOS were longer in GDT than control patients but did not reach statistical significance (median 6.8 vs 4.9 days, P=0.09, and median 8.8 vs 6.7 days, P=0.09, respectively). Fit GDT patients had an increased RfD (median 7.0 vs 4.7 days; P=0.01) and LOS (median 8.8 vs 6.0 days; P=0.01) compared with controls.

**Conclusions:** Intraoperative SV optimization conferred no additional benefit over standard fluid therapy. In an aerobically fit subgroup of patients, GDT was associated with detrimental effects on the primary outcome.


**Objective:** The optimal strategy for fluid management during gastrointestinal surgery remains unclear. Minimizing the variation in arterial pulse pressure, which is induced by mechanical ventilation, is a potential strategy to improve postoperative outcomes. We tested this hypothesis in a prospective, randomized study with lactated Ringer’s solution and 6% hydroxyethyl starch solution.

**Method:** A total of 60 patients who were undergoing gastrointestinal surgery were randomized into a restrictive lactated Ringer’s group (n = 20), a goal-directed lactated
Ringer’s group (n = 20) and a goal-directed hydroxyethyl starch group (n = 20). The goal-directed fluid treatment was guided by pulse pressure variation, which was recorded during surgery using a simple manual method with a Datex Ohmeda S/5 Monitor and minimized to 11% or less by volume loading with either lactated Ringer’s solution or 6% hydroxyethyl starch solution (130/0.4). The postoperative flatus time, the length of hospital stay and the incidence of complications were recorded as endpoints.

**Results:** The goal-directed lactated Ringer’s group received the greatest amount of total operative fluid compared with the two other groups. The flatus time and the length of hospital stay in the goal-directed hydroxyethyl starch group were shorter than those in the goal-directed lactated Ringer’s group and the restrictive lactated Ringer’s group. No significant differences were found in the postoperative complications among the three groups.

**Conclusion:** Monitoring and minimizing pulse pressure variation by 6% hydroxyethyl starch solution (130/0.4) loading during gastrointestinal surgery improves postoperative outcomes and decreases the discharge time of patients who are graded American Society of Anesthesiologists physical status I/II.


**Background:** Both “liberal” and “goal-directed” (GD) therapy use a large amount of perioperative fluid, but
they appear to have very different effects on perioperative outcomes. We sought to determine whether one fluid management strategy was superior to the others.

**Methods:** We selected randomized controlled trials (RCTs) on the use of GD or restrictive versus liberal fluid therapy (LVR) in major adult surgery from MEDLINE, EMBASE, PubMed (1951 to April 2011), and Cochrane controlled trials register without language restrictions. Indirect comparison between the GD and LVR strata was performed.

**Results:** A total of 3861 patients from 23 GD RCTs (median sample size = 90, interquartile range [IQR] 57 to 109) and 1160 patients from 12 LVR RCTs (median sample size > 80, IQR 36 to 151) were considered. Both liberal and GD therapy used more fluid compared to their respective comparative arm, but their effects on outcomes were very different. Patients in the liberal group of the LVR stratum had a higher risk of pneumonia (risk ratio [RR] 2.2, 95% confidence interval [CI] 1.0 to 4.5), pulmonary edema (RR 3.8, 95% CI 1.1 to 13), and a longer hospital stay than those in the restrictive group (mean difference [MD] 2 days, 95% CI 0.5 to 3.4). Using GD therapy also resulted in a lower risk of pneumonia (RR 0.7, 95% CI 0.6 to 0.9) and renal complications (0.7, 95% CI 0.5 to 0.9), and a shorter length of hospital stay (MD 2 days, 95% CI 1 to 3) compared to not using GD therapy. Liberal fluid therapy was associated with an increased length of hospital stay (4 days, 95% CI 3.4 to 4.4), time to first bowel movement (2 days, 95% CI
1.3 to 2.3), and risk of pneumonia (RR ratio 3, 95% CI 1.8 to 4.8) compared to GD therapy.

**Conclusion:** Perioperative outcomes favored a GD therapy rather than liberal fluid therapy without hemodynamic goals. Whether GD therapy is superior to a restrictive fluid strategy remains uncertain.


**Background:** Pancreaticoduodenectomy (PD) can be associated with significant blood loss and transfusion requirements, with potential adverse short- and long-term consequences. The aim of this study was to determine whether acute normovolemic hemodilution (ANH), an established blood conservation technique, reduces perioperative allogeneic transfusions in patients undergoing PD.

**Methods:** One hundred thirty patients undergoing PD were randomized to ANH or standard management (STDM). In the ANH group, intraoperative blood collection was performed to a target hemoglobin of 8.0 g/dL; crystalloid and colloid were used for volume replacement. Strict transfusion triggers were applied during and after operation. Perioperative complications were prospectively assessed and graded for severity.
Results: From July 2005 to May 2009, 209 patients were registered, 79 excluded, 65 were randomized to ANH, and 65 to STD. The groups were well matched for demographic, operative, and histopathologic variables. Patients undergoing ANH received over 2 L more fluid intraoperatively (6250 mL, range 2000-11850) compared with patients undergoing STD (3900 mL, range 2000-9000) (P < 0.001). Transfusion rates were similar (ANH = 16.9%, 30 units vs STD = 18.5%, 33 units; P = 0.82), as was overall perioperative morbidity (ANH = 49.2% vs STD = 47%, P = 0.86). There was, however, a trend toward more grade-3 complications in patients undergoing ANH (32% vs 23.1% STD, P = 0.17), and complications related to the pancreatic anastomosis (leak/fistula/abscess) were significantly higher in the ANH group (21.5% vs 7.7%, P = 0.045). The intraoperative fluid volume was higher for all patients with pancreatic anastomotic complications (n = 19), regardless of randomization arm (ANH 6000 mL, range 2800-11350 mL vs STD 5000 mL, range 2000-11850 mL, P < 0.042).

Conclusion: In this randomized trial of patients undergoing PD, ANH did not reduce allogeneic transfusions and resulted in more pancreatic anastomotic complications, likely related to greater intraoperative fluid administration. The benefits of ANH do not necessarily extend to all procedures, and restrictive intravenous fluid management during PD may help improve postoperative outcome.

Grant FM, Protic M, Gonen M, Allen P, Brennan MF. Intraoperative fluid management and

Background: Considerable debate exists as to appropriate perioperative fluid management. Data from several studies suggest that the amount of fluid administered perioperatively influences surgical outcome. Pancreatic resection is a major procedure in which complications are common. We examined 1,030 sequential patients who had undergone pancreatic resection at Memorial Sloan-Kettering Cancer Center. We documented the prevalence and nature of their complications, and then correlated complications to intraoperative fluid administration.

Methods: We retrospectively examined 1,030 pancreatic resections performed at Memorial Sloan-Kettering Cancer Center between May 2004 and December 2009 from our pancreatic database. Intraoperative administration of colloid and crystalloid was obtained from anesthesia records, and complication data from our institutional database.

Results: The overall in-hospital mortality was 1.7%. Operative mortality was due predominantly to intraabdominal infection. Sixty percent of the mortality resulted from intraabdominal complications related to the procedure. We did not demonstrate a clinically significant relationship between intraoperative fluid administration and complications, although minor statistical significance was suggested.

Conclusions: In this retrospective review of intraoperative fluid administration we were not
able to demonstrate a clinically significant association between postoperative complications and intraoperative crystalloid and colloid fluid administration. A randomized controlled trial has been initiated to address this question.


Background: Evidence-based guidelines on optimal perioperative fluid management have not been established, and recent randomized trials in major abdominal surgery suggest that large amounts of fluid may increase morbidity and hospital stay. However, no information is available on detailed functional outcomes or with fast-track surgery. Therefore, we investigated the effects of two regimens of intraoperative fluids with physiological recovery as the primary outcome measure after fast-track colonic surgery.

Methods: In a double-blind study, 32 ASA I-III patients undergoing elective colonic surgery were randomized to ‘restrictive’ (Group 1) or ‘liberal’ (Group 2) perioperative fluid administration. Fluid algorithms were based on fixed rates of crystalloid infusions and a standardized volume of colloid. Pulmonary function (spirometry) was the primary outcome measure, with secondary outcomes of exercise capacity (submaximal exercise test), orthostatic tolerance, cardiovascular hormonal responses, postoperative ileus (transit of radio-opaque markers), postoperative nocturnal hypoxaemia,
and overall recovery within a well-defined multimodal, fast-track recovery programme. Hospital stay and complications were also noted.

**Results**: ‘Restrictive’ (median 1640 ml, range 935-2250 ml) compared with ‘liberal’ fluid administration (median 5050 ml, range 3563-8050 ml) led to significant improvement in pulmonary function and postoperative hypoxaemia. In contrast, we found significantly reduced concentrations of cardiovascularly active hormones (renin, aldosterone, and angiotensin II) in Group 2. The number of patients with complications was not significantly different between the groups [1 (‘liberal’ group) [corrected] vs 6 (‘restrictive’ group) [corrected] patients, $P = 0.08$].

**Conclusions**: A ‘restrictive’ [corrected] fluid regimen led to a transient improvement in pulmonary function and postoperative hypoxaemia but no other differences in all-over physiological recovery compared with a ‘liberal’ [corrected] fluid regimen after fast-track colonic surgery. Since morbidity tended to be increased with the ‘restrictive’ fluid regimen, future studies should focus on the effect of individualized ‘goal-directed’ fluid administration strategies rather than fixed fluid amounts on postoperative outcome.

**Bowel Preparation**

**Background:** The presence of bowel contents during colorectal surgery has been related to anastomotic leakage, but the belief that mechanical bowel preparation (MBP) is an efficient agent against leakage and infectious complications is based on observational data and expert opinions only. An enema before the rectal surgery to clean the rectum and facilitate the manipulation for the mechanical anastomosis is used for many surgeons. This is analysed separately.

**Objectives:** To determine the security and effectiveness of MBP on morbidity and mortality in colorectal surgery.

**Main results:** At this update six trials and a new comparison (Mechanical bowel preparation versus enema) were added. Altogether eighteen trials were analysed, with 5805 participants; 2906 allocated to MBP (Group A), and 2899 to no preparation (Group B), before elective colorectal surgery.

**Mechanical Bowel Preparation Versus No Mechanical Bowel Preparation results were:**

1. Anastomotic leakage for low anterior resection: 8.8% (38/431) of Group A, compared with 10.3% (43/415) of Group B; Peto OR 0.88 [0.55, 1.40].

2. Anastomotic leakage for colonic surgery: 3.0% (47/1559) of Group A, compared with 3.5% (56/1588) of Group B; Peto OR 0.85 [0.58, 1.26].

3. Overall anastomotic leakage: 4.4% (101/2275) of Group A, compared with 4.5% (103/2258) of Group B; Peto OR 0.99 [0.74, 1.31].
4. Wound infection: 9.6% (223/2305) of Group A, compared with 8.5% (196/2290) of Group B; Peto OR 1.16 [0.95, 1.42].

Sensitivity analyses did not produce any differences in overall results.

**Mechanical Bowel Preparation (A) Versus Rectal Enema (B) results were:**

1. Anastomotic leakage after rectal surgery: 7.4% (8/107) of Group A, compared with 7.9% (7/88) of Group B; Peto OR 0.93 [0.34, 2.52].

2. Anastomotic leakage after colonic surgery: 4.0% (11/269) of Group A, compared with 2.0% (6/299) of Group B; Peto OR 2.15 [0.79, 5.84].

3. Overall anastomotic leakage: 4.4% (27/601) of Group A, compared with 3.4% (21/609) of Group B; Peto OR 1.32 [0.74, 2.36].

4. Wound infection: 9.9% (60/601) of Group A, compared with 8.0% (49/609) of Group B; Peto OR 1.26 [0.85, 1.88].

**Authors’ conclusions:** Despite the inclusion of more studies with a total of 5805 participants, there is no statistically significant evidence that patients benefit from mechanical bowel preparation, nor the use of rectal enemas. In colonic surgery the bowel cleansing can be safely omitted and induces no lower complication rate. The few studies focused in rectal surgery suggested that mechanical bowel preparation could be used selectively, even though no significant effect was found. Further research on patients submitted for elective rectal surgery,
below the peritoneal verge, in whom bowel continuity is restored, and studies with patients submitted to laparoscopic surgeries are still warranted.


**Background:** Colon preparation for elective colon resection to reduce surgical site infection (SSI) remains controversial.

**Results:** Seventy years of surgical literature has documented that mechanical bowel preparation alone does not reduce SSI. A body of clinical trials has documented the benefits of oral antibiotic bowel preparation compared with a placebo in the reduction of SSI. Clinical trials show the addition of the oral antibiotic bowel preparation to appropriate systemic preoperative preventive antibiotics provide the lowest rates of SSI.

**Conclusions:** Mechanical bowel preparation alone does not reduce rates of SSI, but oral antibiotic preparation and systemic preoperative antibiotics are superior when compared with systemic antibiotics alone. Additional clinical trials are necessary to define the best combined overall mechanical and oral antibiotic regimen for elective colon surgery.

**Background/Aims:** Pro-/pre-/synbiotics supplementation seems to provide beneficial effects in various aspects of abdominal pathology. Skepticism exists with respect to their effects on colorectal cancer (CRC) patients. This review presents the potential clinical applications of pro-/pre-/synbiotics in CRC surgery.

**Results:** Incorporation of pre-/pro-/synbiotic formulations in the preoperative mechanical bowel preparation cannot be supported by the current evidence. Limited clinical studies may be promising in supporting their potentially protective role against postoperative infectious complications. Encouraging are the results on their protective role against adjuvant (chemo)radiation-induced diarrhea. Such supplementation may also hold promise to improve postcolectomy gastrointestinal related quality of life.

**Conclusions:** Despite the positive results and plethora of agents, bacterial combinations and concentrations, the inconsistency in administration, the inhomogeneity of comparison groups and lack of stringent clinical endpoints remain obstacles in the effort to establish a definitive clinical strategy at this time. Further work is warranted to gain a keen understanding of their clinical value in CRC patients.

**Conclusion:**

- Traditional practice of fluid management was based on “individual experience” and anecdotal reports. Modern evidence based practice looks at scientific evidence available for the peri-operative fluid management.
Fluids should be tailored to the needs of the particular patient and the type of surgery using better haemodyanamic monitors and not by using set formulae.

Mechanical Bowel preparation for colonic surgeries have no evidence and should not be used routinely.

There is no proven role of probiotic, prebiotic or symbiotic in colon cancer surgeries.

References

Does Perioperative Goal-directed Fluid Therapy Improve Outcomes after Non Cardiac Surgery?

Major surgery generates a strong systemic inflammatory response and an overall substantial increase in oxygen demand. Physiologic compensatory responses maintain CVS function at a higher than normal level after surgery. Organ failure occurs when these responses do not compensate adequately. It is therefore essential to avoid hypovolemia and to optimise cardiovascular function in the perioperative period. Titration of fluid administration to hemodynamic goals may be a solution, allowing correction of hypovolemia and restoration of tissue perfusion and oxygenation, while avoiding complications related to hypoperfusion as well as complications due to fluid overload.

The traditional hemodynamic goals of achieving pre-specified filling pressures (CVP or PAOP) are flawed as both CVP and PAOP have been shown to correlate poorly with left ventricular preload. In addition, they do
not predict whether or not the cardiac output will increase in response to fluid loading. Augmenting cardiac output and oxygen transport variables to arbitrary predetermined supranormal values using fluids and inotropes has been shown to be useful in improving outcomes in the perioperative period. However this approach also suffers from lack of individualization of therapy. It is now possible using minimally invasive cardiac output monitoring, such as the oesophageal Doppler and arterial waveform analysis to determine the stroke volume and preload responsiveness on a beat-to-beat basis. Using relatively simple, minimally invasive hemodynamic monitoring, it is possible to individualise therapy by maximising SV using fluid challenges. Other parameters studied include the mixed venous and central venous oxygen saturation.

Several RCTs and meta-analyses have been performed to determine whether perioperative GDT improves outcomes. However the results have been variable, and depend on the outcome studied, patient population, the nature and timing of interventions, as well as the hemodynamic goal. Most studies have demonstrated a reduction in complications and morbidity, without a significant effect on mortality.

This systematic review and meta-analysis summarizes the clinical effects of increasing perioperative blood flow using fluids with or without inotropes/vasoactive drugs to explicit defined goals in adults. We included randomized controlled trials of adult patients (aged 16 years or older) undergoing surgery. We included 31 studies of 5292 participants. There was no difference in mortality at the longest follow-up: 282/2615 (10.8%) died in the control group and 238/2677 (8.9%) in the treatment group, RR of 0.89 (95% CI: 0.76-1.05; P=0.18). However, the results were sensitive to analytical methods and withdrawal of studies with methodological limitations. The intervention reduced the rate of three morbidities (renal failure, respiratory failure, and wound infections) but not the rates of arrhythmia, myocardial infarction, congestive cardiac failure, venous thrombosis, and other types of infections. The number of patients with complications was also reduced by the intervention. Hospital length of stay was reduced in the treatment group by 1.16 days. There was no difference in critical care length of stay. The primary analysis of this review showed no difference between groups but this result was sensitive to the method of analysis, withdrawal of studies with methodological limitations, and was dominated by a single large study. Patients receiving this intervention stayed in hospital 1 day less with fewer complications. It is unlikely that the intervention causes harm. The balance of current evidence does not support widespread implementation of this approach to reduce mortality but does suggest
that complications and duration of hospital stay are reduced.


Introduction: Several single-centre studies and meta-analyses have shown that perioperative goal-directed therapy may significantly improve outcomes in general surgical patients. We hypothesized that using a treatment algorithm based on pulse pressure variation, cardiac index trending by radial artery pulse contour analysis, and mean arterial pressure in a study group (SG), would result in reduced complications, reduced length of hospital stay and quicker return of bowel movement postoperatively in abdominal surgical patients, when compared to a control group (CG).

Methods: 160 patients undergoing elective major abdominal surgery were randomized to the SG (79 patients) or to the CG (81 patients). In the SG hemodynamic therapy was guided by pulse pressure variation, cardiac index trending and mean arterial pressure. In the CG hemodynamic therapy was performed at the discretion of the treating anaesthesiologist. Outcome data were recorded up to 28 days postoperatively.
Results: The total number of complications was significantly lower in the SG (72 vs. 52 complications, \( p = 0.038 \)). In particular, infection complications were significantly reduced (SG: 13 vs. CG: 26 complications, \( p = 0.023 \)). There were no significant differences between the two groups for return of bowel movement (SG: 3 vs. CG: 2 days postoperatively, \( p = 0.316 \)), duration of post anesthesia care unit stay (SG: 180 vs. CG: 180 minutes, \( p = 0.516 \)) or length of hospital stay (SG: 11 vs. CG: 10 days, \( p = 0.929 \)).

Conclusions: This multi-center study demonstrates that hemodynamic goal-directed therapy using pulse pressure variation, cardiac index trending and mean arterial pressure as the key parameters leads to a decrease in postoperative complications in patients undergoing major abdominal surgery.


Introduction: Goal-directed therapy (GDT) has been shown to improve outcome when commenced before surgery. This requires pre-operative admission to the intensive care unit (ICU). In cardiac surgery, GDT has proved effective when commenced after surgery. The aim of this study was to evaluate the effect of post-operative GDT on the incidence of complications and duration of hospital stay in patients undergoing general surgery.
Methods: This was a randomised controlled trial with concealed allocation. High-risk general surgical patients were allocated to post-operative GDT to attain an oxygen delivery index of 600 ml min^-1 m^-2 or to conventional management. Cardiac output was measured by lithium indicator dilution and pulse power analysis. Patients were followed up for 60 days.

Results: Sixty-two patients were randomised to GDT and 60 patients to control treatment. The GDT group received more intravenous colloid (1,907 SD ± 878 ml versus 1,204 SD ± 898 ml; p < 0.0001) and dopexamine (55 patients (89%) versus 1 patient (2%; p < 0.0001). Fewer GDT patients developed complications (27 patients (44%) versus 41 patients (68%); p = 0.003, relative risk 0.63; 95% confidence intervals 0.46 to 0.87). The number of complications per patient was also reduced (0.7 SD ± 0.9 per patient versus 1.5 SD ± 1.5 per patient; p = 0.002). The median duration of hospital stay in the GDT group was significantly reduced (11 days (IQR 7 to 15) versus 14 days (IQR 11 to 27); p = 0.001). There was no significant difference in mortality (seven patients (11.3%) versus nine patients (15%); p = 0.59).

Conclusion: Post-operative GDT is associated with reductions in post-operative complications and duration of hospital stay. The beneficial effects of GDT may be achieved while avoiding the difficulties of pre-operative ICU admission.


**Background:** Intraoperative hypovolemia is common and is a potential cause of organ dysfunction, increased postoperative morbidity, length of hospital stay, and death. The objective of this prospective, randomized study was to assess the effect of goal-directed intraoperative fluid administration on length of postoperative hospital stay.

**Methods:** One hundred patients who were to undergo major elective surgery with an anticipated blood loss greater than 500 ml were randomly assigned to a control group (n = 50) that received standard intraoperative care or to a protocol group (n = 50) that, in addition, received intraoperative plasma volume expansion guided by the esophageal Doppler monitor to maintain maximal stroke volume. Length of postoperative hospital stay and postoperative surgical morbidity were assessed.

**Results:** Groups were similar with respect to demographics, surgical procedures, and baseline hemodynamic variables. The protocol group had a significantly higher stroke volume and cardiac output at the end of surgery compared with the control group. Patients in the protocol group had a shorter duration of hospital stay compared with the control group: 5 +/- 3 versus 7 +/- 3 days (mean +/- SD), with a median of 6 versus 7 days, respectively (p = 0.03). These patients also tolerated oral intake of solid food earlier than the control group: 3 +/- 0.5 versus 4.7 +/- 0.5 days (mean
+/− SD), with a median of 3 versus 5 days, respectively (p = 0.01).

**Conclusions:** Goal-directed intraoperative fluid administration results in earlier return to bowel function, lower incidence of postoperative nausea and vomiting, and decrease in length of postoperative hospital stay.

**Summary**

- Although perioperative goal-directed therapy has not been conclusively shown to reduce mortality, it does reduce the incidence of complications.

- For every 100 patients exposed to the intervention one can expect 13/100 to avoid having complications; 2/100 to avoid renal impairment; 5/100 to avoid respiratory failure; and 4/100 to avoid postoperative wound infection. Patients remain in hospital 1 day less and there is no increase in harm.

- Given the potential volume of complications after high-risk surgery, the direct costs of treating these complications as well as the indirect costs related to prolonged hospital length of stay, this intervention should be adopted in patients at high risk of perioperative complications.
Intra-operative Strategies to Improve Outcomes

Intraoperative Glycemic Control

Introduction
Hyperglycemia is common in perioperative period and is associated with adverse outcomes. Although intensive glycemic control (target serum glucose <110 mg/dL) was initially shown to be beneficial in critically ill patients, recent critical care suggested that very tight control is associated with higher incidence of hypoglycemia episodes and more liberal control (150-180 mg%) produces equally good outcomes. This review aims to summarise the current evidence on management of hyperglycaemia in perioperative period.

**Aims:** Peri-operative hyperglycemia is a risk factor for postoperative morbidity and mortality. However, the role of specific glycemic targets in reducing this risk has not been defined, particularly among patients with diabetes. Thus, our objective was to conduct a meta-analysis relating distinct peri-operative glycemic targets and postoperative outcomes in patients with diabetes.

**Methods:** A systematic review was performed by two authors utilizing pre-specified terms: “diabetes mellitus” and “perioperative” and “mortality” and “blood glucose” or “strict glucose control” or “intensive insulin therapy” in PUBMED, CENTRAL and EMBASE. Glycemic control was considered strict when perioperative targets ranged between 100 and 150mg/dL (5.6-8.3mmol/l), moderate when the targets ranged between 150 and 200mg/dL 8.3-11.1mmol/l), and liberal when the target was >200mg/dL (11.1mmol/l). The data were combined utilizing the Dersimoan-Laird random-effects method. The primary endpoint was postoperative mortality with secondary endpoints of postoperative atrial fibrillation, wound infection, and stroke.

**Results:** The literature search yielded 760 studies, of which only 6 met inclusion criteria. When compared with a liberal target, pooled data showed that a moderate glycemic target was associated with reduced postoperative mortality (OR=0.48, 95% CI 0.24-0.76) and stroke (OR=0.61, 95% CI 0.38-0.98), but no differences in atrial fibrillation or wound infection were found. There were no significant differences in postoperative outcomes between moderate versus strict perioperative glycemic target.
Conclusions: Pooled results suggest that in patients with diabetes, a moderate peri-operative glycemic target (150-200mg/dl [5.6-8.3mmol/l]) is associated with reduction in postoperative mortality and stroke compared with a liberal target (>200mg/dl [11.1mmol/l]), whereas no significant additional benefit was found with more strict glycemic control (<150mg/dl [5.6mmol/l])


Objective: The purpose of this study was to test the hypothesis that a liberal blood glucose strategy (121-180 mg/dL) is not inferior to a strict blood glucose strategy (90-120 mg/dL) for outcomes in patients after first-time isolated coronary artery bypass grafting and is superior for glucose control and target blood glucose management.

Methods: A total of 189 patients undergoing coronary artery bypass grafting were investigated in this prospective randomized study to compare 2 glucose control strategies on patient perioperative outcomes. Three methods of analyses (intention to treat, completer, and per protocol) were conducted. Observed power was robust (>80%) for significant results.

Results: The groups were similar on preoperative hemoglobin A1c and number of diabetic patients. The
liberal group was found to be noninferior to the strict group for perioperative complications and superior on glucose control and target range management. The liberal group had significantly fewer patients with hypoglycemic events (<60 mg/dL; P < .001), but severe hypoglycemic events (<40 mg/dL) were rare and no group differences were found (P = .23). These results were found with all 3 methods of analysis except for blood glucose variability, maximum blood glucose, and perioperative atrial fibrillation.

**Conclusions:** This study demonstrated that maintenance of blood glucose in a liberal range after coronary artery bypass grafting led to similar outcomes compared with a strict target range and was superior in glucose control and target range management. On the basis of the results of this study, a target blood glucose range of 121 to 180 mg/dL is recommended for patients after coronary artery bypass grafting as advocated by the Society of Thoracic Surgeons.


**Background:** In some studies, tight glycemic control with insulin improved outcomes in adults undergoing cardiac surgery, but these benefits are unproven in critically ill children at risk for hyperinsulinemic hypoglycemia. We tested the hypothesis that tight glycemic control reduces morbidity after pediatric cardiac surgery.
Methods: In this two-center, prospective, randomized trial, we enrolled 980 children, 0 to 36 months of age, undergoing surgery with cardiopulmonary bypass. Patients were randomly assigned to either tight glycemic control (with the use of an insulin-dosing algorithm targeting a blood glucose level of 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) or standard care in the cardiac intensive care unit (ICU). Continuous glucose monitoring was used to guide the frequency of blood glucose measurement and to detect impending hypoglycemia. The primary outcome was the rate of health care-associated infections in the cardiac ICU. Secondary outcomes included mortality, length of stay, organ failure, and hypoglycemia.

Results: A total of 444 of the 490 children assigned to tight glycemic control (91%) received insulin versus 9 of 490 children assigned to standard care (2%). Although normoglycemia was achieved earlier with tight glycemic control than with standard care (6 hours vs. 16 hours, P<0.001) and was maintained for a greater proportion of the critical illness period (50% vs. 33%, P<0.001), tight glycemic control was not associated with a significantly decreased rate of health care-associated infections (8.6 vs. 9.9 per 1000 patient-days, P=0.67). Secondary outcomes did not differ significantly between groups, and tight glycemic control did not benefit high-risk subgroups. Only 3% of the patients assigned to tight glycemic control had severe hypoglycemia (blood glucose <40 mg per deciliter [2.2 mmol per liter]).

Conclusions: Tight glycemic control can be achieved with a low hypoglycemia rate after cardiac surgery in
children, but it does not significantly change the infection rate, mortality, length of stay, or measures of organ failure, as compared with standard care.


**Background:** Surgical site infections (SSIs) are associated with significant morbidity, mortality, and resource utilization and are potentially preventable. Peri-operative hyperglycaemia has been associated with increased SSIs and previous recommendations have been to treat glucose levels above 200 mg/dL. However, recent studies have questioned the optimal glycaemic control regimen to prevent SSIs. Whether the benefits of strict or intensive glycaemic control with insulin infusion as compared to conventional management outweigh the risks remains controversial.

**Objectives:** To summarise the evidence for the impact of glycaemic control in the peri-operative period on the incidence of surgical site infections, hypoglycaemia, level of glycaemic control, all-cause and infection-related mortality, and hospital length of stay and to investigate for differences of effect between different levels of glycaemic control.

**Search Strategy:** A search strategy was developed to search the following databases: Cochrane Wounds Group Specialised Register (searched 25 March 2009), The Cochrane Central Register of Controlled Trials, The Cochrane Library 2009, Issue 1; Ovid MEDLINE (1950
to March Week 2 2009); Ovid EMBASE (1980 to 2009 Week 12) and EBSCO CINAHL (1982 to March Week 3 2009). The search was not limited by language or publication status.

**Selection Criteria**: Randomised controlled trials (RCTs) were eligible for inclusion if they evaluated two (or more) glycaemic control regimens in the peri-operative period (within one week pre-, intra-, and/or post-operative) and reported surgical site infections as an outcome.

**Data Collection and Analysis**: The standard method for conducting a systematic review in accordance with the Cochrane Wounds Group was used. Two review authors independently reviewed the results from the database searches and identified relevant studies. Two review authors extracted study data and outcomes from each study and reviewed each study for methodological quality. Any disagreement was resolved by discussion or by referral to a third review author.

**Main Results**: Five RCTs met the pre-specified inclusion criteria for this review. No trials evaluated strict glycaemic control in the immediate pre-operative period or outside the intensive care unit. Due to heterogeneity in patient populations, peri-operative period, glycaemic target, route of insulin administration, and definitions of outcome measures, combination of the results of the five included trials into a meta-analysis was not appropriate. The methodological quality of the trials was variable. In terms of outcomes, only one trial demonstrated a significant reduction in SSIs with strict
glycaemic control, but the quality of this trial was difficult to assess as a result of poor reporting; furthermore the baseline rate of SSIs was high (30%). The other trials were either underpowered to detect a difference in SSIs, due to a low baseline rate (less than or equal to 5%), or did not report SSIs as a single outcome but as part of a composite. Of the three trials reporting hypoglycaemia (which was not consistently defined) all had a higher rate in the strict glycaemic control group but none attributed significant morbidity to the hypoglycaemia. Adequacy of glucose control between groups was measured differently among studies. Studies could not be compared due to differences in target ranges, and were susceptible to measurement bias due to differences in frequency of measurement and lack of blinding by the providers following the glycaemic protocols. Infection-related mortality was not reported in any of the trials, and no trials demonstrated a significant difference in all-cause mortality. Length of hospital stay was significantly reduced in the strict glycaemic control groups in only one trial.

Authors’ Conclusions: There is insufficient evidence to support strict glycaemic control versus conventional management (maintenance of glucose < 200 mg/dL) for the prevention of SSIs. No trials were found that evaluated strict glycaemic control in the immediate pre-operative period or outside the setting of an intensive care unit. The trials were limited by small sample size, inconsistencies in the definitions of the outcome measures and methodological quality. Further large
randomised trials are required to address this question and may be most appropriately performed in patients at high risk for SSIs.

**Summary**

- Current evidence suggests that strict glycemic control (< 110 mg%) does not confer additional benefit as compared to less intensive control (150 – 180 mg%) in diabetic or non-diabetic patients, when we look for differences in various outcomes such as mortality, stroke or surgical site infection.

**2. Intraoperative hypothermia**

Inadvertent hypothermia, defined as core body temperature d”36.0°C, is another common problem intra and postoperatively. Hypothermia within the perioperative environment has many undesired physiological effects that are associated with postoperative morbidity which includes coagulopathy leading to increased blood loss and need for blood transfusion. Postoperatively it leads to shivering, increased surgical site infections, cardiovascular events, decubitus ulcers and increased hospital length of stay. There are different options for treating and/or preventing hypothermia within the adult perioperative environment, which include active and passive warming methods.

**Background**: Perioperative hypothermia is a common complication during general anaesthesia. Although rewarming of patients before surgery has been used as a preventive measure and some guidelines recommend it, the implementation of prewarming for every surgical patient is cumbersome. Therefore we sought to determine the efficacy of two novel prewarming methods that could facilitate prewarming in daily practice.

**Methods**: Prospective, randomized, multi-centre, controlled study. After IRB approval and informed consent, 90 patients undergoing surgery of 30-120 min duration with general anaesthesia were randomly assigned to three groups: 1) Standard preoperative insulation (Group A), 2) Passive preoperative insulation with a commercial prewarming suit (Group B), 3) Active preoperative prewarming with a forced-air warmer connected to a prewarming suit (Group C). All patients received warmed IV fluids and intraoperative forced air warming after induction of anaesthesia. Oral temperatures were recorded in the preoperative and postoperative periods. Intraoperative core temperatures were measured with an oesophageal probe.

**Results**: Repeated-measures analysis of variance (ANOVA) and post hoc Scheffé’s test identified a significantly higher core temperature in the actively prewarmed group (Group C) compared to both passive groups (A, B) at 15, 30, 45, 60, and 75 min (p <0.05) after induction of anaesthesia and at the end of surgery. During the first 30 min after admission at PACU, also higher oral temperatures were measured in Group C, compared with both passive insulation groups.
Conclusions: In our study active prewarming with a forced-air warmer and an insulating prewarming suit achieves significantly higher core temperatures during anaesthesia and at the end of surgery and avoids hypothermia at the end of surgery compared to commercial or conventional insulation techniques.


**Background:** Several adverse consequences are caused by mild perioperative hypothermia. Maintaining normothermia with patient warming systems, today mostly with forced air (FA), has thus become a standard procedure during anesthesia. Recently, a polymer-based resistive patient warming system was developed. We compared the efficacy of a widely distributed FA system with the resistive-polymer (RP) system in a prospective, randomized clinical study.

**Methods:** Eighty patients scheduled for orthopedic surgery were randomized to either FA warming (Bair Hugger warming blanket #522 and blower #750, Arizant, Eden Prairie, MN) or RP warming (Hot Dog Multi-Position Blanket and Hot Dog controller, Augustine Biomedical, Eden Prairie, MN). Core temperature, skin temperature (head, upper and lower arm, chest, abdomen, back, thigh, and calf), and room temperature (general and near the patient) were recorded continuously.
Results: After an initial decrease, core temperatures increased in both groups at comparable rates (FA: 0.33 degrees C/h +/- 0.34 degrees C/h; RP: 0.29 degrees C/h +/- 0.35 degrees C/h; P = 0.6). There was also no difference in the course of mean skin and mean body (core) temperature. FA warming increased the environment close to the patient (the workplace of anesthesiologists and surgeons) more than RP warming (24.4 degrees C +/- 5.2 degrees C for FA vs 22.6 degrees C +/- 1.9 degrees C for RP at 30 minutes; P(AUC) <0.01).

Conclusion: RP warming performed as efficiently as FA warming in patients undergoing orthopedic surgery.


Background: The PerfecTemp is an underbody resistive warming system that combines servocontrolled underbody warming with viscoelastic foam pressure relief. Clinical efficacy of the system has yet to be formally evaluated. We therefore tested the hypothesis that intraoperative distal esophageal (core) temperatures with the PerfecTemp (underbody resistive) warming system are noninferior to upper-body forced-air warming in patients undergoing major open abdominal surgery under general anesthesia.

Methods: Adults scheduled for elective major open abdominal surgery (liver, pancreas, gynecological, and
colopectal surgery) under general anesthesia were enrolled at 2 centers. Patients were randomly assigned to underbody resistive or forced-air warming. Resistive heating started when patients were transferred to the operating room table; forced-air warming started after patients were draped. The primary outcome was noninferiority of intraoperative time-weighted average core temperature, adjusted for baseline characteristics and using a buffer of 0.5°C.

**Results:** Thirty-six patients were randomly assigned to underbody resistive heating and 34 to forced-air warming. Baseline and surgical characteristics were generally similar. We had sufficient evidence (P=0.018) to conclude that underbody resistive warming is not worse than (i.e., noninferior to) upper-body forced-air warming in the time-weighted average intraoperative temperature, with a mean difference of -0.12°C [95% confidence interval (CI) -0.37 to 0.14]. Core temperatures at the end of surgery averaged 36.3°C [95% CI 36 to 36.5] in the resistive warming patients and 36.6°C [95% CI 36.4 to 36.8] in those assigned to forced-air warming for a mean difference of -0.34°C [95% CI -0.69 to 0.01].

**Conclusions:** Mean intraoperative time-weighted average core temperatures were no different, and significantly noninferior, with underbody resistive heating in comparison with upper-body forced-air warming. Underbody resistive heating may be an alternative to forced-air warming.
Moola S, Lockwood C. Effectiveness of strategies for the management and/or prevention of hypothermia within the adult perioperative environment. Int J Evid Based Healthc 2011;9: 337-45

Background: Inadvertent hypothermia is common in patients undergoing surgical procedures with a reported prevalence of perioperative hypothermia ranging from 50% to 90%. Hypothermia within the perioperative environment may have many undesired physiological effects that are associated with postoperative morbidity. There are different options for treating and/or preventing hypothermia within the adult perioperative environment, which include active and passive warming methods. This systematic review was undertaken to provide comprehensive evidence on the most effective strategies for prevention and management of inadvertent hypothermia in the perioperative environment.

Objective: The objective of this review was to identify the most effective methods for the treatment and/or prevention of hypothermia in intraoperative or postoperative patients.

Inclusion criteria: Adult patients ≥ 18 years of age, who underwent any type of surgery were included in this review. Types of interventions included were any type of linen or cover, aluminium foil wraps, forced-air warming devices, radiant warming devices and fluid warming devices. This review considered all identified prospective studies that used a clearly described process for randomisation, and/or included a control group. The
primary outcome of interest was change in core body temperature.

**Review methods:** Two independent reviewers assessed methodological validity of papers selected for retrieval and any disagreements were resolved through discussion.

**Results:** Nineteen studies with a combined 1451 patients who underwent different surgical procedures were included in this review. Meta-analysis was not possible. Forced-air warming in pregnant women scheduled for caesarean delivery under regional anaesthesia prevented maternal and foetal hypothermia. Intravenous and irrigating fluids warmed (38-40°C) to a temperature higher than that of room temperature by different fluid warming devices (both dry and water heated) proved significantly beneficial to patients in terms of stable haemodynamic variables, and higher core temperature at the end of the surgery. Water garment warmer was significantly (P < 0.05) effective than forced-air warming in maintaining intraoperative normothermia in orthotopic liver transplantation patients. Extra warming with forced air compared to routine thermal care was effective in reducing the incidence of surgical wound infections and postoperative cardiac complications. Passive warming with reflective heating blankets or elastic bandages wrapped around the legs tightly were found to be ineffective in reducing the incidence or magnitude of hypothermia.

**Conclusion:** There are significant benefits associated with forced-air warming. Evidence supports
commencement of active warming preoperatively and monitoring it throughout the intraoperative period. Single strategies such as forced-air warming were more effective than passive warming; however, combined strategies, including preoperative commencement, use of warmed fluids plus forced-air warming as other active strategies were more effective in vulnerable groups (age or durations of surgeries).

**Summary**

- Clinically relevant hypothermia (Core temperature < 36 degrees C) is associated with major adverse outcomes (increased infectious complications, morbid cardiac events, coagulation disorders, prolonged length of hospital stay, and increased costs).

- Evidence supports commencement of active warming preoperatively and monitoring it throughout the intraoperative period.

- Combined strategies, including preoperative commencement of warming, use of warmed fluids plus forced-air warming have been beneficial in patients vulnerable to hypothermia.

3. Low Tidal Volume Ventilation

**Introduction**

Critical Care literature over last 2 decades suggested that high or normal tidal volume ventilation can cause volutrauma to the lungs in patients with ARDS. This was confirmed in a large randomised controlled trial conducted by ARDSNET group. Induction of
anaesthesia itself causes atelectasis and reduction in FRC. It is not known whether volutrauma occurs in normal lungs with the routinely practiced 10 ml/kg tidal volume. There have been suggestions that low tidal volume ventilation might be beneficial even in patients undergoing ventilation during anaesthesia.


**Background:** Lung-protective ventilation with the use of low tidal volumes and positive end-expiratory pressure is considered best practice in the care of many critically ill patients. However, its role in anesthetized patients undergoing major surgery is not known.

**Methods:** In this multicenter, double-blind, parallel-group trial, we randomly assigned 400 adults at intermediate to high risk of pulmonary complications after major abdominal surgery to either nonprotective mechanical ventilation or a strategy of lung-protective ventilation. The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery.

**Results:** The two intervention groups had similar characteristics at baseline. In the intention-to-treat analysis, the primary outcome occurred in 21 of 200 patients (10.5%) assigned to lung-protective ventilation, as compared with 55 of 200 (27.5%) assigned to nonprotective ventilation (relative risk, 0.40; 95% confidence interval [CI], 0.24 to 0.68; P=0.001). Over
the 7-day postoperative period, 10 patients (5.0%) assigned to lung-protective ventilation required noninvasive ventilation or intubation for acute respiratory failure, as compared with 34 (17.0%) assigned to nonprotective ventilation (relative risk, 0.29; 95% CI, 0.14 to 0.61; P=0.001). The length of the hospital stay was shorter among patients receiving lung-protective ventilation than among those receiving nonprotective ventilation (mean difference, -2.45 days; 95% CI, -4.17 to -0.72; P=0.006).

**Conclusion:** As compared with a practice of nonprotective mechanical ventilation, the use of a lung-protective ventilation strategy in intermediate-risk and high-risk patients undergoing major abdominal surgery was associated with improved clinical outcomes and reduced health care utilization.


Several reports in the literature have described the effects of positive end-expiratory pressure (PEEP) level upon functional residual capacity (FRC) in ventilated patients during general anesthesia. This study compares FRC in mechanically low tidal volume ventilation with different PEEP levels during upper abdominal surgery.

**Methods:** Before induction of anesthesia (awake) for nine patients with upper abdominal surgery, a tight-seal facemask was applied with 2 cmH₂O pressure support
ventilation and 100 % O\textsubscript{2} during FRC measurements conducted on patients in a supine position. After tracheal intubation, lungs were ventilated with bilevel airway pressure with a volume guarantee (7 ml/kg predicted body weight) and with an inspired oxygen fraction (\text{FiO}_2) of 0.4. PEEP levels of 0, 5, and 10 cmH\textsubscript{2}O were used. Each level of 5 and 10 cmH\textsubscript{2}O PEEP was maintained for 2 h. FRC was measured at each PEEP level.

**Results:** FRC awake was significantly higher than that at PEEP 0 cmH\textsubscript{2}O (\(P < 0.01\)). FRC at PEEP 0 cmH\textsubscript{2}O was significantly lower than that at 10 cmH\textsubscript{2}O (\(P < 0.01\)). \text{PaO}_2/\text{FiO}_2 awake was significantly higher than that for PEEP 0 cmH\textsubscript{2}O (\(P < 0.01\)). \text{PaO}_2/\text{FiO}_2 at PEEP 0 cmH\textsubscript{2}O was significantly lower than that for PEEP 5 cmH\textsubscript{2}O or PEEP 10 cmH\textsubscript{2}O (\(P < 0.01\)). Furthermore, PEEP 0 cmH\textsubscript{2}O, PEEP 5 cmH\textsubscript{2}O after 2 h, and PEEP 10 cmH\textsubscript{2}O after 2 h were correlated with FRC (\(R = 0.671, P < 0.01\)) and \text{PaO}_2/\text{FiO}_2 (\(R = 0.642, P < 0.01\)).

**Conclusion:** Results suggest that PEEP at 10 cmH\textsubscript{2}O is necessary to maintain lung function if low tidal volume ventilation is used during upper abdominal surgery.

*Talab HF, Zabani IA, et al. Intraoperative Ventilatory Strategies for Prevention of Pulmonary Atelectasis in Obese Patients Undergoing Laparoscopic Bariatric Surgery*  

**Background:** Atelectasis occurs regularly after induction of general anesthesia, persists postoperatively, and may contribute to significant postoperative morbidity and
additional health care costs. Laparoscopic surgery has been reported to be associated with an increased incidence of postoperative atelectasis. It has been shown that during general anesthesia, obese patients have a greater risk of atelectasis than nonobese patients. Preventing atelectasis is important for all patients but is especially important when caring for obese patients.

**Methods:** We randomly allocated 66 adult obese patients with a body mass index between 30 and 50 kg/m^2^ scheduled to undergo laparoscopic bariatric surgery into 3 groups. According to the recruitment maneuver used, the zero end-expiratory pressure (ZEEP) group (n = 22) received the vital capacity maneuver (VCM) maintained for 7–8 s applied immediately after intubation plus ZEEP; the positive end-expiratory pressure (PEEP) 5 group (n = 22) received the VCM maintained for 7–8 s applied immediately after intubation plus 5 cm H_2O of PEEP; and the PEEP 10 group (n = 22) received the VCM maintained for 7–8 s applied immediately after intubation plus 10 cm H_2O of PEEP. All other variables (e.g., anesthetic and surgical techniques) were the same for all patients. Heart rate, noninvasive mean arterial blood pressure, arterial oxygen saturation, and alveolar-arterial Pao_2 gradient (A-a Pao_2) were measured intraoperatively and postoperatively in the postanesthesia care unit (PACU). Length of stay in the PACU and the use of a nonrebreathing O_2 mask (100% Fio_2) or reintubation were also recorded. A computed tomographic scan of the chest was performed preoperatively and postoperatively after discharge from the PACU to evaluate lung atelectasis.
**Results:** Patients in the PEEP 10 group had better oxygenation both intraoperatively and postoperatively in the PACU, lower atelectasis score on chest computed tomographic scan, and less postoperative pulmonary complications than the ZEEP and PEEP 5 groups. There was no evidence of barotrauma in any patient in the 3 study groups.

**Conclusions:** Intraoperative alveolar recruitment with a VCM followed by PEEP 10 cm H$_2$O is effective at preventing lung atelectasis and is associated with better oxygenation, shorter PACU stay, and fewer pulmonary complications in the postoperative period in obese patients undergoing laparoscopic bariatric surgery.


**Background:** Mechanical ventilation with high tidal volumes aggravates lung injury in patients with acute lung injury or acute respiratory distress syndrome. The authors sought to determine the effects of short-term mechanical ventilation on local inflammatory responses in patients without preexisting lung injury.

**Methods:** Patients scheduled to undergo an elective surgical procedure (lasting ≥ 5 h) were randomly assigned to mechanical ventilation with either higher tidal volumes of 12 ml/kg ideal body weight and no positive end-expiratory pressure (PEEP) or lower tidal volumes of 6 ml/kg and 10 cm H$_2$O PEEP. After induction of
anesthesia and 5 h thereafter, bronchoalveolar lavage fluid and/or blood was investigated for polymorphonuclear cell influx, changes in levels of inflammatory markers, and nucleosomes.

**Results:** Mechanical ventilation with lower tidal volumes and PEEP (n = 21) attenuated the increase of pulmonary levels of interleukin (IL)-8, myeloperoxidase, and elastase as seen with higher tidal volumes and no PEEP (n = 19). Only for myeloperoxidase, a difference was found between the two ventilation strategies after 5 h of mechanical ventilation ($P < 0.01$). Levels of tumor necrosis factor $\alpha$, IL-1$\alpha$, IL-1$\beta$, IL-6, macrophage inflammatory protein 1$\alpha$, and macrophage inflammatory protein 1$\beta$ in the bronchoalveolar lavage fluid were not affected by mechanical ventilation. Plasma levels of IL-6 and IL-8 increased with mechanical ventilation, but there were no differences between the two ventilation groups.

**Conclusion:** The use of lower tidal volumes and PEEP may limit pulmonary inflammation in mechanically ventilated patients without preexisting lung injury. The specific contribution of both lower tidal volumes and PEEP on the protective effects of the lung should be further investigated.

**Choi G, Wolthuis EK et al Mechanical Ventilation with Lower Tidal Volumes and Positive End-expiratory Pressure Prevents Alveolar Coagulation in Patients without Lung Injury Anesthesiology 2006;105:689-695**

**Background:** Alveolar fibrin deposition is a hallmark of acute lung injury, resulting from activation of
coagulation and inhibition of fibrinolysis. Previous studies have shown that mechanical ventilation with high tidal volumes may aggravate lung injury in patients with sepsis and acute lung injury. The authors sought to determine the effects of mechanical ventilation on the alveolar hemostatic balance in patients without preexistent lung injury.

**Methods:** Patients scheduled for an elective surgical procedure (lasting ≥ 5 h) were randomly assigned to mechanical ventilation with either higher tidal volumes of 12 ml/kg ideal body weight and no positive end-expiratory pressure (PEEP) or lower tidal volumes of 6 ml/kg and 10 cm H$_2$O PEEP. After induction of anesthesia and 5 h later bronchoalveolar lavage fluid and blood samples were obtained, and markers of coagulation and fibrinolysis were measured.

**Results:** In contrast to mechanical ventilation with lower tidal volumes and PEEP (n = 21), the use of higher tidal volumes without PEEP (n = 19) caused activation of bronchoalveolar coagulation, as reflected by a marked increase in thrombin–antithrombin complexes, soluble tissue factor, and factor VIIa after 5 h of mechanical ventilation. Mechanical ventilation with higher tidal volumes without PEEP caused an increase in soluble thrombomodulin in lavage fluids and lower levels of bronchoalveolar activated protein C in comparison with lower tidal volumes and PEEP. Bronchoalveolar fibrinolytic activity did not change by either ventilation strategy.

**Conclusions:** Mechanical ventilation with higher tidal volumes and no PEEP promotes procoagulant changes,
which are largely prevented by the use of lower tidal volumes and PEEP.

**Summary**

- Intraoperative low tidal volume ventilation appears beneficial in patients undergoing abdominal surgery most probably by reducing inflammatory changes.
- It appeared to reduce the postoperative pulmonary complications and reduced the hospital length of stay.
- It is possible that traditionally acceptable high tidal volumes are more harmful than previously realized. Intraoperative use of PEEP also appears to reduce atelectasis and increase the FRC.
- Current evidence suggests that we should use low tidal volume ventilation and PEEP in all patients undergoing anaesthesia.
Hepatic resection results in significant morbidity and mortality primarily related to intraoperative blood loss and associated haemodynamic instability. Intra- or post-operative massive blood transfusion carries risks of infection, coagulopathy, acute lung injury, multiple organ failure, and also promotes tumor recurrence due to immunosuppression. Hence, various methods, including Pringle’s maneuver, unilateral hepatic hilum occlusion and normothermic total hepatic vascular exclusion have been adopted to reduce intra-operative blood loss. Though total hepatic vascular exclusion or clamping inferior vena cava can reduce blood loss during hepatectomy, they are associated with significant hepatic injury and are technically difficult. Though studies have reported that low central venous pressure (CVP), <5mm Hg, during liver resection could significantly decrease intraoperative blood loss, decrease the incidence of postoperative complications and shorten the hospital
stay, value of intraoperative CVP monitoring and role of low CVP has been questioned by recent studies.


**Background:** Although low central venous pressure (CVP) anesthesia has been used to minimize blood loss during hepatectomy, the efficacy of this technique remains controversial. We therefore assessed the association between blood loss and CVP during hepatic resection, and examined significant determinants associated with intraoperative hemorrhage during hepatectomy in living donors.

**Methods:** Between April 2004 and April 2008, 984 living donors who underwent a hepatic resection were assessed retrospectively. Univariate and multivariate analyses were performed to explore the relationships between intraoperative blood loss and several variables including CVP.

**Results:** The mean intraoperative blood loss was 691.3 +/- 365.5 ml. Only four donors required packed red blood cell transfusions (mean, 1.5 U). The mean duration of hepatic resection was 92.1 +/- 26.3 min. The mean, maximum, and minimum values of CVP measured during hepatectomy were 4.6 +/- 1.7, 5.3 +/- 1.8, and 4.0 +/- 1.8 mmHg, respectively, and were not significantly correlated with intraoperative blood loss. On multivariate analysis, predictors of hemorrhage were liver fatty change, gender, and body weight, but none
of the mean CVP, surgeons, anesthesiologists, anesthesia duration, resected liver volume, hepatectomy type, systolic blood pressure, heart rate, or body temperature were significant.

**Conclusions**: CVP during hepatic resection was not associated with intraoperative blood loss in living liver donors, suggesting that CVP may not be an important factor in predicting blood loss during hepatectomy in healthy subjects.


**Background**: Central venous pressure (CVP) is the standard method of volume status evaluation during hepatic resection. CVP monitoring requires preoperative placement of a central venous catheter (CVC), which can be associated with increased time, cost, and adverse events. Stroke volume variation (SVV) is a preload index that can be used to predict an individual’s fluid responsiveness through an existing arterial line. The purpose of this study was to determine if SVV is as safe and effective as CVP in measuring volume status during hepatic resection.

**Methods**: Two cohorts of 40 consecutive patients (80 total) were evaluated during hepatic resection between December 2010 and August 2012. The initial evaluation group of 40 patients had continuous CVP
monitoring and SVV monitoring performed simultaneously to establish appropriate SVV parameters for hepatic resection. A validation group of 40 patients was then monitored with SVV alone to confirm the accuracy of the established SVV parameters. Type of hepatic resection, transection time, blood loss, complications, and additional operative and postoperative factors were collected prospectively. SVV was calculated using the Flotrac™/Vigileo™ System.

**Results:** The evaluation group included 40 patients [median age 62 (29–82) years; median body mass index (BMI) 27.7 (16.5–40.6)] with 18 laparoscopic, 22 open, and 24 undergoing major (≥ 3 segments) hepatectomy. Median transection times were 43 (range 20–65) min, median blood loss 250 (range 20–950) cc, with no Pringle maneuver utilized. In this evaluation group, a CVP of –1 to 1 significantly correlated to a SVV of 18–21 ($R^2 = 0.85, p < 0.001$). The validation group included 40 patients [median age 61 (35–78) years; median BMI 28.1 (17–41.2)], with 24 laparoscopic, 16 open, and 33 undergoing major hepatectomy. Using a SVV goal of 18 to 21, median transection time was 55 (25–78) min, median blood loss of 255 (range 100–1,150) cc, again without the use of a Pringle maneuver.

**Conclusions:** SVV can be used safely as an alternative to CVP monitoring during hepatic resection with equivalent outcomes in terms of blood loss and parenchymal transection time. Using SVV as a predictor of fluid status could prove to be advantageous by avoiding the need for CVC insertion and therefore
eliminating the risk of CVC related complications in patients undergoing hepatic resection.


Aim: To investigate the effect of low central venous pressure (LCVP) on blood loss during hepatectomy for hepatocellular carcinoma (HCC).

Methods: By the method of sealed envelope, 50 HCC patients were randomized into LCVP group (n = 25) and control group (n = 25). In LCVP group, CVP was maintained at 2-4 mmHg and systolic blood pressure (SBP) above 90 mmHg by manipulation of the patient’s posture and administration of drugs during hepatectomy, while in control group hepatectomy was performed routinely without lowering CVP. The patients’ preoperative conditions, volume of blood loss during hepatectomy, volume of blood transfusion, length of hospital stay, changes in hepatic and renal functions were compared between the two groups.

Results: There were no significant differences in patients’ preoperative conditions, maximal tumor dimension, pattern of hepatectomy, duration of vascular occlusion, operation time, weight of resected liver tissues, incidence of post-operative complications, hepatic and renal functions between the two groups. LCVP group had a markedly lower volume of total intraoperative blood loss and blood loss during hepatectomy than the control group, being $903.9 \pm 180.8 \text{ mL}$ vs $2329.4 \pm \text{ mL}$.
2538.4 (W = 495.5, P < 0.01) and 672.4 ± 429.9 mL vs 1662.6 ± 1932.1 (W = 543.5, P < 0.05). There were no remarkable differences in the pre-resection and post-resection blood losses between the two groups. The length of hospital stay was significantly shortened in LCVP group as compared with the control group, being 16.3 ± 6.8 d vs 21.5 ± 8.6 d (W = 532.5, P < 0.05).

**Conclusion**: LCVP is easily achievable in technique. Maintenance of CVP ≤ 4 mmHg can help reduce blood loss during hepatectomy, shorten the length of hospital stay, and has no detrimental effects on hepatic or renal function.

_Eid EA, Sheta SA, Mansour E. Low Central Venous Pressure Anaesthesia in Major Hepatic Resection Middle East j Anaesthesiol 2005;18: 367-377_

Blood loss and transfusion requirements are major determinants of morbidity and mortality following liver resection. This study evaluates the association of low central venous pressure [LCVP] with blood loss and blood transfusion during liver resection.

Thirty consecutive hepatic resections were studied prospectively concerning CVP, volume of blood loss and volume of blood transfusion and renal outcome. Data were analyzed for those with a CVP ≤ 5 mmHg, and ≥ 5 mmHg. A multivariate analysis assessed potential confounding factors in the comparison. The mean blood loss in patients with a CVP of 5 mmHg or less was ≤ 500 ml and that in those with a CVP > 5 mmHg was ≥ 2000 ml. (p <0.0001). Only two patients with a CVP of
≤ 5 mmHg had a blood transfusion whereas 11 patients with a CVP > 5 mmHg required transfusion. No incidences of air embolism or permanent renal shutdown have been reported. It is concluded that the volume of blood loss and blood transfusion during liver resection correlates with the CVP during parenchymal transection. Lowering the CVP to less than 5 mmHg is a simple and effective technique to reduce blood loss during liver resection and delete the need for blood transfusion with its hazard.

**Summary**

- Though age old teaching had been maintaining low CVP for liver resection to reduce blood loss, recent large studies do not confirm these findings. Partly this may be due to advanced technologies used for haemostasis during intra-operative period like CUSA and harmonic cautery.

- CVP monitoring may not be required in normal healthy subjects and in uncomplicated liver resections.

- Most modern haemodynamic monitors have ability to monitor pulse pressure variation (PPV) which could be used as an alternative method of volume responsiveness and can be used to guide precise fluid therapy thus avoiding hypovolemia and at the same time minimizing risk of hypervolemia.

- If low CVP anaesthesia is used care should be taken to prevent air embolism and vital organ hypoperfusion.
Liver resection is widely practiced for cholangiocarcinomas and various neoplastic lesions of the liver. Surgical resection of the liver has in recent years become the treatment of choice for colo-rectal liver metastasis, as it is associated with improved survival. Also, with increasing number of split liver transplants, number of donor hepatectomies has increased. Liver resection poses many challenges for the anaesthetist, including intra-operative haemodynamic instability, post-operative pain, and perioperative coagulopathy. The use of epidural analgesia in this patient group potentially confers several benefits, including improved intra-operative haemodynamic stability and improved post-operative pain control. However patients undergoing liver resection typically develop coagulopathy intra and post-operatively even when liver function tests are normal pre-operatively. Therefore the advantages of epidural analgesia have to be balanced against the risks
of epidural haematoma and abscess associated with epidural catheterization.


**Methods:** Both MEDLINE and the Cochrane Library were searched for papers published in English on anaesthesia for liver surgery from 1 January 2000 to 31 January 2012. Studies that included hepatectomy in live donors were excluded as were laparoscopic surgery studies. After consideration of the literature, we have selected four areas of current controversy in the field of epidural analgesia and liver surgery for the focus of this review. These four areas were its safety, its efficacy, the impact of increased intravenous fluid administration needed during the technique and the role of epidural anaesthesia in enhanced recovery protocols.

**Conclusions:** Epidural anaesthesia is often considered the reference standard for pain relief following major abdominal surgery, and has been recommended in ERAS protocols. However, the provision of analgesia for liver surgery raises some unique challenges, none more so than the coagulopathy that frequently develops in the postoperative period, particularly following major hepatic resection. Whether this mild coagulopathy does, in fact, increase the risk of epidural haematoma in these patients is currently not known, and none of the studies we have reviewed are in any way sufficiently powered to answer this question. What is known, however, is that this coagulopathy does result in delayed epidural
catheter removal in a number of patients and/or the administration of fresh frozen plasma in an attempt to correct the increased PT/INR. These factors put some patients at increased risk of infection and possible epidural abscess formation, and also the known risks associated with administering fresh frozen plasma. Several studies suggest that the quality of analgesia provided by intrathecal morphine is as acceptable as that produced by thoracic epidural analgesia. Indeed, intrathecal morphine appears to have a number of advantages, particularly in the context of ERAS programmes, as patients are able to mobilise independently more rapidly, have less hypotension and receive significantly less peri-operative fluids, and as result, have shorter lengths of hospital stay. Many of the studies we have reviewed have small numbers, were retrospective.


**Background:** The aim of this study was to quantify the duration and severity of postoperative coagulopathy in order to establish the optimal time for epidural catheter removal.

**Methods:** In a 2-year retrospective study, 140 consecutive patients underwent major liver resection.

**Results:** Epidural catheters were present in 123 patients (87.9%). Resections were: 33 (26.8%) right hepatectomy
(with or without left metastasectomy), 9 (7.3%) left hemihepatectomy (with or without right metastasectomy), 37 (30.1%) trisectionectomy (extended hemihepatectomy) and 44 (35.8%) non-anatomical metastasectomy. Surgery was quantified by segments resected (4 [range: 1-7]). Vascular inflow occlusion was used in 65.6%. Ischaemic time was 26.5 min (range: 0-104 min). Platelet count fell postoperatively and was lowest on day 2 (205±72 X 10^9/L). There was a significant increase in prothrombin time, activated partial thromboplastin time and International Normalised Ratio (INR) postoperatively, peaking on day 2 (21.5±5.6 s, 37.9±5.8 s and 1.9±0.5, respectively). Changes persisted beyond day 6. Epidural catheters were removed on day 5 (1-11), with a protocol criterion of INR <1.2. Actual INR on day 5 was 1.49±0.36.

**Conclusion:** No epidural or spinal haematoma was recorded.


**Background:** Randomized trials show equivocal benefit of epidural analgesia (EA) for patients undergoing abdominal operations. Partial hepatectomy is often performed using low central venous pressure anesthesia to reduce intraoperative blood loss. We examined effects of pain management strategy on blood pressure, transfusion, and complications in patients undergoing hepatic resection with either EA or IV analgesia (IVA).
**Study Design**: Data on patients undergoing hepatectomy from 2001 to 2004 at Emory University Hospital were analyzed according to route of perioperative pain management. Patient and treatment factors were analyzed for associations with transfusion and morbidity.

**Results**: From 2001 through 2004, 367 patients underwent elective partial hepatectomy at Emory University Hospital. EA patients were more likely to be older, men, and with malignancy. There were no differences between the groups in extent of resection, operative time, blood loss, or starting hematocrit level. The EA group had lower mean arterial pressure in recovery (86.6+/-14.0 mmHg versus 94.5+-13.2 mmHg, p < 0.001) and were more likely to be transfused with packed red cells during the hospital course (44.5% versus 27.9%, p < 0.001). On multivariate analysis, age greater than 65 years, American Society of Anesthesiologists grade>2, starting hematocrit<38%, operative time>300 minutes, blood loss>1 L, and use of EA were associated with increased numbers of patients receiving packed red blood cells. Complications and length of stay were similar for both groups.

**Conclusions**: Epidural Analgesia was independently associated with increased risk of packed red blood cell transfusion after hepatectomy. EA did not appear to minimize complications or shorten hospital stay. Caution should be exercised when considering EA use in hepatic resection.

The use of epidural catheters has been a subject of active debate in living liver donors because of the possible postoperative coagulation derangement and the subsequent risk of epidural hematoma. The aim of this study was to evaluate the safety of epidural catheters in relation to the changes in coagulation profile based on a review of previously published literature and the results of our 360 donors. In both the literature and in our cases, platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) in cases of heparin administration showed significant changes (P < 0.05), especially after right lobectomy. Platelet count reached its nadir on postoperative day (POD) 2-3, while PT and aPTT reached their peaks on POD 1-2 and at the end of the operation, respectively. In our donors, the ranges of platelet count, PT, and aPTT for the first 3 PODs were 54-359 x 10^3/μL, 0.99-2.38 international normalized ratio (INR), and 25.9-300 seconds, respectively, and of note, 5 donors (1.4%) had a platelet count of < 80 x 10^3/μL and 9 donors (2.5%) had a PT of >2.0 INR. Epidural catheterizations were performed in 242 donors, and the catheters were removed on POD 3-4 in 177 donors (73.1%). Mean (range) of platelet count, PT, and aPTT on the day of catheter removal were 168.4 ± 42.9 (82-307) x 10^3/μL, 1.33 ± 0.18 (0.99-1.93) INR, and 40.9 ±4.8 (32.0-70.6) seconds, respectively. No epidural hematoma was observed in this study.
Conclusion- The careful use of an epidural catheter appears to be safe, regardless of the type of hepatectomy in living liver donors and in spite of postoperative coagulation derangements. Moreover, a patient’s coagulation profile must be monitored regularly, especially for the 4 days after the operation, and it should be within acceptable ranges for the safe extraction of epidural catheters.


Background: Liver surgery may cause postoperative coagulation disturbances, even in patients with normal preoperative coagulation function undergoing uncomplicated hepatectomy, raising concerns about the safety of this technique. In this study, the safety of epidural catheters in patients undergoing resections was examined. In addition, the coagulation profile was prospectively compared in patients undergoing minor or major liver resection under combined general-epidural anesthesia.

Method: 136 consecutive patients undergoing hepatic resection, who had no preexisting coagulopathies, and did not require a perioperative transfusion of blood or blood products were studied prospectively. All the patients were given thoracic epidural plus general anaesthesia. Epidural catheters were removed when patients had normal coagulation profiles, and platelets $> 50 \times 10^3$/mm$^3$. 
**Results:** 136 patients undergoing a hepatic resection were divided into 2 groups (major and minor hepatectomy) and all were given a thoracic epidural. Patients in the minor hepatectomy group underwent a resection of 1 or 2 segments (231 g on average) and the major group had resection of ≥3 segments (894 g on average). Blood loss was 445 mL and 885 mL, respectively. The rise in prothrombin time (PT) was more pronounced in the major hepatectomy group. In the postanesthesia care unit and on PODs 1, 2, and 3, abnormal PT values were found in 68%, 72%, 50%, and 33% of the patients in the Major Resection group, respectively. The corresponding numbers for the Minor Resection group were 28%, 39%, 16%, and 6%, respectively. Major hepatectomy group had a significant reduction in platelet count: 5% of patients had a platelet count of <100 X 10^3/mm^3 on Day 3. An inverse relation between PT, platelet count, and the quantity of liver removed was found. Because of coagulation disorders, the epidural catheter remained in place for 7 days in 9% of the patients in the major hepatectomy group and fresh frozen plasma was administered to 2 patients to normalize their coagulation profile before removal of the catheter.

**Conclusion** It is relatively safe to use a continuous epidural in these patients, but the rare incidence of spinal hematoma makes relative risk difficult to establish. In this study of 136 patients, the maximum risk of epidural hematoma was estimated at 2.2%. If this analgesic technique is used, one must realize that removal of the catheter may have to be delayed due to coagulopathy, bloodproducts might have to be administered when the
catheter is removed, coagulation values have to be monitored closely postoperatively as well as before the epidural catheter is removed, and the patients have to be checked daily for early signs of medullar compression.

**Summary**

- Most of the studies have shown that derangement in coagulation profile is common in the postoperative period but epidural haematoma has not been reported in any of them.
- Therefore it would seem prudent to monitor the post operative coagulation profile in these patients and wait for the coagulation profile to normalize or administer FFP to correct it before removing the catheter.
Does the Use of Ultrasonography Improve the Success Rate and Efficacy of Nerve Blocks?

The advent of ultrasonography has revolutionized the practice of regional anaesthesia. The use of ultrasound permits visualization of the relationship between the anatomical structures and the needle throughout the procedure. This can potentially increase the accuracy of blocks, reduce the volume of local anaesthetic needed and decrease procedure-related complications. However, the extent of the effect of this intervention on outcomes of nerve blocks needs to be evaluated.


Aim: To compare the efficacy and safety of ultrasound (US) vs nerve stimulation (NS) guidance for peripheral nerve catheter placement.
**Methods:** This meta-analysis was performed according to the PRISMA statement and the recommendations of the Cochrane Collaboration.

**Results:** Fifteen randomized controlled trials including 977 patients satisfied the inclusion criteria. Peripheral nerve catheters placed under US guidance showed a higher RR of 1.14 (95% CI: 1.02-1.27; P=0.02) for an overall successful block in comparison with NS. However, postoperative pain scales at movement (numeric rating scale: 0-10) were comparable between US- vs NS-guided peripheral nerve catheters 24 (MD: 0.08; 95% CI: -0.77 to 0.94; P=0.85) and 48 (MD: 1.0; 95% CI: -0.3 to 2.3; P=0.13) h after surgery. Patients receiving a US-guided peripheral nerve catheter had a lower RR of 0.13 (95% CI: 0.04-0.38; P=0.0002) for an accidental vascular puncture.

**Conclusions:** There is evidence that US-guided peripheral nerve catheters show a higher success rate and a lower risk for an accidental vascular puncture compared with NS guidance. However, this difference resulted only in marginally lower postoperative pain scores at rest. Nevertheless, these results were influenced by heterogeneity and should be interpreted with caution.


**Aim:** To determine if the use of ultrasound guidance (vs non-ultrasound techniques) improves the success rate of nerve blocks.
**Design:** Meta-analysis of randomized controlled trials (RCTs) in the published literature. 16 RCTs of patients undergoing elective surgical procedures were studied.

**Results:** Ultrasound guidance (vs all non-ultrasound techniques) was associated with a significant increase in the success rate of nerve blocks [relative risk (RR) = 1.11 (95% confidence interval [CI]: 1.06 to 1.17, \( P < 0.0001 \)]. When compared with nerve stimulator techniques only, ultrasound guidance was still associated with an increase in the success rate (RR = 1.11 [95% CI: 1.05 to 1.17, \( P = 0.0001 \)). For specific blocks, ultrasound guidance (vs all non-ultrasound) was associated with a significant increase in successful brachial plexus (all) nerve blocks (RR = 1.11 [95% CI: 1.05 to 1.20, \( P = 0.0001 \]), sciatic popliteal nerve block (RR = 1.22 [95% CI: 1.08 to 1.39, \( P = 0.002 \)) and brachial plexus axillary nerve block (RR = 1.13 [95% CI: 1.00 to 1.26, \( P = 0.05 \)) but not brachial plexus infraclavicular nerve block (RR = 1.25 [95% CI: 0.88 to 1.76, \( P = 0.22 \]).

**Conclusions:** Ultrasound-guided peripheral nerve block is associated with an increased overall success rate when compared with nerve stimulation or other methods. Ultrasound-guided techniques also increase the success rate of some specific blocks.


**Objective:** To assess the clinical use of ultrasonographic localization of the epiduralspace, and to evaluate the
Design: Randomized prospective study. 300 parturients, 85 of whom had conventional delivery and 65 underwent caesarean section.

Results: Using ultrasound for structure detection, the rate of puncture attempts were significantly (p < 0.013) reduced from 2.18 +/- 1.07 to 1.35 +/- 0.61. The mean rate of necessary puncture levels was 1.30 +/- 0.55 and with ultrasound detection 1.136 +/- 0.36 (p < 0.029). Complete analgesia was achieved in 147 patients with ultrasound detection versus 138 patients in the Control group (p < 0.03). The maximum VAS pain score in the control group was 1.3 +/- 2.1 versus 0.8 +/- 1.5 in the Ultrasound group (p < 0.006). The rate of side effects were reduced significantly: 99 patients in the Control group had no side effects compared with 120 patients from the Ultrasound group who were free of side effects. Patient acceptance of the technique in the Ultrasound group was significantly higher than in the Control group.

Conclusion: The clinical use of ultrasound for epidural catheter placement may improve regional anesthesia. The use of ultrasound resulted in superior quality in all measured endpoints.

Summary

- In experienced hands, ultrasound provides a higher success rate and a lower risk for an accidental vascular puncture compared with nerve stimulator guidance.
• Individual studies have demonstrated that ultrasound may reduce complication rates and improve quality, performance time, and time to onset of blocks.

• Though there is limited evidence, ultrasound may have a role to improve epidural anesthesia in parturients.
Is Ultrasound Guidance Mandatory for Central Venous Cannulation?

The risk of complications during central venous catheterization (CVC) is reported to be between 2% and 15%. These include pneumothorax (0-6.6%), carotid artery puncture (6%), subclavian artery puncture (0.5%-4%), hemothorax (1%) and unsuccessful catheterization (12%). The use of ultrasound during cannulation of major vessels should improve success rate and reduce complications. However, there also remains a possibility that ultrasound could create an unhealthy dependence on technology for future generations of anesthesiologists.

- Two dimensional (2-D) imaging ultrasound guidance is recommended as the preferred method for insertion of central venous catheters (CVCs) into the internal jugular vein (IJV) in adults and children in elective situations.

- The use of two dimensional (2-D) imaging ultrasound guidance should be considered in most clinical circumstances where CVC insertion is necessary either electively or in an emergency situation.

- It is recommended that all those involved in placing CVCs using two dimensional (2-D) imaging ultrasound guidance should undertake appropriate training to achieve competence.

- Audio guided Doppler ultrasound guidance is not recommended for CVC insertion.


Aim: To systematically review the literature comparing success rates between ultrasonic- and landmark-guided CVC placement by ED physicians.

Methods: PubMed and EMBASE databases were searched for randomized controlled trials from 1965 to 2010 for studies including adults requiring emergent CVC placement except during cardiopulmonary resuscitation.
**Intervention:** CVC placement using real-time ultrasonic guidance.

**Comparator:** CVC placement using anatomical landmarks.

**Analysis:** Success rates between CVC placement methods using a Forest Plot (95% CI)

**Results:** Search identified 944 articles of which 938 were excluded by title/abstract relevance, two not randomized, one cardiac arrest, one no landmark control, one success rate not calculated. A single study of 130 patients (65 ultrasonic versus 65 landmark-guided) selected for internal jugular vein placement remained. Successful internal jugular CVC was significantly (p=0.02) more likely in the ultrasound-guided (93.9%) compared with landmark-guided (78.5%) techniques with an OR of 1.2 (95% CI 1.0 to 1.4). Complications rates were significantly (p=0.04) lower in ultrasonic (4.6%) versus landmark (16.9%) technique, OR=3.7 (95% CI 1.1 to 12.5).

**Conclusion:** Only one single high quality study illustrated that ED ultrasound- versus landmark-guided internal jugular catheter placement had higher success rates with lower complication rates.


**Objectives:** To assess the evidence for the clinical effectiveness of ultrasound guided central venous cannulation.
Design: Systematic review and meta-analysis of randomized controlled trials including patients scheduled for central venous access using real time two dimensional ultrasonography or Doppler needles and probes compared with the anatomical landmark method of cannulation.

Data sources: 15 electronic bibliographic databases, covering biomedical, science, social science, health economics, and grey literature.

Data synthesis: 18 trials (1646 participants) were identified. Compared with the landmark method, real time two dimensional ultrasound guidance for cannulating the internal jugular vein in adults was associated with a significantly lower failure rate both overall (relative risk 0.14, 95% confidence interval 0.06 to 0.33) and on the first attempt. Limited evidence favored two-dimensional ultrasound guidance for subclavian vein and femoral vein procedures in adults. Three studies in infants confirmed a higher success rate with two-dimensional ultrasonography for internal jugular procedures (0.15, 0.03 to 0.64). Doppler-guided cannulation of the internal jugular vein in adults was more successful than the landmark method (0.39, 0.17 to 0.92), but the landmark method was more successful for subclavian vein procedures (1.48, 1.03 to 2.14). No significant difference was found between these techniques for cannulation of the internal jugular vein in infants. An indirect comparison of relative risks suggested that two dimensional ultrasonography would be more successful than Doppler guidance for subclavian vein procedures in adults (0.09, 0.02 to 0.38).
Conclusions: Evidence supports the use of two-dimensional ultrasonography for central venous cannulation.


Aim: The purpose of this study was to determine whether junior residents had higher rates of first cannulation and overall success at central venous catheter insertions with the use of ultrasound (US) guidance compared to the landmark technique.

Methods: This is a secondary analysis of data from a prospective randomized controlled study of junior residents from January 2007 through September 2008, which assessed the impact of simulation training on central venous catheter insertion success rates. Blinded independent raters observed in-hospital central venous catheter insertions using a procedural checklist. Success at first cannulation and successful insertion were the primary outcomes. Secondary outcomes included rates of technical errors and mechanical complications.

Results: Independent raters observed 480 central venous catheter insertions by 115 residents. Successful first cannulation occurred in 27% of landmark compared to 49% of dynamic US-guided (P < .01), and 50% of static US-guided (P = .01) cannulations. Insertion success occurred for 55% of landmark compared to 80% of dynamic US-guided (P < .01) and 80% of static US-guided (P < .01) cannulations. Dynamic US guidance
was associated with increased odds of first cannulation success compared to the landmark technique (odds ratio [OR], 2.24; 95% confidence interval [CI], 1.37-3.67) and successful insertion (OR, 3.80; 95% CI, 2.34-6.19). Static US guidance was associated with increased odds of first cannulation success compared to the landmark technique (OR, 2.59; 95% CI, 1.25-5.39) and successful insertion (OR, 3.48; 95% CI, 1.54-7.87). The results were independent of central venous catheter insertion training, patient comorbidities, and resident specialties. There was no difference related to mechanical complications between the procedures.

**Conclusions**: Dynamic and static US guidance during central venous catheter insertion was associated with improved in-hospital first cannulation rates and overall success rates of insertions by junior residents.

**Summary**

- Ultrasound-guided cannulation of the internal jugular vein is superior to landmark technique and has higher success rates and lower complications in adults and children.
- Pre-location of IJV prior to insertion maybe as effective as real-time cannulation under ultrasound in adults.
- Doppler ultrasound guidance is not recommended for CVC insertion.
Nitrous Oxide Versus Air: Is the Debate Still on?

Nitrous oxide is the world’s oldest general anesthetic, but there is a long history of debate regarding its appropriate role in modern surgical anesthesia. Advantages of N2O include its analgesic potency, its rapid kinetics and its low cost. Furthermore, N2O seems to suppress memory and consciousness and thus decreases the incidence of awareness. The disadvantages of N2O include diffusion hypoxia, diffusion into closed spaces, decreased methionine synthase activity, nausea and vomiting, as well as an enhancement of the greenhouse effect. [1] Nitrous oxide has been shown to be associated with teratogenicity in animal models however, the hazards in humans from low levels of waste anaesthetic gases appear to be minimal or absent. [2]

Another important concern with use of nitrous oxide has been its association with increased cardiac risk. Nitrous oxide causes an acute increase in plasma homocysteine by irreversible inactivation of vitamin $B_{12}$, which has been proposed as the cause for the increased
perioperative myocardial infarction risk. Previously studies on nitrous oxide use have demonstrated a dose-dependent negative inotropic effect due to a direct effect on the myocardium. N2O delays the functional recovery of the ischaemic or stunned myocardium. N2O increases mortality by lethal arrhythmia in the presence of coronary stenosis. [3]. The ENIGMA trial showed that avoidance of nitrous oxide and the concomitant increase in inspired oxygen concentration decreased the incidence of complications after major surgery, but did not significantly affect the duration of hospital stay. However the results are difficult to interpret as the nitrous oxide-free group received high FiO2. Post-hoc analysis demonstrated a trend to a lower risk of myocardial infarction in the nitrous oxide-free group. Recently, a study with large patient database,, a post hoc analysis of the POISE study and one RCT (VINO study) questioned the harmful effects of nitrous oxide. So should use of nitrous oxide be avoided in those patients with known cardiovascular risk factors? The results of the ENIGMA-II trial will provide a more definitive answer.


Background: Nitrous oxide is widely used in anesthesia, often administered at an inspired concentration around 70%. Although nitrous oxide interferes with vitamin B12, folate metabolism, and deoxyribonucleic acid synthesis and prevents the use of high inspired oxygen concentrations; the consequences of these effects are unclear.
**Methods:** Patients having major surgery expected to last at least 2 h were randomly assigned to nitrous oxide–free (80% oxygen, 20% nitrogen) or nitrous oxide–based (70% N2O, 30% oxygen) anesthesia. Patients and observers were blind to group identity. The primary endpoint was duration of hospital stay. Secondary endpoints included duration of intensive care stay and postoperative complications; the latter included severe nausea and vomiting, and the following major complications: pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness, and death within 30 days of surgery.

**Results:** Of 3,187 eligible patients, 2,050 consenting patients were recruited. Patients in the nitrous oxide–free group had significantly lower rates of major complications (odds ratio, 0.71; 95% confidence interval, 0.56–0.89; P = 0.003) and severe nausea and vomiting (odds ratio, 0.40; 95% confidence interval, 0.31–0.51; P < 0.001), but median duration of hospital stay did not differ substantially between groups (7.0 vs. 7.1 days; P < 0.06). Among patients admitted to the intensive care unit postoperatively, those in the nitrous oxide–free group were more likely to be discharged from the unit on any given day than those in the nitrous oxide group (hazard ratio, 1.35; 95% confidence interval, 1.05–1.73; P = 0.02).

**Conclusions:** Avoidance of nitrous oxide and the concomitant increase in inspired oxygen concentration decreases the incidence of complications after major surgery, but does not significantly affect the duration of
hospital stay. The routine use of nitrous oxide in patients undergoing major surgery should be questioned.

**Leslie K, Myles PS, Chan MT et al. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. Anesth Analg. 2011;112: 387-93.**

**Background:** There is a plausible pathophysiologic rationale for increased long-term cardiovascular morbidity and mortality in patients receiving significant exposure to nitrous oxide. However, this relationship has not been established clinically. The ENIGMA trial randomized 2050 patients having non-cardiac surgery lasting more than 2 hours to nitrous oxide-based or nitrous oxide-free anesthesia. We conducted a follow-up study of the ENIGMA patients to evaluate the risk of cardiovascular events in the longer term.

**Methods:** The trial case report forms and medical records of all study patients were reviewed. The date and cause of death and occurrence of myocardial infarction or stroke were recorded. A telephone interview was then conducted with all surviving patients. The primary endpoint of the study was survival.

**Results:** The median follow-up time was 3.5 (range: 0 to 5.7) years. Three hundred eighty patients (19%) had died since the index surgery, 91 (4.5%) were recorded as having myocardial infarction, and 44 (2.2%) had a stroke during the entire follow-up period. Nitrous oxide did not significantly increase the risk of death [hazard ratio = 0.98 (95% confidence interval, CI: 0.80 to 1.20; P = 0.82)]. The adjusted odds ratio for myocardial
infarction in patients administered nitrous oxide was 1.59 (95% CI: 1.01 to 2.51; $P = 0.04$) and for stroke was 1.01 (95% CI: 0.55 to 1.87; $P = 0.97$).

**Conclusions:** The administration of nitrous oxide was associated with increased long-term risk of myocardial infarction, but not of death or stroke in patients enrolled in the ENIGMA trial. The exact relationship between nitrous oxide administration and serious long-term adverse outcomes will require confirmation by an appropriately designed large randomized controlled trial.


**Background:** Nitrous oxide causes an acute increase in plasma homocysteine that is more pronounced in patients with the methylenetetrahydrofolate reductase (MTHFR) C677T or A1298C gene variant. In this randomized controlled trial, the authors sought to determine whether patients carrying the MTHFR C677T or A1298C variant had a higher risk for perioperative cardiac events after nitrous oxide anesthesia and whether this risk could be mitigated by B-vitamins.

**Methods:** The authors randomized adult patients with cardiac risk factors undergoing noncardiac surgery, to receive nitrous oxide plus intravenous B-vitamins before and after surgery, or to nitrous oxide and placebo. Serial cardiac biomarkers and 12-lead electrocardiograms were
obtained. The primary study endpoint was the incidence of myocardial injury, as defined by cardiac troponin I increase within the first 72 h after surgery.

**Results:** A total of 500 patients completed the trial. Patients who were homozygous for either MTHFR C677T, or A1298C gene variant (n=98; 19.6%) had no increased rate of postoperative cardiac troponin I increase compared with wild-type and heterozygous patients (11.2 vs. 14.0%; relative risk 0.96; 95% CI, 0.85-1.07; P=0.48). B-vitamins blunted the rise in homocysteine, but had no effect on cardiac troponin I increase compared with patients receiving placebo (13.2 vs. 13.6%; relative risk 1.02; 95% CI 0.78 to 1.32; P=0.91).

**Conclusions:** Neither MTHFR C677T and A1298C gene variant, nor acute homocysteine increase are associated with perioperative cardiac troponin I increase after nitrous oxide anesthesia. B-vitamins blunt nitrous oxide-induced homocysteine increase but have no effect on cardiac troponin I increase.


**Background:** In this post hoc subanalysis of the Perioperative Ischemic Evaluation (POISE) trial, we sought to determine whether nitrous oxide was associated with the primary composite outcome of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal cardiac arrest within 30 days of randomization.
Methods: The POISE trial of perioperative β-blockade was undertaken in 8351 patients. Nitrous oxide anesthesia was defined as the co-administration of nitrous oxide in patients receiving general anesthesia, with or without additional neuraxial blockade or peripheral nerve blockade. Logistic regression, with inverse probability weighting using estimated propensity scores, was used to determine the association of nitrous oxide with the primary outcome, MI, stroke, death, and clinically significant hypotension.

Results: Nitrous oxide was administered to 1489 (29%) of the 5133 patients included in this analysis. Nitrous oxide had no significant effect on the risk of the primary outcome (112 [7.5%] vs 248 [6.9%]; odds ratio [OR], 1.08; 95% confidence interval [CI], 0.82-1.44; 99% CI, 0.75-1.57; P = 0.58), MI (89 [6.0] vs 204 [5.6]; OR, 0.99; 95% CI, 0.75-1.31; 99% CI, 0.69-1.42; P = 0.94), stroke (6 [0.4%] vs 28 [0.8%]; OR, 0.85; 95% CI, 0.26-2.82; 99% CI, 0.17-4.11; P = 0.79), death (40 [2.7%] vs 100 [2.8%]; OR, 1.04; 95% CI, 0.61-1.81; 99% CI, 0.51-2.15; P = 0.88) or clinically significant hypotension (219 [14.7%] vs 544 [15.0%]; OR, 0.92; 95% CI, 0.74-1.15; 99% CI, 0.70-1.23; P = 0.48).

Conclusions: In this post hoc sub-analysis, nitrous oxide was not associated with an increased risk of adverse outcomes in the POISE trial patients. This analysis was limited by the observational nature of the data and the lack of information on the concentration and duration of nitrous oxide administration. Further randomized controlled trial evidence is required.
**Abstract**

**Background:** Nitrous oxide (N2O) has been widely used in clinical anesthesia for >150 years. However, use of N2O has decreased in recent years because of concern about the drug’s metabolic side effects. But evidence that routine use of N2O causes clinically important toxicity remains elusive. We therefore evaluated the relationship between intraoperative N2O administration and 30-day mortality as well as a set of major inpatient postoperative complications (including mortality) in adults who had general anesthesia for non-cardiac surgery.

**Methods:** We evaluated 49,016 patients who had non-cardiac surgery at the Cleveland Clinic between 2005 and 2009. Among 37,609 qualifying patients, 16,961 were given N2O (“nitrous,” 45%) and 20,648 were not (“non-nitrous,” 55%). Ten thousand seven hundred fifty-five nitrous patients (63% of the total) were propensity score-matched with 10,755 non-nitrous patients. Matched nitrous and non-nitrous patients were compared on 30-day mortality and a set of 8 in-hospital morbidity/mortality outcomes.

**Results:** Inhalation of N2O intraoperatively was associated with decreased odds of 30-day mortality (odds ratio [OR]: 97.5% confidence interval, 0.67, 0.46-0.97; P = 0.02). Furthermore, nitrous patients had an
estimated 17% (OR: 0.83, 0.74-0.92) decreased odds of experiencing major in-hospital morbidity/mortality than non-nitrous (P < 0.001). Among the individual morbidities, intraoperative N2O use was only associated with significantly lower odds of having pulmonary/respiratory morbidities (OR, 95% Bonferroni-adjusted CI: 0.59, 0.44-0.78).

**Conclusions:** Intraoperative N2O administration was associated with decreased odds of 30-day mortality and decreased odds of in-hospital mortality/morbidity. Aside from its specific and well-known contraindications, the results of this study do not support eliminating N2O from anesthetic practice.

McGregor DG, Lanier WL, Pasternak JJ et al

**Background:** Laboratory studies suggest that nitrous oxide augments brain injury after ischemia or hypoxia. The authors examined the relation between nitrous oxide use and outcomes using data from the Intraoperative Hypothermia for Aneurysm Surgery Trial.

**Methods:** The Intraoperative Hypothermia for Aneurysm Surgery Trial was a prospective randomized study of the impact of intraoperative hypothermia (temperature = 33 degrees C) versus normothermia (temperature = 36.5 degrees C) in patients with aneurysmal subarachnoid hemorrhage undergoing
surgical clipping. Anesthesia was dictated by a limited-options protocol with the use of nitrous oxide determined by individual anesthesiologists. All patients were assessed daily for 14 days after surgery or until hospital discharge. Neurologic and neuropsychological testing were conducted at 3 months after surgery. Outcome data were analyzed via both univariate tests and multivariate logistic regression analysis correcting for factors thought to influence outcome. An odds ratio (OR) greater than 1.0 denotes a worse outcome in patients receiving nitrous oxide.

**Results:** Outcome data were available for 1,000 patients, of which 373 received nitrous oxide. There was no difference between groups in the development of delayed ischemic neurologic deficit. At 3 months after surgery, there were no significant differences between groups in any outcome variable: Glasgow Outcome Score (OR, 0.84; 95% confidence interval [CI], 0.63-1.14; P = 0.268), National Institutes of Health Stroke Scale (OR, 1.29; 95% CI, 0.96-1.73; P = 0.087), Rankin Disability Score (OR, 0.84; 95% CI, 0.61-1.15; P = 0.284), Barthel Activities of Daily Living Index (OR, 1.01; 95% CI, 0.68-1.51; P = 0.961), or neuropsychological testing (OR, 1.26; 95% CI, 0.85-1.87; P = 0.252).

**Conclusions:** In a population of patients at risk for ischemic brain injury, nitrous oxide use had no overall beneficial or detrimental impact on neurologic or neuropsychological outcomes.

Abstract:
Some, but not all studies have suggested intra-operative use of nitrous oxide is correlated with postoperative nausea and vomiting. We performed a meta-analysis of randomised controlled trials to compare the incidence of nausea and vomiting in adults following general anaesthesia with or without nitrous oxide. We retrieved 30 studies (incorporating 33 separate trials) that investigated a ‘nitrous oxide group’ (total 2297 patients) vs a ‘no-nitrous oxide group’ (2301 patients). Omitting nitrous oxide significantly reduced postoperative nausea and vomiting (pooled relative risk 0.80, 95% CI 0.71-0.90, p = 0.0003). However, the absolute incidence of nausea and vomiting was high in both the nitrous oxide and no-nitrous oxide groups (33% vs 27%, respectively). In subgroup analysis, the maximal risk reduction was obtained in female patients (pooled relative risk 0.76, 95% CI 0.60-0.96). When nitrous oxide was used in combination with propofol, the antiemetic effect of the latter appeared to compensate the emetogenic effect of nitrous oxide (pooled relative risk 0.94, 95% CI 0.77-1.15). We conclude that avoiding nitrous oxide does reduce the risk of postoperative nausea and vomiting, especially in women, but the overall impact is modest.


Abstract

**Background:** Globally there are >200 million major surgical procedures undertaken annually, and about 20% of these involve patients who have coronary artery disease. Many receive nitrous oxide, which impairs methionine synthase, thus inhibiting folate synthesis and increasing postoperative homocysteine levels. Nitrous oxide anesthesia leads to postoperative endothelial dysfunction, and there is some evidence that it increases myocardial ischemia and, possibly, myocardial infarction. We have initiated the Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial to test the hypothesis that in inpatients undergoing anesthesia for major noncardiac surgery, avoidance of nitrous oxide will reduce the incidence of death and major cardiovascular events.

**Methods:** ENIGMA-II is a 7,000-patient, international randomized trial involving patients at risk of coronary artery disease undergoing noncardiac surgery. The patients, health care providers (except for the anesthesiologists), data collectors, and outcome adjudicators are blinded to whether patients receive nitrous oxide-containing or nitrous oxide-free anesthetic. The primary outcome is a composite of death and major nonfatal events (ie, myocardial infarction, cardiac arrest, pulmonary embolism, and stroke) at 30 days after surgery.
Results: At present, ENIGMA-II has randomized >1,000 patients in 22 hospitals in 5 countries. To date, patients’ mean age is 70 years, 66% are men, 38% have a history of coronary artery disease, 19% have a history of cerebrovascular disease, and 84% have a history of hypertension. Most patients have undergone intra-abdominal 28%, vascular 32%, and orthopedic 16% surgery.

Conclusions: The ENIGMA-II Trial will be the largest study yet conducted to ascertain the benefits and risks of removing nitrous oxide from the gas mixture in anesthesia. The results of this large international trial will guide the clinical care of the hundreds of millions of adults undergoing noncardiac surgery annually.

(Results of ENIGMA II trial are awaited)

Summary
- Avoiding nitrous oxide reduces the risk of postoperative nausea and vomiting, especially in women
- The association of nitrous oxide with increased long-term risk of myocardial infarction is currently under scrutiny
- Nitrous oxide does increase plasma homocysteine level, however reduction of homocysteine levels by pretreatment with Vitamin B12 does not reduce the incidence of adverse perioperative cardiac events (VINO trial)
- POISE and IHAST showed no association between nitrous oxide and increased risk of stroke.
• ENIGMA-II has been designed to answer the question: does nitrous oxide contribute to postoperative myocardial infarction, stroke and pulmonary embolism? The results are keenly awaited.

References
Peri-operative Blood Transfusion and Cancer Recurrence - What is the Evidence?

Introduction:
Though transfusion-related immune modulation (TRIM) is a well established phenomenon, its effects on cancer recurrence after a curative resection remain controversial.

Though the association between perioperative allogeneic blood transfusion and risk for recurrence has been well demonstrated in colorectal cancer in randomized trials, there is insufficient data (few retrospective studies) to prove that this may be true for other types of cancer. Since recurrence depends on several factors, the potential impacts of these on cancer recurrence are complex to understand from retrospective studies.

The presence of leucocytes in allogeneic blood units may be the cause of some of the immunological derangements observed after transfusions. It was thus
thought, that leuco-depleted pRBCs would induce less immune suppression, and possibly have a beneficial effect by resulting in fewer recurrences. However, there is still no convincing evidence in human trials to support this.


Objective: To determine the effect of allogeneic blood transfusion (ABT) on clinical outcomes in patients with colorectal cancer undergoing surgery.

Background: Perioperative ABTs may be associated with adverse clinical outcomes.

Methods: Systematic review of the literature with odds ratio (OR) and incidence rate ratio (IRR) meta-analyses of predefined clinical outcomes based on a MEDLINE search.

Results: In total, 20,795 colorectal cancer (CRC) patients observed for more than 59.2 ± 26.1 months (108,838 patient years) were included, of which 58.8% were transfused. ABT was associated with increased all-cause mortality OR = 1.72 (95% confidence interval [CI] 1.55-1.91, P < 0.001); I² = 23.3% (0-51.1) and IRR = 1.31 (1.23-1.39, P < 0.001), I² = 0.0% (0-37.0). ABT was also associated with increased ORs (95% CI,P) for cancer -related mortality of 1.71 (1.43-2.05, P <0.001), combined recurrence-metastasis-death 1.66
(1.41-1.97, P < 0.001), postoperative infection 3.27 (2.05-5.20, P < 0.001), and surgical re-intervention 4.08 (2.18-7.62, <0.001). IRR (95% CI, P) was 1.45 (1.26-1.66, <0.001) for cancer-related mortality and 1.32 (1.19-1.46, <0.001) for recurrence-metastasis-death. Mean length of hospital stay was significantly longer in transfused compared with non-transfused patients (17.8 ± 4.8 versus 13.9 ± 4.7 days, P = 0.005).

**Conclusion:** In patients with colorectal cancer (CRC) undergoing surgery, ABTs are associated with adverse clinical outcomes, including increased mortality. Measures aimed at limiting the use of ABTs should be investigated further


**Background:** The improvement of renal allograft survival by pre-transplantation transfusions alerted to the potential detrimental effect of transfusions in cancer treatment.

**Objectives:** This meta-analysis evaluates the role of perioperative blood transfusions (PBT) on colorectal cancer recurrence. This is accomplished by updating the results of a previously published meta-analysis (Amato 2006) to December 2009.

**Search strategy:** Papers were retrieved using Medline, EMBASE, the Cochrane Library, trials
web-based registries, or the CCG Database. The search strategy was: \{colon OR rectal OR colorectal\} WITH \{cancer OR tumor OR neoplasm\} AND transfusion. The publication bias was balanced by reviewing the proceedings of international congresses.

**Selection criteria:** Patients undergoing curative resection of colorectal cancer (classified either as Dukes stages A-C, Astler-Coller stages A-C2, or TNM stages T1-3a/N0-1/M0) were included if they had received blood products within one month of surgery. Excluded were patients with distant metastases and studies with short follow-up or no data.

**Data collection and analysis:** A specific form was used for data collection. Data was cross-checked, using the most recent publication in case of repetitive ones. Papers’ quality was evaluated using the method by Evans and Pollock. Odds ratios (OR, with 95% confidence intervals) were computed for each study, and pooled estimates were generated by RevMan (version 5). When available, data were stratified for risk factors of cancer recurrence.

**Main results:** Updating the previous review through December 2009 identified 41 additional papers, for a grand total of 278 references. Two-hundred and forty-two of them were excluded because they analyzed survival (n=27), were repetitive (n=29), letters/reviews (n=71) or had no data (n=115). Thirty-six studies on 12,127 patients remained included: 23 showed a detrimental effect of PBT; 22 used multivariable analyses, and 14 found an independent PBT effect. Pooled
estimates of PBT effect on recurrence in randomised studies yielded an OR of 1.42 (95% CI, 1.20 to 1.67) against transfused patients. Stratified meta-analyses confirmed these findings also by site and stage of disease, regardless of timing, type, and in a dose-related fashion, although heterogeneity was detected. Data on surgical techniques was not available for further analysis.

Authors’ conclusions: This updated meta-analysis confirms the previous findings and supports the association of PBT on the recurrence of curable colorectal cancers. However, since heterogeneity was detected and the effect of surgical technique could not be assessed, a causal relationship cannot still be claimed. Carefully restricted indications for PBT seem necessary.


Objective: Perioperative blood transfusions may adversely affect survival in patients with colorectal malignancy, although definite proof of a causal relationship has never been reported.

Background: We report the long-term outcomes of a randomized controlled trial performed between 1986 and 1991 to compare the effects of allogeneic blood transfusions and an autologous blood transfusion program in colorectal cancer patients.

Methods: All 475 randomized patients operated upon for colorectal cancer were tracked via a national
computerized record-linkage system to investigate survival and cause of death. Kaplan-Meier survival curves were constructed and multivariate Cox regression analysis was performed to study 20 years’ overall survival. Colorectal cancer-specific survival was analyzed over the 10-year time period after surgery.

**Results:** The overall survival percentage at 20 years after surgery was worse in the autologous group (21%) compared to the allogeneic group (28%) (P = 0.041; log-rank test). Cox regression, allowing for tumor stage, age, and sex, resulted in a hazard ratio (autologous vs allogeneic group) for overall mortality of 1.24 (95% confidence interval 1.00-1.54; P = 0.051). Colorectal cancer-specific survival at 10 years for the whole study group was 48% and 60% for the autologous and allogeneic group, respectively (P = 0.020; log-rank test). The adjusted hazard ratio was 1.39 (95% confidence interval 1.05-1.83; P = 0.045).

**Conclusions:** At long-term follow-up colorectal cancer patients did not benefit from autologous transfusion compared with standard allogeneic transfusion. On the contrary, the overall and colorectal cancer-specific survival rates were worse in the patients in the autologous transfusion group.

**Summary:**

1. Perioperative blood product transfusions cause immune modulation in the recipient which may have effects on cancer recurrence

2. The association between perioperative allogeneic blood transfusion and risk for recurrence has been
well demonstrated in colorectal cancer in randomized trials and this association is stronger when larger volumes of blood are administered.

3. Though retrospective studies suggest increased recurrence rates with transfusions in other types of cancer, further prospective studies will be needed to confirm these results.

4. There is no evidence that leucoreduction ameliorates the immunomodulatory effect of blood transfusion.

5. Intraoperative autologous transfusion appears to be safe, but it remains unclear whether it offers any advantages over administration of allogeneic blood transfusions with reference to cancer recurrence. However, in colorectal cancers, survival rates are worse in the patients who get autologous transfusion
Does Exposure to Anaesthesia affect the Developing Brain?

Introduction
All currently used anaesthetics and sedatives have been found to be neurotoxic in neonatal animal studies.\textsuperscript{1,2} Anaesthetics cause neuronal degeneration not by necrosis following ischaemia; but by a programmed cellular suicide, called apoptosis. Anaesthetic agents decrease trophic factors in the brain such as brain derived neurotrophic factor (BDNF) - a protein integral to neuronal survival, growth and differentiation.\textsuperscript{1} Anaesthetics also inhibit neurogenesis and alter the development of dendritic spine architecture and important developmental processes in synapse formation (Synaptogenesis).\textsuperscript{3} Anaesthesia causes neuronal impairment in hippocampus which is an important brain structure for memory and learning. Dose and duration-dependent neuronal apoptosis in response to Ketamine, Propofol, Nitrous oxide and Isoflurane has been documented in neonatal rodents and non-human primates.
However, the relevance of these findings to paediatric anaesthesia is not known. Also, the available information is from the retrospective analysis of children who have received anaesthesia with halothane and nitrous oxide as per the standard practice of the earlier decades. Hence, the conclusions of these retrospective analysis may not be extrapolated to the effects of anaesthetics like sevoflurane, dexmedetomidine, etc. in current anaesthesia practice. To answer this question, two prospective multicentre clinical studies (The PANDA study and GAS) are currently underway to address anaesthetic neurotoxicity in children. However, these studies will analyse the effects of a single exposure to anaesthetics.

The PANDA (Paediatric Anesthesia Neurodevelopmental Assessment) study is a large-scale, multisite, ambidirectional sibling-matched cohort study in the USA. It aims to assess the effects of anaesthetic exposure for inguinal hernia repair within the first 3 years of life in a retrospectively identified cohort of 1000 children or 500 sibling pairs on prospectively measured neurodevelopmental performance, compared with that of an unexposed sibling.  

Another large-scale study is the GAS study in which patients’ intelligence quotient and neuro-developmental outcome will be compared at 2 years following a congenital inguinal hernia repair performed either with general sevoflurane anaesthesia or with caudal or spinal anaesthesia.  

Hansen and co-workers are using a database of all 45000 children who underwent surgical operations in
Denmark from 1977 to 1990 prior to 1 year of age, comparing their academic achievement with that of the general Danish population.¹


Introduction: There is data amassing in the literature regarding the potentially adverse effects of anaesthesia exposure on the developing human brain. The purpose of this article is to summarize current relevant data from clinical studies in this area.

Results: From the initial search, 23 articles were identified as potentially relevant, with publication dates spanning from 1978 to 2012. Twelve studies were deemed irrelevant to the research questions. The results of neurocognitive assessment from eight of the remaining eleven studies had showed some differences in the performances of children exposed to anaesthesia. The control population in these studies was highly variable. The age at which the subjects were exposed to anaesthesia ranged from prenatal to 4 years in the majority of studies with one including children aged up to 12 years when exposed.

Discussion: Although there is clinical data suggesting a possible detrimental effect, the evidence is best considered preliminary and inconclusive at this stage. Many of the outcome measures were lacking in specificity and standardization in most cases. Parents should be counseled to not avoid necessary invasive procedures
for fear of a currently ill-defined risk. However, deferral of elective procedures beyond the first few years of life should be contemplated.


**Background:** Annually, millions of children are exposed to anesthetic agents that cause apoptotic neurodegeneration in immature animals. To explore the possible significance of these findings in children, we investigated the association between exposure to anesthesia and subsequent (1) learning disabilities (LDs), (2) receipt of an individualized education program for an emotional/behavior disorder (IEP-EBD), and (3) scores of group-administered achievement tests.

**Methods:** This was a matched cohort study in which children (N=8548) born between January 1, 1976, and December 31, 1982, in Rochester, Minnesota, were the source of cases and controls. Those exposed to anesthesia (n =350) before the age of 2 were matched to unexposed controls (n =700) on the basis of known risk factors for LDs. Multivariable analysis adjusted for the burden of illness, and outcomes including LDs, receipt of an IEP-EBD, and the results of group administered tests of cognition and achievement were outcomes.

**Results:** Exposure to multiple, but not single, anesthetic/surgery significantly increased the risk of developing LDs (hazard ratio: 2.12 [95% confidence interval: 1.26 –
3.54), even when accounting for health status. A similar pattern was observed for decrements in group administered tests of achievement and cognition. However, exposure did not affect the rate of children receiving an individualized education program.

**Conclusions:** Repeated exposure to anesthesia and surgery before the age of 2 was a significant independent risk factor for the later development of LDs but not the need for educational interventions related to emotion/behavior. We cannot exclude the possibility that multiple exposures to anesthesia/surgery at an early age may adversely affect human neurodevelopment with lasting consequence.


**Abstract**

Experimental evidence of anesthesia-induced neurotoxicity has caused serious concern about the long-term effect of commonly used volatile anesthetic agents on young children. Several observational studies based on existing data have been conducted to address this concern with inconsistent results. We conducted a meta-analysis to synthesize the epidemiologic evidence on the association of anesthesia/surgery with neurodevelopmental outcomes in children. Using Bayesian metanalytic approaches, we estimated the synthesized odds ratios (OR) and 95% credible interval (CrI) as well as the predictive distribution of a future study given the
synthesized evidence. Data on 7 unadjusted and 6 adjusted measures of association were abstracted from 7 studies. The synthesized OR based on the 7 unadjusted measures for the association of anesthesia/surgery with an adverse behavioral or developmental outcome was 1.9 (95% CrI 1.2, 3.0). The most likely unadjusted OR from a future study was estimated to be 2.2 (95% CrI 0.6, 6.1). The synthesized OR based on the 6 adjusted measures for the association of anesthesia/surgery with an adverse behavioral or developmental outcome was 1.4 (95% CrI 0.9, 2.2). The most likely adjusted OR from a future study was estimated to be 1.5 (95% CrI 0.5, 4.0). We conclude that the existent epidemiologic evidence suggests a modestly elevated risk of adverse behavioral or developmental outcomes in children who were exposed to anesthesia/surgery during early childhood. The uncertainty with the existent epidemiologic evidence, however, is considerable, implying that the value of additional research using existent data sources to enhance the evidence base is diminishing.


Abstract
Recent animal studies have shown that commonly used anesthetic agents may have serious neurotoxic effects on the developing brain. The purpose of this study was
to assess the association between surgery for hernia repair and the risk of behavioral and developmental disorders in young children. We performed a retrospective cohort analysis of children who were enrollees of the New York State Medicaid program. Our analysis involved following a birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life, and a sample of 5050 children frequency-matched on age with no history of hernia-repair before age 3. After controlling for age, sex, and complicating birth-related conditions such as low birth weight, children who underwent hernia repair under 3 years of age were more than twice as likely as children in the comparison group to be subsequently diagnosed with a developmental or behavioral disorder (adjusted hazard ratio 2.3, 95% confidence interval 1.3, 4.1). Our findings add to recent evidence of the potential association of surgery and its concurrent exposure to anesthetic agents with neurotoxicity and underscore the need for more rigorous clinical research on the long-term effects of surgery and anesthesia in children.


Objective: To study the association between exposure to procedures performed under general anesthesia before age 2 years and development of attention-deficit/hyperactivity disorder (ADHD).
**Patients and Methods:** Study patients included all children born between January 1, 1976, and December 31, 1982, in Rochester, MN, who remained in Rochester after age 5. Cases of ADHD diagnosed before age 19 years were identified by applying stringent research criteria. Cox proportional hazards regression assessed exposure to procedures requiring general anesthesia (none, 1, 2 or more) as a predictor of ADHD using a stratified analysis with strata based on a propensity score including comorbid health conditions.

**Results:** Among the 5357 children analyzed, 341 ADHD cases were identified (estimated cumulative incidence, 7.6%; 95% confidence interval [CI], 6.8%-8.4%). For children with no postnatal exposure to procedures requiring anesthesia before the age of 2 years, the cumulative incidence of ADHD at age 19 years was 7.3% (95% CI, 6.5%-8.1%). For single and 2 or more exposures, the estimates were 10.7% (95% CI, 6.8%-14.4%) and 17.9% (95% CI, 7.2%-27.4%), respectively. After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple (hazard ratio, 1.95; 95% CI, 1.03-3.71), but not single (hazard ratio, 1.18; 95% CI, 0.79-1.77), procedures requiring general anesthesia was associated with an increased risk for ADHD.

**Conclusion:** Children repeatedly exposed to procedures requiring general anesthesia before age 2 years are at increased risk for the later development of ADHD even after adjusting for comorbidities.

Background: Over the past decade, the safety of anesthetic agents in children has been questioned after the discovery that immature animals exposed to anesthesia display apoptotic neurodegeneration and long-term cognitive deficiencies. We examined the association between exposure to anesthesia in children under age 3 and outcomes in language, cognitive function, motor skills, and behavior at age 10.

Methods: We performed an analysis of the Western Australian Pregnancy Cohort (Raine) Study, which includes 2868 children born from 1989 to 1992. Of 2608 children assessed, 321 were exposed to anesthesia before age 3, and 2287 were unexposed.

Results: On average, exposed children had lower scores than their unexposed peers in receptive and expressive language (Clinical Evaluation of Language Fundamentals: Receptive [CELF-R] and Expressive [CELF-E]) and cognition (Colored Progressive Matrices [CPM]). After adjustment for demographic characteristics, exposure to anesthesia was associated with increased risk of disability in language (CELF-R: adjusted risk ratio [aRR], 1.87; 95% confidence interval [CI], 1.20-2.93, CELF-E: aRR, 1.72; 95% CI, 1.12-2.64), and cognition (CPM: aRR, 1.69; 95% CI, 1.13-2.53). An increased aRR for disability in language and cognition persisted even with a single exposure to anesthesia.
(CELF-R aRR, 2.41; 95% CI, 1.40-4.17, and CPM aRR, 1.73; 95% CI, 1.04-2.88).

Conclusions: Our results indicate that the association between anesthesia and neuropsychological outcome may be confined to specific domains. Children in our cohort exposed to anesthesia before age 3 had a higher relative risk of language and abstract reasoning deficits at age 10 than unexposed children.

Summary

• Anesthetic agents (NMDA antagonists, GABA agonists, isoflurane, nitrous oxide) cause dose and duration dependent neuronal degeneration in neonatal animals.

• Children repeatedly exposed to procedures requiring general anesthesia before age 2 years are at increased risk for the later development of Attention Deficit Hyperactive Disorder and learning disabilities.

• Given the phenomenon’s potential serious effects on paediatric health, further research is required to decide optimum age for exposure to anesthetics for elective procedures, and to develop protective strategies, if required

References

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Does Type of Anaesthesia Affect Cancer Outcomes?

There are millions of new cases of cancer detected each year worldwide and the incidence is increasing especially in the developing countries. Many of these patients will require surgery as part of their treatment. Recurrence and metastasis remain the most feared outcomes and are the usual causes of mortality. As more and more cancer patients undergo surgery, there is increasing awareness of the potential impact of anaesthetics on cancer cell biology. Also, there is a growing interest in the role played by regional versus general anaesthesia in the long term outcomes of cancer patients. There have been implications that anaesthetic and analgesic techniques for primary cancer surgery may not only influence the biology of cancer cells but also affect cell mediated immunity. Handling and manipulation of tumor during surgery may lead to the release of tumor cells into vascular and lymphatic circulations. Surgical stress, together with subsequent neuro-endocrine, metabolic and inflammatory responses results in
significant suppression of cell-mediated immunity. The combination of compromised host immune defence and tumor seeding renders the perioperative period susceptible to tumor metastasis and/or recurrence.

Several studies have looked at the association between the anaesthetic technique used during primary cancer surgery and recurrence or metastases. The purpose of this review is-

1) To summarize the current body of evidence for any relationship between anaesthesia technique and cancer recurrence.
2) To identify appropriate direction for future research and clinical management.

Secondary Analyses of Prospective RCTs designed to test hypotheses other than cancer recurrence


Objective: To compare long term recurrence of cancer and survival of patients having major abdominal surgery for cancer.

Design: Long term follow-up of prospective randomised controlled clinical trial in which patients were randomly assigned to receive general anaesthesia with or without epidural block for at least three postoperative days.
**Setting:** 23 hospitals in Australia, New Zealand, and Asia.

**Participants:** 503 adult patients who had potentially curative surgery for cancer.

**Main outcome measure:** Cancer-free survival (analysis was by intention to treat).

**Results:** Long term follow-up data were available for 94% (n=446) of eligible participants. The median time to recurrence of cancer or death was 2.8 (95% confidence interval 0.7 to 8.7) years in the control group and 2.6 (0.7 to 8.7) years in the epidural group (P=0.61). Recurrence free survival was similar in both epidural and control groups (hazard ratio 0.95, 95% confidence interval 0.76 to 1.17; P=0.61).

**Conclusion:** Use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival.


**Purpose:** To determine the effect of adjunctive epidural local anesthetic and opioid infusion on disease recurrence following radical prostatectomy for adenocarcinoma under general anesthesia.

**Methods:** This article describes a secondary analysis of subjects undergoing radical prostatectomy who had
participated previously in a randomized controlled trial evaluating pain control, blood loss, and the need for perioperative allogeneic blood transfusion. The patients were randomly allocated to receive either general anesthesia alone (control group; n = 50) or combined general/epidural anesthesia (study group; n = 49). A long-term follow-up chart review was undertaken to determine clinically evident or biochemical (Prostate Specific Antigen > 0.2 ng x mL(-1)) recurrence of prostate cancer. Comparison by group was undertaken using survival analysis.

**Results**: Median disease-free survival for the study as a whole was 1644 days, and the longest recorded survival was 3403 days. Biochemical recurrence of prostate cancer was observed in 11/49 study subjects and 17/50 control subjects. There was one death from prostate cancer in each group and a total of five deaths in the study group and six deaths in the control group. The hazard ratio for recurrence in the study group compared with the control group was 1.33 (95% confidence intervals 0.64-2.77; P = 0.44 by log-rank test).

**Conclusion**: No difference was observed between the epidural and control groups in disease-free survival at a median follow-up time of 4.5 years. There is a need for large randomized controlled trials to determine the ability of epidural analgesia to alter disease recurrence rates following radical prostatectomy.
Meta-analyses and systematic reviews of retrospective and prospective studies


Animal models have shown that regional anesthesia (combined with or without general anesthesia) would attenuate the surgical stress response by preserving immune function and result in better long-term outcome. In order to test the hypothesis that cancer patients who had surgery with epidural anesthesia (EA) would have better outcome (either overall survival [OS] or recurrence-free survival [RFS]) than those who were general anesthesia (GA), we performed this meta-analysis. By searching relevant literature, a total of 14 studies containing 18 sub-studies (seven in OS analysis and eleven in RFS analysis) were identified and meta-analyzed. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the strength of association. For OS, the random-effects model was used to analyze the data and demonstrated an OS benefit in favour of EA compared with GA alone (HR = 0.84, 95% CI 0.74–0.96, P = 0.013). The influence analysis showed the robustness of the results. Specifically, a significantly positive association between EA and improved OS was observed in colorectal cancer (HR = 0.65, 95% CI 0.43–0.99, P = 0.045). For RFS, the random-effects model was used to analyze the data and no significant relationship between RFS benefit and EA (HR = 0.88, 95% CI 0.64–1.22, P = 0.457) was
detected. In conclusion, our meta-analysis suggests that epidural anesthesia and/or analgesia might be associated with improved overall survival in patients with operable cancer undergoing surgery (especially in colorectal cancer), but it does not support an association between epidural anesthesia and cancer control. Prospective studies are needed to determine whether the association between epidural use and survival is causative.


**Background:** The perioperative period of major oncologic surgery is characterized by immunosuppression, angiogenesis, and an increased load of circulating malignant cells. It is a window period in which cancer cells may seed, invade, and proliferate. Thus, it has been hypothesized that the use of regional anesthesia with the goal of reducing surgical stress and opioid and volatile anesthetic consumption would avoid perioperative immune suppression and angiogenesis and ultimately cancer recurrence.

**Questions/purposes:** We performed a systematic review of the literature on the use of regional anesthesia and postoperative analgesia to improve cancer-related survival after oncologic surgery. Our primary topic of interest is survival after orthopaedic oncologic surgery, but because that literature is limited, we also have systematically reviewed the question of survival after breast, gastrointestinal and genitouranlogous cancers.
Methods: We searched the PubMed and Embase databases with the search terms: “anesthesia and analgesia”, “local neoplasm recurrence”, “cancer recurrence”, “loco-regional neoplasm recurrence”, “disease-free survival”, and “cumulative survival rates”. Our initial search of the two databases provided 836 studies of which 693 were rejected. Of the remaining 143 studies, only 13 articles qualified for inclusion in this systematic review, based on defined inclusion criteria. All these studies had retrospective design. Due to the high heterogeneity among the identified studies and the complete absence of randomized controlled trials from the literature on this topic, the results of a metaanalysis would be heavily confounded; hence, we instead performed a systematic review of the literature.

Results: No eligible studies addressed the question of whether regional anesthesia and analgesia have an impact on survival after musculoskeletal cancer surgery. Only one relevant clinical study was identified on regional breast cancer survival; it suggested a benefit. The literature on gastrointestinal and genitourinary surgery was larger but mixed, although some preliminary studies do suggest a benefit of regional anesthesia on survival after oncologic surgery in those patient populations.

Conclusions: Although basic science studies suggest a potential benefit of regional anesthesia and stress response reduction in cancer formation, we found little clinical evidence to support the theory that regional anesthesia and analgesia improve overall patient survival after oncologic surgery.
Summary

- Evidence from current available data can only generate a platform for the need of prospective randomised trials to prove an association between anaesthetic technique and cancer recurrence. There is no evidence to back a need to change anaesthetic practice.

- All of these trials suffer from the limitations associated with multimodal anaesthesia and the inability of these studies to eliminate confounders and determine the contribution of each individual anaesthetic factor to cancer recurrence.

- The use of regional anaesthesia during primary cancer surgery has not been conclusively proven to improve cancer outcomes.
Does the Use of Regional Anaesthesia Improve Peri-operative Outcomes?

It is a well known and accepted fact that, regional anaesthesia is known to provide superior analgesia in comparison with other opioid based techniques. Epidural analgesia has shown to promote early mobilization and reduce rehabilitation time especially following joint surgeries, reduce pulmonary morbidity, reduce time to extubation after major thoracic and vascular procedures, reduce ileus, venous thrombosis (DVT) and thereby reduce hospital stay. Recent evidence also points to a lower incidence of chronic postsurgical pain with epidural analgesia. Whether regional anaesthesia actually influences outcome after surgery is inconclusive. Several meta-analyses have attempted to answer this question, with controversial results. Many studies have been inconclusive, with methodological weaknesses (underpowered, failure to control patient inclusion criteria, other influences on outcome, variable end point criteria) making it difficult to compare results.
of different studies. Nevertheless, the weight of evidence suggests that regional anaesthesia has the potential to improve outcome from surgery.


Background: Regional anaesthesia may reduce the risk of persistent (chronic) pain after surgery, a frequent and debilitating condition. We compared regional anaesthesia vs conventional analgesia for the prevention of persistent postoperative pain (PPP).

Methods: We searched the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and CINAHL from their inception to May 2012, limiting the results to randomized, controlled, clinical trials (RCTs), supplemented by a hand search in conference proceedings. We included RCTs comparing regional vs conventional analgesia with a pain outcome at 6 or 12 months. The two authors independently assessed methodological quality and extracted data. We report odds ratios (ORs) with 95% confidence intervals (CIs) as our summary statistic based on random-effects models. We grouped studies according to surgical interventions.

Results: We identified 23 RCTs. We pooled data from 250 participants in three trials after thoracotomy with outcomes at 6 months. Data favoured epidural anaesthesia for the prevention of PPP with an OR of 0.33 (95% CI 0.20-0.56). We pooled two studies investigating paravertebral block for breast cancer
surgery; pooled data of 89 participants with outcomes at 6 months favoured paravertebral block with an OR of 0.37 (95% CI 0.14-0.94). Adverse effects were reported sparsely.

**Conclusions:** Epidural anaesthesia and paravertebral block, respectively, may prevent PPP after thoracotomy and breast cancer surgery in about one out of every four to five patients treated. Small numbers, performance bias, attrition, and incomplete outcome data especially at 12 months weaken our conclusions.


**Background:** Epidural block is widely used to manage major abdominal surgery and postoperative analgesia, but its risks and benefits are uncertain. We compared adverse outcomes in high-risk patients managed for major surgery with epidural block or alternative analgesic regimens with general anesthesia in a multicentre randomized trial.

**Methods:** 915 patients undergoing major abdominal surgery with one of nine defined comorbid states to identify high-risk status were randomly assigned intraoperative epidural anesthesia and postoperative epidural analgesia for 72 h with general anesthesia (site of epidural selected to provide optimum block) or control. The primary endpoint was death at 30 days or major postsurgical morbidity. Analysis by intention to
treat involved 447 patients assigned epidural and 441 control.

**Findings:** 255 patients (57·1%) in the epidural group and 268 (60·7%) in the control group had at least one morbidity endpoint or died (p=0·29). Mortality at 30 days was low in both groups (epidural 23 [5·1%], control 19 [4·3%], p=0·67). Only one of eight categories of morbid endpoints in individual systems (respiratory failure) occurred less frequently in patients managed with epidural techniques (23% vs. 30%, p=0·02). Postoperative epidural analgesia was associated with lower pain scores during the first 3 postoperative days. There were no major adverse consequences of epidural catheter insertion.

Interpretation: Most adverse morbid outcomes in high-risk patients undergoing major abdominal surgery are not reduced by use of combined epidural and general anesthesia and postoperative epidural analgesia. However, the improvement in analgesia, reduction in respiratory failure, and the low risk of serious adverse consequences suggest that many high-risk patients undergoing major intraabdominal surgery will receive substantial benefit from combined general and epidural anesthesia intraoperatively with continuing postoperative epidural analgesia. We found no evidence that perioperative epidural analgesia significantly influences major morbidity or mortality after major abdominal surgery.

postoperative mortality and morbidity with epidural or spinal anesthesia: results from overview of randomized trials. BMJ 2000; 321: 1493–97

Objectives: To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anesthesia on postoperative morbidity and mortality.

Design: Systematic review of all trials with randomization to intraoperative neuraxial blockade or not.

Studies: 141 trials, including 9559 patients for which data were available before 1 January 1997. Trials were eligible irrespective of their primary aims, concomitant use of general anesthesia, publication status, or language. Trials were identified by extensive search methods, and substantial amounts of data were obtained or confirmed by correspondence with trialists.

Main outcome measures: All cause mortality, deep vein thrombosis, pulmonary embolism, myocardial infarction, transfusion requirements, pneumonia, other infections, respiratory depression, and renal failure.

Results Overall mortality was reduced by about a third in patients allocated to neuraxial blockade (103 deaths/4871 patients versus 144/4688 patients, odds ratio = 0.70, 95% confidence interval 0.54 to 0.90, P = 0.006). Neuraxial blockade reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59% (all P < 0.001).
There were also reductions in myocardial infarction and renal failure. Although there was limited power to assess subgroup effects, the proportional reductions in mortality did not clearly differ by surgical group, type of blockade (epidural or spinal), or in those trials in which neuraxial blockade was combined with general anesthesia compared with trials in which neuraxial blockade was used alone.

**Conclusions** Neuraxial blockade reduces postoperative mortality and other serious complications. The size of some of these benefits remains uncertain, and further research is required to determine whether these effects are due solely to benefits of neuraxial blockade or partly to avoidance of general anesthesia. Nevertheless, these findings support more widespread use of neuraxial blockade.

**Summary**

- Superior analgesic efficacy of regional anesthesia and benefits in terms of early mobilization, reduced pulmonary complications, DVT, persistent pain and length of hospital stay have been demonstrated.
- It still remains unclear whether regional anesthesia has a role in reducing major morbidity and mortality.
Management of Acute Post-thoracotomy Pain: Epidural versus Paravertebral block - What is the Current Choice?

Introduction
Thoracotomy is associated with severe postoperative pain and marked impairment of respiratory function. In comparison to other types of surgery, pain after thoracotomy is particularly intense and prolonged. Managing post thoracotomy pain is challenging since the acute postoperative pain management has to be optimal to allow good rehabilitation and also prevent development of incapacitating chronic pain. Epidural analgesia is considered to be the best method of pain relief and it is used routinely in many thoracic surgery centers. However, side-effects include respiratory depression, hypotension, urinary retention, incomplete (or failed) block, and, in rare cases, paraplegia. Techniques such as paravertebral blockade (PVB) may offer comparable effectiveness in terms of analgesia with
a better side-effect profile. Some authors consider PVB to be a valid alternative because it is simple, safe, easy to learn, and has a low incidence of complications.


**Introduction:** A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was: in patients undergoing thoracic surgery, is paravertebral block (PVB) as effective as epidural analgesia for pain management?

**Methods:** Altogether > 184 papers were found using the reported search, seven of which represented the best evidence to answer the clinical question. All studies agreed that PVB is at least as effective as epidural analgesia for pain control post-thoracotomy.

**Results:** In one paper, the visual analogue pain score (VAS) at rest and on cough was significantly lower in the paravertebral group ($P=0.02$ and $0.0001$, respectively). Pulmonary function, as assessed by peak expiratory flow rate (PEFR), was significantly better preserved in the paravertebral group. The lowest PEFR as a fraction of preoperative control was 0.73 in the paravertebral group in contrast with 0.54 in the epidural group ($P<0.004$). Oximetric recordings were better in the paravertebral group (96%) compared to the epidural group (95%) ($P=0.0001$). Another article reported that statistically significant differences (forced vital capacity
46.8% for PVB and 39.3% for epidural group \( P<0.05 \); forced expiratory volume in 1 s (FEV1) 48.4% in PVB group and 35.9% in epidural group, \( P<0.05 \) were reached in day 2 and continued until day 3. Plasma concentrations of cortisol, as marker of postoperative stress, increased markedly in both groups, but the increment was statistically different in favour of the paravertebral group (\( P=0.003 \)). Epidural block was associated with frequent side-effects urinary retention (42%), nausea (22%), itching (22%) and hypotension (3%) and, rarely, respiratory depression (0.07%). Additionally, it prolonged operative time and was associated with technical failure or displacement (8%). Epidurals were also related to a higher complication rate (atelectasis/pneumonia) compared to the PVB (2 vs. 0). PVB was found to be of equal efficacy to epidural anaesthesia, but with a favourable side effect profile, and lower complication rate.

**Conclusion:** The reduced rate of complications was most marked for pulmonary complications and was accompanied by quicker return to normal pulmonary function. We conclude that intercostal analgesia, in the form of PVB, can be at least as effective as epidural analgesia.


**Introduction:** Thoracotomy induces severe postoperative pain and impairment of pulmonary
function, and therefore regional analgesia has been intensively studied in this procedure. Thoracic epidural analgesia is commonly considered the “gold standard” in this setting; however, evaluation of the evidence is needed to assess the comparative benefits of alternative techniques, guide clinical practice and identify areas requiring further research.

**Methods:** In this systematic review of randomized trials we evaluated thoracic epidural, paravertebral, intrathecal, intercostal, and interpleural analgesic techniques, compared to each other and to systemic opioid analgesia, in adult thoracotomy. Postoperative pain, analgesic use, and complications were analyzed.

**Results:** Continuous paravertebral block was as effective as thoracic epidural analgesia with local anesthetic (LA) but was associated with a reduced incidence of hypotension. Paravertebral block reduced the incidence of pulmonary complications compared with systemic analgesia, whereas thoracic epidural analgesia did not. Thoracic epidural analgesia was superior to intrathecal and intercostal techniques, although these were superior to systemic analgesia; interpleural analgesia was inadequate.

**Conclusions:** Either thoracic epidural analgesia with LA plus opioid or continuous paravertebral block with LA can be recommended. Where these techniques are not possible, or are contraindicated, intrathecal opioid or intercostal nerve blocks are recommended despite insufficient duration of analgesia, which requires the use of supplementary systemic analgesia. Quantitative meta-analyses were limited by heterogeneity in study design,
and subject numbers were small. Further well designed studies are required to investigate the optimum components of the epidural solution and to rigorously evaluate the risks/benefits of continuous infusion paravertebral and intercostal techniques compared with thoracic epidural analgesia.

**Summary**

- Data emerging from recent studies as mentioned above suggest that paravertebral block is as effective in comparison to thoracic epidural analgesia for post thoracotomy pain, with better side effect profile.

- There are a few isolated reports of complications associated with paravertebral block.

- The decision to opt for a paravertebral block or a thoracic epidural analgesia should be based on risk/benefit ratio for the individual patient.
Acute postoperative pain management is a major medical challenge faced by the clinicians. Postoperative pain management by anaesthesiologists is developing over the past few decades and has evolved into acute pain services. Due to the use of more complex modalities like patient controlled analgesia and thoracic epidural techniques, the American Society of Anesthesiology (ASA; Task Force on Pain Management, Acute Pain Section, (2012) recommend that anesthesiologists provide leadership by integrating pain management practices into the various aspects of perioperative care. Untreated post surgical pain risks the development of persistent post surgical pain which may further increase the development of chronic pain. There is very little data to support whether a dedicated acute pain service (APS) really improves outcome measures in terms of pain relief, cost effectiveness and patient satisfaction.

This is a randomized, controlled clinical trial comparing the costs and effects of acute pain service care on clinical outcomes versus conventional pain management on the ward. Patients included in the trial were considered by their anesthesiologist to be suitable for either arm.

Methods: Four hundred twenty-three patients undergoing major elective surgery were randomized either to an anesthesiologist-led, nurse-based acute pain service group with patient controlled analgesia or to a control group with IM or IV boluses of opioid analgesia. Both groups were treated with medications to treat opioid-related adverse effects and received the usual care from health professionals assigned to the ward. The main outcome measures were quality of recovery scores, pain intensity measures, global measure of treatment effectiveness, and overall pain treatment cost. Cost-effectiveness acceptability curves were drawn to detect a difference in the joint cost-effect relationship between groups.

Results: There was no difference in quality of recovery score on postoperative day 1 between treatment and control groups (mean difference, 0; 95% confidence interval [CI], -0.7 to 0.7; P = 0.94) or in the rate of improvement in quality of recovery score (mean difference, -0.1; 95% CI, -0.4 to 0.1; P = 0.34). The proportion of patients with 1 or more days of highly effective pain management was higher in the acute pain
service group than in the control group (86% vs. 75%; \( P < 0.01 \)). Costs were higher in the acute pain service group (mean difference, US$46; 95% CI, $44 to $48 per patient; \( P < 0.001 \)). A cost-effectiveness acceptability curve showed that the acute pain service was more cost effective than was control for providing highly effective pain management if the decision maker was willing to pay more than US$546 per patient per 1 day with highly effective treatment.

**Conclusion:** In extending the role of the acute pain service to a specific group of major surgical procedures, the acute pain service was likely to be cost effective.


**Study Objective:** To analyze, from a societal perspective, the cost-effectiveness and cost-utility of acute pain management after inception of a nurse-based Acute Pain Service (APS) in a general hospital.

**Design:** Open, observational, interventional study.

**Setting:** Post anesthesia care unit and surgical wards of a university hospital center.

**Patients:** 1975 surgical in-patients who had undergone various types of surgery.

**Interventions:** Visual analog scale (VAS) pain scores and all systemic analgesics prescribed by anesthesiologists and administered by ward nurses were recorded before and after APS inception. All costs (drugs,
disposal, and working time of nurses) related to the APS were identified. Pain measurements were performed by VAS every 4 hours over 3 consecutive days post-surgery and transformed into a health state scale, with 0 being equivalent to absence of pain and 10 to the worst imaginable pain. Using these data, analgesic effectiveness (cost-utility analysis) was expressed as postoperative pain days averted (PPDA) in the two surveys. To perform the cost-effectiveness analysis, we focused on postoperative complications, duration of hospital stay, and postoperative mortality rate.

**Main Results:** VAS pain scores decreased in the post-APS phase (p < 0.001). One the first day, PPDA was 0.075, on the second day PPDA was 0.05, and the third day PPDA was 0.0375. Cost of analgesic drugs and disposal, as well as nursing hours, increased. The incremental cost of pain management after APS inception amounted to 19 EURO per patient per day, resulting in an incremental cost-effectiveness ratio of 350.77 EURO per PPDA gained. The cost-effectiveness analysis showed minor improvement (reduction of postoperative complication rate in some surgical specialties). Duration of hospital stay and postoperative mortality rate did not change.

**Conclusions:** A hospital-wide, comprehensive, postoperative pain management program provides an overall positive result for the health care system by improving postoperative pain and morbidity. This service is cost-effective, costing 19 EURO per patient per day. A cost-utility analysis for short-term assessment of quality
of life showed no benefit in determining usefulness of such a pain management program.


**Introduction:** Quality improvement approaches have been used to evaluate pain management. The purpose of this study was two-fold: to obtain a baseline data of incidence of severity of pain and patient’s level of satisfaction during postoperative period and also to evaluate the changes over time on pain severity, in pain interference with function, patient satisfaction, and time required to deliver the analgesics after implementation of pain protocols.

**Methods:** Two hundred patients were administered a questionnaire adapted from American Pain Society’s patient outcome questionnaire in a two-phased manner. One hundred patients were included in the survey during January 2004 and a year later a similar cohort of 100 were administered the same questionnaire to evaluate for changes in quality of postoperative management over time.

**Results:** This self-report survey found a significantly high patient satisfaction in the setting of significant postoperative pain. There is a statistically significant reduction in the severity of ‘average pain’ after implementation of pain protocols, however, it did not translate into improvement in the patient satisfaction.
Conclusion: The issue of patient satisfaction is complex and needs a systematic program recommended by American Pain society’s quality improvement guidelines.

Summary

- Current evidence for the role of acute pain service in improving perioperative outcomes is inadequate
- APS has a role in improving pain scores and in early rehabilitation
- APS is an essential part of an integrated multimodal rehabilitation programme
Introduction:
Surgical care is an integral component of health care throughout the world and it is estimated that more than 234 million operations are performed annually.\textsuperscript{1} The perioperative mortality rate varies from 0.4 to 0.8\% in developed countries, with major morbidity ranging from 3 to 17\% and these numbers are likely to be higher in developing countries.\textsuperscript{1} As part of its “Safe Surgery Saves Lives” campaign, the World Health Organization has undertaken a number of projects to promote perioperative patient safety.\textsuperscript{2} One of these initiatives has been to identify ten crucial steps in the perioperative process which are vital to patient safety, and which if implemented rigorously can change surgical outcomes. These ten measures have been incorporated into a surgical safety checklist which can be implemented in hospitals worldwide.\textsuperscript{2}
Implementation of the surgical safety checklist occurs at three phases during the peri-operative period: the **sign-in**, which takes place before the induction of anaesthesia, the **time-out**, which is carried out before the surgical incision and the **sign-out**, which is completed before the patient leave the operating room. At each of these stages, application of the checklist ensures that members of the operating team identify themselves, enumerate anticipated critical events and comply with procedures which can impact patient outcomes. Based on the WHO surgical safety checklist, other tools such as the SURPASS (Surgical Patient Safety System) which is a comprehensive, multidisciplinary surgical safety checklist including pre-, intra- and post-operative factors, have been developed.\(^3\)

**Review of literature:**
Several studies have looked at the impact of the WHO surgical safety checklist and other such tools on perioperative patient safety.


**Background:** Surgery has become an integral part of global health care, with an estimated 234 million operations performed yearly. Surgical complications are common and often preventable. We hypothesized that a program to implement a 19-item surgical safety checklist designed to improve team communication and
# Surgical Safety Checklist (First Edition)

## Before Induction of Anaesthesia

### Sign Out
- Patient has Confirmed
  - Identify
  - Site
  - Procedure
  - Consent
- Site Marked/Not Applicable
- Anaesthesia Safety Check Completed
- Pulse Oximeter on Patient and Functioning
  - Does Patient have A : Known Allergy?
    - No
    - Yes
  - Difficult Airway/Aspiration Risk
    - No
    - Yes, and Equipment/Assistance Available
  - Risk of >500ml blood loss (7ml/kg in Children)
    - No
    - Yes, and adequate intravenous access and fluids planned

## Before Skin Incision

### Time Out
- Confirm all Team Members have introduced themselves by Name and Role
- Surgeon, Anaesthesia Professional and Nurse verbally confirm
  - Patient
  - Site
  - Procedure
- Anticipated Critical Events
  - Surgeon Reviews: What are the critical or unexpected steps, Operative duration, anticipated blood loss?
  - Anaesthesia Team Reviews : Are there any patient-specific concerns?
  - Nursing Team Reviews: Has sterility (including indicator results) been confirmed? Are there equipment issues or any concerns?
- Has antibiotic prophylaxis been given within the last 60 minutes?
  - Yes
  - Not Applicable
- Is essential imaging displayed?
  - Yes
  - Not Applicable

## Before Patient Leaves Operating Room

### Sign Out
- Nurse verbally confirms with the team:
  - The Name of the procedure Recorded
  - That instrument, sponge and needle counts are correct (or not applicable)
  - How the specimen is labelled (including patient name)
  - Whether there are any equipment problems to be addressed
- Surgeon, Anaesthesia professional and nurse review the key concerns for recovery and management of this patient

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The checklist is not intended to be comprehensive. Additions and Modifications to fit LOCA: Practice are encouraged.
consistency of care would reduce complications and deaths associated with surgery.

**Methods**: Between October 2007 and September 2008, eight hospitals in eight cities (Toronto, Canada; New Delhi, India; Amman, Jordan; Auckland, New Zealand; Manila, Philippines; Ifakara, Tanzania; London, England; and Seattle, WA) representing a variety of economic circumstances and diverse populations of patients participated in the World Health Organization’s Safe Surgery Saves Lives program. We prospectively collected data on clinical processes and outcomes from 3733 consecutively enrolled patients 16 years of age or older who were undergoing noncardiac surgery. We subsequently collected data on 3955 consecutively enrolled patients after the introduction of the Surgical Safety Checklist. The primary end point was the rate of complications, including death, during hospitalization within the first 30 days after the operation.

**Results**: The rate of death was 1.5% before the checklist was introduced and declined to 0.8% afterward (P=0.003). Inpatient complications occurred in 11.0% of patients at baseline and in 7.0% after introduction of the checklist (P<0.001).

**Conclusions**: Implementation of the checklist was associated with concomitant reductions in the rates of death and complications among patients at least 16 years of age who were undergoing noncardiac surgery in a diverse group of hospitals.


**Background:** Adverse events in patients who have undergone surgery constitute a large proportion of iatrogenic illnesses. Most surgical safety interventions have focused on the operating room. Since more than half of all surgical errors occur outside the operating room, it is likely that a more substantial improvement in outcomes can be achieved by targeting the entire surgical pathway.

**Methods:** We examined the effects on patient outcomes of a comprehensive, multidisciplinary surgical safety checklist, including items such as medication, marking of the operative side, and use of postoperative instructions. The checklist was implemented in six hospitals with high standards of care. All complications occurring during admission were documented prospectively. We compared the rate of complications during a baseline period of 3 months with the rate during a 3-month period after implementation of the checklist, while accounting for potential confounders. Similar data were collected from a control group of five hospitals.

**Results:** In a comparison of 3760 patients observed before implementation of the checklist with 3820 patients observed after implementation, the total number of complications per 100 patients decreased from 27.3 (95% confidence interval [CI], 25.9 to 28.7) to 16.7 (95% CI, 15.6 to 17.9), for an absolute risk reduction of 10.6 (95% CI, 8.7 to 12.4). The proportion of patients with one or more complications decreased from 15.4%
to 10.6% (P<0.001). In-hospital mortality decreased from 1.5% (95% CI, 1.2 to 2.0) to 0.8% (95% CI, 0.6 to 1.1), for an absolute risk reduction of 0.7 percentage points (95% CI, 0.2 to 1.2). Outcomes did not change in the control hospitals.

**Conclusions:** Implementation of this comprehensive checklist was associated with a reduction in surgical complications and mortality in hospitals with a high standard of care.


The concept of using a checklist in surgical and anaesthetic practice was energized by publication of the WHO Surgical Safety Checklist in 2008. It was believed that by routinely checking common safety issues, and by better team communication and dynamics, perioperative morbidity and mortality could be improved. The magnitude of improvement demonstrated by the WHO pilot studies was surprising. These initial results have been confirmed by further detailed work demonstrating that surgical checklists, when properly implemented, can make a substantial difference to patient safety. However, introducing surgical checklists is not as straightforward as it seems, and requires leadership, flexibility, and teamwork in a different way to that which is currently practiced. Future work should be aimed at ensuring effective implementation of the WHO Surgical Safety Checklist, which will benefit our patients on a global scale.
Summary

- Safety checklists can have considerable positive impact on perioperative outcomes
- This effect is dependent on proper implementation of the checklist
- Good communication and teamwork are essential components of the checklist process

References

