Review

Clinical review: Evidence-based perioperative medicine?

Hanif Meeran[1] and Michael PW Grocott[2]

[1]Research Fellow, Centre for Anaesthesia, University College London, UK
[2]Research Fellow, Surgical Outcomes Research Centre, University College London Hospitals, UK

Corresponding author: Michael PW Grocott, mike.grocott@ucl.ac.uk

Published online: 19 August 2004
This article is online at http://ccforum.com/content/9/1/81

Critical Care 2005, **9**:81-85 (DOI 10.1186/cc2932)

Abstract

The present article outlines the basic principles of Evidence Based Medicine (EBM) and how they should guide clinical practice. The evidence supporting a selection of perioperative interventions is assessed against objective criteria. Many of the perioperative interventions that have been widely adopted into clinical practice are supported by very limited evidence. Conversely a high level of evidence supports other interventions that have not been so widely adopted. This may be due to concerns about limitations in the design and conduct of some of the clinical trials.

Keywords anaesthesia, evidence based medicine, perioperative, surgery

Introduction

The present article outlines the basic principles of evidence-based medicine (EBM) and how they should guide clinical practice. Criteria by which items of evidence are judged and the hierarchy of levels of evidence will be reviewed. The evidence supporting a selection of commonly discussed 'perioperative medicine' interventions will be presented and will then be assessed using these objective criteria. The physiological rationale and scientific basis for these interventions will not be discussed in detail.

Evidence-based medicine

EBM is "the integration of best research evidence with clinical expertise and patient values to optimise clinical outcomes and quality of life" [1]. There is often tension between empiricism and EBM: the 'knowledge' of practitioners gained from 'experience' may not agree with the results of an EBM approach to clinical practice [1]. As physicians we recognise that there is an element of art in the practice of medicine. We must also recognise, however, that data derived from rigorous clinical experiments should be more compelling than personal anecdote.

When considering preventative and therapeutic interventions a hierarchy of levels of evidence exists from the highest standard (systematic reviews and large randomised controlled trials [RCTs]), to the lowest level (consensus statements and expert opinion) (see Table 1 for levels of evidence in relation to therapeutic interventions). [2,3]. Clinical practice should, where possible, be guided by Level 1 evidence. In some cases, however, it is not possible to obtain this level of evidence for particular interventions; for example, when conducting the relevant trial would require excessive resources or would be considered unethical. In this situation the highest available standard of evidence should be used (see Table 1).

The well-conducted RCT is the most robust and reliable experimental methodology for comparing preventative and therapeutic clinical interventions. RCTs are designed to demonstrate that any observed differences in outcome between patients allocated to different interventions (A versus B, or A versus control) occur not simply as a result of chance, and that bias is minimised. To this end, RCT design frequently involves blinding of some or all of the involved parties (investigators, patients, carers) to allocation of treatment until after the study is complete. The aim of blinding is to reduce the risk of unrecognised bias being introduced by participants when they are aware of intervention allocation. A RCT is commonly held to be 'large' if it includes at least 1000 patients [4]; few studies in the perioperative setting come close to meeting this criterion.

EBM = evidence-based medicine; ICU = intensive care unit; RCT = randomised controlled trial.

Table 1

Levels of evidence for therapeutic interventions

Level of evidence		Therapy/prevention, aetiology/harm
1	A	Systematic review (with homogeneity*) of randomised controlled trials
	B	Individual randomised controlled trial (with narrow confidence interval)
	C	All or none
2	A	Systematic review (with homogeneity) of cohort studies
	B	Individual cohort study (including low-quality randomised controlled trial [e.g. < 80% follow-up])
	C	'Outcomes' research; ecological studies
3	A	Systematic review (with homogeneity*) of case–control studies
	B	Individual case–control study
4		Case series (and poor-quality cohort and case–control studies)
5		Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Modified from [http://www.cebm.net/levels_of_evidence.asp]. *By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.

Systematic reviews or overviews are an attempt to avoid the subjective approach of classical narrative review where authors use self-selected references to support an established argument. A well-conducted systematic review should have the following elements: a clearly framed question or objective, the use of an appropriate methodology to search for all relevant literature, and a systematic approach to study selection, assessment of study quality, data extraction and data analysis. Meta-analysis is the use of quantitative methods to summarise the results of a systematic review [5]. Systematic reviews have a useful role both in quantitative pooling of data using the techniques of meta-analysis and by providing qualitative summaries of original reports in a specific area.

Objective methods exist for quality assessment of studies [6,7], and this is an important element of the systematic review process. The old adage 'rubbish in, rubbish out' succinctly summarises the futility of performing a meta-analysis of poor quality studies and then imbuing the summary statistic with any significance. The inclusion of 'poor quality' studies may bias the results of systematic reviews [6].

Heterogeneity reduces the validity of the result of a systematic review. This heterogeneity can be clinical (e.g. variations in the intervention or setting) or can be statistical (e.g. variations in the outcomes suggesting that the studies may not having been addressing the same question) [5]. Evidence of heterogeneity suggests that it may be inappropriate to group together the selected studies.

When assessing preventative or therapeutic interventions the best evidence may be provided by a systematic review of all relevant RCTs. However a systematic review of older, smaller or weaker studies, or demonstrating significant heterogeneity, may be inferior to a large well conducted and generisable RCT.

Founded in 1993, the Cochrane Collaboration is an international, independent, nonprofit organisation that produces and disseminates systematic reviews of healthcare interventions, and promotes the search for evidence in the form of clinical trials and other studies of interventions (http://www.cochrane.org/index0.htm). The major product of the collaboration is the Cochrane Database of Systematic Reviews, published quarterly as part of the Cochrane Library (http://www.cochrane.org/reviews/clibintro.htm). The Cochrane Anaesthesia Review Group (http://www.cochrane-anaesthesia.suite.dk/) is one of the many subject-specific collaborative review groups affiliated to the Cochrane Collaboration, and includes within its scope anaesthesia, perioperative medicine, intensive care medicine, prehospital medicine, and resuscitation and emergency medicine. Reviews conducted under the auspices of the Cochrane Collaboration use a clearly defined methodology, and external peer review is integral to each stage of the review process.

Meta-analyses may be subject to bias in the same way as individual RCTs. Publication bias, English-language bias, citation bias, multiple publication bias, database bias and study inclusion bias are recognised and are covered in detail elsewhere [8]. Specific tests for assessing bias are available (e.g. Funnel plot for publication bias) [9,10]. Reviews published by the Cochrane Collaboration seem to show less evidence of bias (13% versus 38% of reviews studied) than systematic reviews selected at random from major journals [9].

Large RCTs and systematic reviews may disagree, and this occurs at a rate greater than chance alone would predict.

Table 2

Comparison of evidence available for a selection of commonly discussed perioperative interventions

Intervention	Cochrane systematic review	Systematic review	Large randomised controlled trial	Randomised controlled trial	Level 1 evidence (mortality)
Optimisation	1	2	1	>10	Yes (systematic review)
Beta-blockade	0	0	0	3	Yes (small randomised controlled trial only)
Regional anaesthesia	3	>10	0	>10	Yes (systematic review)
Enteral nutrition	0	2	0	>10	No
High O_2	0	0	0	2	No
Normothermia	0	0	0	4	No
Critical care	0	0	0	0	No

When both the magnitude and uncertainty of treatment effects were considered, large trials disagreed with meta-analyses in 10–23% of cases [4].

Perioperative interventions and EBM?

We have chosen to consider a subjectively generated list of perioperative interventions commonly considered to be elements of the practice of the anaesthetist or the perioperative physician. For each intervention we describe the extent of the supporting literature (RCTs and systematic reviews), the level of evidence and the outcome supported (mortality, length of stay, morbidity). We have searched PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed), the Cochrane Library (http://www.cochrane.org/reviews/clibintro.htm) and the internet based "Evidence-based Perioperative Medicine" resource (http://www.hcuge.ch/anesthesie/anglais/evidence/arevusyst.htm) for systematic reviews and RCTs. Where there are more than 10 RCTs addressing a particular question we have not listed them separately.

Table 2 summarises the evidence (RCTs and systematic reviews) supporting each listed intervention. However due to limitations in the design and conduct of these studies there is considerable controversy amongst professionals that care for patients in the perioperative setting as to whether some of these interventions are as effective as the data suggest.

'Optimisation'

The observation that patients who survive major surgery have elevated cardiac output and oxygen delivery values led to the development of goal-directed therapy, otherwise known as haemodynamic optimisation. Cardiac output and oxygen delivery are augmented by the administration of intravenous fluids, with or without the addition of inotropic agents such as dobutamine or dopexamine. A treatment algorithm guided by haemodynamic monitoring drives therapy. Treatment goals are often supranormal values of blood-flow-related variables (e.g. cardiac index, oxygen delivery, stroke volume).

Two systematic reviews with meta-analyses studying this strategy in the perioperative setting have concluded that mortality is reduced using this approach [11,12]. The first review showed a significant reduction in mortality if therapy was initiated preoperatively (two trials, 195 patients). The second review of 21 trials (13 perioperative trials, >1008 patients) revealed significant mortality reduction when patients were treated before the development of organ failure, when there were control group mortalities >20% and when therapy produced differences in oxygen delivery between the control and protocol groups [12]. An additional systematic review of perioperative fluid volume optimisation following proximal femoral fracture (two studies, 130 patients) showed a reduction in the hospital length of stay in the intervention group [13]. However, a recent large perioperative RCT failed to show any benefit [14]. The large RCT has been criticised on a number of design and conduct issues, and the systematic reviews exhibit significant heterogeneity. This is a good example of a large RCT producing a different result from previous systematic reviews.

Beta-adrenergic receptor blockade

Cardiovascular disease is an important cause of perioperative morbidity and mortality. This is thought to be due to sympathetic over-activity increasing heart rate, myocardial workload and the incidence of arrhythmias. Perioperative blockade of beta-adrenergic receptors may be protective against cardiovascular complications such as myocardial infarction and arrhythmias, and therefore may reduce mortality.

Three (small) randomised trials examined the use of beta-blockers in surgical patients with known or suspected coronary disease [15–17]. Two of these trials demonstrated a significant reduction in mortality in the intervention group. However, one study (200 patients undergoing elective major noncardiac surgery) stopped beta-blockers prior to surgery in patients in the control group who were already taking them, and this is inconsistent with current guidelines [15]. In the other study (112 patients presenting for elective major

vascular surgery), patients were preselected on the basis of positive dobutamine stress echocardiograms from an initial cohort of 1351 patients, which makes it difficult to generalise these data to a population not selected in this manner [16]. In the third study (107 patients undergoing elective knee arthroplasty), a reduced prevalence and duration of postoperative myocardial ischaemia detected with Holter monitoring was demonstrated [17].

There are no large RCTs (>1000 patients) or systematic reviews that demonstrate the effect of this intervention on mortality. Nonetheless, the results of these small studies suggest that perioperative beta-blockade improves outcome in patients with known or suspected heart disease. The American College of Cardiology and American Heart Association guidelines now recommend this strategy [18]. A large international RCT is currently being conducted to test the hypothesis that perioperative administration of beta-adrenergic blockers in patients with risk factors for ischaemic heart disease reduces mortality (the 'POISE' study).

Regional anaesthesia/analgesia

Improved postoperative pain relief is important for patient comfort and may decrease the hospital stay and lead to reductions in morbidity. Improved blood flow consequent on sympatholysis has additional potential benefits, including a reduction in thromboembolic complications and improved gastrointestinal function.

A large number of RCTs in this area have been summarised in several systematic reviews with meta-analysis. Pooled analysis of 141 randomised trials involving a total of 9559 patients revealed a 30% reduction in mortality associated with neuraxial blockade and significant reductions in thromboembolic and respiratory complications [19]. Pain relief with epidural analgesia with local anaesthetic agents has been demonstrated to be superior to parenteral opioids alone in a meta-analysis of 100 studies [20]. Regional anaesthesia for hip fracture surgery when compared with general anaesthesia produced comparable results for most of the outcomes studied (16 trials, 2191 patients). Regional anaesthesia may have reduced short-term mortality, but no conclusions could be drawn for longer-term mortality [21]. For hip and knee replacement surgery short-term postoperative pain relief was improved with regional anaesthesia but minor complications were more frequent, and there were insufficient data to draw conclusions on the frequency of rare complications from epidural analgesia, postoperative morbidity or mortality, functional outcomes, or length of hospital stay [22]. Following abdominal surgery, the time to return of gastrointestinal function was reduced with epidural anaesthesia but there were insufficient data to comment on mortality [23].

Nutrition

The concept that improving nutritional status and minimising catabolism will improve perioperative outcome has been tested in a large number of RCTs, and two systematic reviews have addressed questions in this area. A systematic review of 11 studies with 837 patients demonstrated that early enteral feeding postoperatively after gastrointestinal surgery reduced infection rates and the length of stay but did not significantly reduce mortality [24]. When compared with enteral nutrition, total parenteral nutrition does not influence the death rate of surgical patients, but may reduce the complication rate, especially in malnourished patients [25].

Supplemental oxygen therapy

The bactericidal activity of neutrophils is mediated by oxidative killing by the production of superoxide radicals, the rate of generation of which is proportional to the partial pressure of oxygen. At surgical wound sites this is likely to be low due to disrupted vascular supply and decreased blood flow perioperatively. Resistance to infection may be enhanced by the administration of supplemental oxygen to increase tissue oxygenation and augment neutrophil function. A moderate-sized randomised trial (500 patients undergoing elective general surgery) in which 30% or 80% oxygen was administered perioperatively demonstrated a reduction in wound infection in the higher FiO_2 group [26]. However, a more recent small study of similar design found an increase in infection in those administered the higher FiO_2 [27]. There are no RCTs or systematic reviews that demonstrate a beneficial effect of this intervention on mortality.

Maintenance of normothermia

Inhibition of physiological temperature control mechanisms, peripheral redistribution of body heat during general anaesthesia and the cool operating room environment contribute to perioperative hypothermia. Immune cell function becomes impaired as a consequence of low tissue oxygenation and hypothermia. Temperature reduction also has an adverse effect on collagen deposition. These factors have an unfavourable effect on surgical wound healing.

Four small to moderate-sized clinical studies (60–300 patients) have compared active warming (normothermia) with the standard of care (resulting in mild hypothermia) [28–31]. In 200 patients undergoing elective colorectal surgery, those randomised to receive active warming had a reduced incidence of wound infection [29]. In 60 patients undergoing primary hip arthroplasties, the postoperative blood loss and transfusion requirements were significantly greater in the hypothermic patients [31]. In 300 patients undergoing abdominal, thoracic or vascular surgical procedures with documented coronary artery disease, or risk factors for coronary disease, perioperative cardiac events and ventricular tachycardia occurred less frequently in the normothermic group [28]. In 150 patients undergoing elective major abdominal surgery, a decreased duration of postanaesthetic recovery was observed in the normothermic group [30]. There are no RCTs or systematic reviews that demonstrate a beneficial effect of this intervention on mortality.

Critical care provision

Differences in case-mix-adjusted mortality have been noted between countries where levels of critical care provision differ [32].

In a systematic review of 27 studies, high-intensity ICU physician staffing versus low-intensity ICU physician staffing was associated with reduced hospital and ICU mortality and with reduced hospital and ICU length of stay [33]. No RCTs (large or small) or systematic reviews exist to test the hypothesis that critical provision postoperatively reduces mortality.

Conclusions

Many of the perioperative interventions that have been widely adopted into clinical practice are supported by very limited evidence. For a number of interventions the data are either limited in quantity or quality, or are inconsistent. Systematic reviews are no better than the studies that they bring together, and those that include many small studies are often limited by problems of heterogeneity. Systematic reviews should be conducted with the same methodological rigour expected for RCTs. Systematic reviews conducted under the auspices of the Cochrane Collaboration have an established methodology and peer review process, and they may be less prone to bias than non-Cochrane systematic reviews.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS: **Evidence based medicine: what it is and what it isn't.** *BMJ* 1996, **312:**71-72.
2. Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S: **Grades of recommendation for antithrombotic agents.** *Chest* 1998, **114(Suppl):**441S-444S.
3. *Levels of Evidence and Grades of Recommendation [electronic citation].* Oxford: Oxford Centre for Evidence-Based Medicine; 2004 [http://www.cebm.net/levels_of_evidence.asp#levels].
4. Ioannidis JP, Cappelleri JC, Lau J: **Issues in comparisons between meta-analyses and large trials.** *JAMA* 1998, **279:** 1089-1093.
5. Egger M, Smith GD, Phillips AN: **Meta-analysis: principles and procedures.** *BMJ* 1997, **315:**1533-1537.
6. Schulz KF, Chalmers I, Hayes RJ, Altman DG: **Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials.** *JAMA* 1995, **273:**408-412.
7. Juni P, Altman DG, Egger M: **Systematic reviews in health care: assessing the quality of controlled clinical trials.** *BMJ* 2001, **323:**42-46.
8. Egger M, Smith GD: **Bias in location and selection of studies.** *BMJ* 1998, **316:**61-66.
9. Egger M, Davey SG, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ* 1997, **315:** 629-634.
10. Sterne JA, Egger M, Smith GD: **Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis.** *BMJ* 2001, **323:**101-105.
11. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C: **Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence.** *Crit Care Med* 1996, **24:**517-524.
12. Kern JW, Shoemaker WC: **Meta-analysis of hemodynamic optimization in high-risk patients.** *Crit Care Med* 2002, **30:**1686-1692.
13. Price J, Sear J, Venn R: **Perioperative fluid volume optimization following proximal femoral fracture.** *Cochrane Database Syst Rev* 2002, **1:**CD003004.
14. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, *et al.*: **A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients.** *N Engl J Med* 2003, **348:**5-14.
15. Mangano DT, Layug EL, Wallace A, Tateo I: **Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia.** *N Engl J Med* 1996, **335:**1713-1720.
16. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, *et al.*: **The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress.** *N Engl J Med* 1999, **341:**1789-1794.
17. Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P: **Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia.** *Anesth Analg* 2000, **90:**1257-1261.
18. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, *et al.*: **ACC/AHA guideline update for perioperative cardiovascular evaluation.** *Anesth Analg* 2002, **94:**1052-1064.
19. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, *et al.*: **Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials.** *BMJ* 2000, **321:**1493-1497.
20. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr, Wu CL: **Efficacy of postoperative epidural analgesia: a meta-analysis.** *JAMA* 2003, **290:**2455-2463.
21. Parker MJ, Urwin SC, Handoll HH, Griffiths R: **General versus spinal/epidural anaesthesia for surgery for hip fractures in adults.** *Cochrane Database Syst Rev* 2000, **2:**CD000521.
22. Choi PT, Bhandari M, Scott J, Douketis J: **Epidural analgesia for pain relief following hip or knee replacement.** *Cochrane Database Syst Rev* 2003, **3:**CD003071.
23. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB: **Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after.** *Cochrane Database Syst Rev* 2000, **4:**CD001893.
24. Lewis SJ, Egger M, Sylvester PA, Thomas S: **Early enteral feeding versus 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials.** *BMJ* 2001, **323:**773-776.
25. Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW: **Total parenteral nutrition in the surgical patient: a meta-analysis.** *Can J Surg* 2001, **44:**102-111.
26. Greif R, Akca O, Horn EP, Kurz A, Sessler DI: **Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group.** *N Engl J Med* 2000, **342:**161-167.
27. Pryor KO, Fahey TJ, III, Lien CA, Goldstein PA: **Surgical site infection and the routine use of perioperative hyperoxia.** *JAMA* 2004, **291:**79-87.
28. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C: **Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial.** *JAMA* 1997, **277:**1127-1134.
29. Kurz A, Sessler DI, Lenhardt R: **Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group.** *N Engl J Med* 1996, **334:**1209-1215.
30. Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F: **Mild intraoperative hypothermia prolongs postanesthetic recovery.** *Anesthesiology* 1997, **87:**1318-1323.
31. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A: **Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty.** *Lancet* 1996, **347:**289-292.
32. Bennett-Guerrero E, Hyam JA, Shaefi S, Prytherch DR, Sutton GL, Weaver PC, Mythen MG, Grocott MP, Parides MK: **Comparison of P-POSSUM risk-adjusted mortality rates after surgery between patients in the USA and the UK.** *Br J Surg* 2003, **90:**1593-1598.
33. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL: **Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review.** *JAMA* 2002, **288:** 2151-2162.