



Preface

During recent decades, anaesthesiologists in clinical practice have been facing an increasing amount of work. Not only do we have to increase effectivity and efficacy—duties involving teaching and quality assurance take up more and more of our time. It becomes increasingly difficult to keep up to date with new developments within our specific fields and areas of interest and practice. Every year more than 2 million articles are published in biomedical journals.

The concept of evidence-based medicine should be seen as an aid to the clinical practitioner by condensing medical knowledge into focused systematic reviews of high quality.

Working with evidence-based medicine means (1) framing clinically relevant questions, (2) performing a comprehensive search, (3) evaluating search results, (4) synthesising results into either systematic reviews, clinical guideline or likewise for other clinicians to use, and (5) evaluating the process—always striving to optimise methods to make results more reliable.

The aim of this issue of Best Practice and Research is to give the practising anaesthesiologist or trainee a tool to get updated on the current best evidence within some areas of clinical anaesthesia.

The authors which have contributed to this issue are all familiar with the principles of conducting evidence-based medicine. The first chapter deals with preoperative evaluation. Though evidence within this area is scarce, Dr Solca has managed to produce a very instructive review of what is known and what is not. The next chapter is about reducing the risk of postoperative complications by intervening on the patients' lifestyle—in this case smoking habits. This is an area where research has just recently begun, but seems very promising. With proper implementation lifestyle intervention may well reduce both complications and suffering, and maybe even reduce health care expenses. The next three chapters deal with common areas of anaesthesia, where many controversies have been debated lately. The three authors give their points of view on regional versus general anaesthesia, fluid therapy and perioperative beta blockade. Acupuncture has been used for anaesthesia purposes in China for centuries. Recently, Western countries have opened up a little for the use of acupuncture in relation to anaesthesia. Anne Lee gives us an update on what is evidence based and what is not. Dr Lars Rasmussen has reviewed the problems of postoperative cognitive dysfunction and Dr Heidegger has written a chapter on patient satisfaction.

Finally, Dr Pedersen has written a very interesting chapter on the impact of evidence based medicine on organisation and economics in health care. I hope that

the readers will find the chapters in this issue both interesting and useful in their clinical practice.

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I

Evidence-based preoperative evaluation

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Preoperative assessment is a complex and multidisciplinary task. It encompasses surgical and anaesthesia assessment, preoperative testing, preparation of patients for surgery, and obtaining consent to the surgery. The scope of this chapter is to review the available evidence on anaesthesia preoperative evaluation (who, when and how to conduct it) and its relevance to clinical practice, and to indicate areas for future research.

Key words: preoperative care; anaesthesia evaluation.

Preoperative evaluation or assessment is an extremely large and complex field, leading to a vast medical literature and clinical guidance documents. Accessing the US National Library of Medicine online database¹ with a very simple search query for 'preoperative assessment' yields a very large number of papers: 10,576 overall, 7573 restricting the search to the field Title/Abstract, and 4836 limiting the search to the last 10 years. Even looking solely at reviews, the numbers are impressive: 1429, 1004, and 720, respectively. The search strategy is not very efficient, as it retrieves a number of papers whose main message is not exactly relevant to this chapter's topic, but the figures above testify to the importance of the topic.

One can assume, from such a large base of knowledge, that solid evidence might be available; unfortunately, this is not the case, and we are still left with a great deal of uncertainty on the subject. This is very likely due to the complexity of the subject, as it encompasses multiple professional involvements: nursing, anaesthesiology, different surgical specialties, laboratory medicine, and sometimes cardiology, pulmonology, radiology, etc. We will limit this chapter to the anaesthesia preoperative evaluation for elective procedures, defined as 'the process of clinical assessment that precedes the delivery of anaesthesia care for surgery and for non-surgical procedures'.² Furthermore, this chapter is not intended to be another systematic review of original

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research, but published evidence-based literature (systematic reviews, meta-analyses, clinical practice guidelines, health technology assessments) has been revised using the methodology of the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.³

Interest in the topic arose in the 1980s, albeit with a strong accent on patient safety and concern about rising costs of health services and limitation of available resources, both in the United States⁴⁻⁶ and in Europe.⁷⁻⁹ Toward the mid 1990s attention shifted to the appropriateness of the service provided to patients, and a number of health technology assessments appeared in the literature¹⁰⁻¹² with the main intention of increasing the cost-benefit ratio of ordering, and performing, preoperative testing of patients, and avoiding inappropriate exposure of patients to the hazards of false-positive or -negative results of useless tests. At the same time, many national anaesthesia societies published clinical guidelines^{2,13-17} in order to help fellow anaesthesiologists improve their practice through the application of evidence-based criteria in performing preoperative patients' assessment, a very important part of perioperative care and key to the successful, uneventful and streamlined management of patients.

All guidelines concur in advising that anaesthesia preoperative evaluation should be performed, even though not a single paper exists in the literature exploring systematic avoidance of such an evaluation versus performing it (as is the standard throughout the world). Probably the fact is that not performing the evaluation would expose anaesthesiologists to legal and contractual issues. In contrast, the question of how and when it should be performed, and by whom, remains totally open.

Properly trained nurses within anaesthesia departments are probably invaluable in performing at least a consistent portion of the evaluation¹⁸⁻²⁰, particularly in the psychological preparation for surgery.²¹ Primary care physicians are also ideally placed to be involved in the preoperative assessment of their patients²², relieving anaesthesia departments of a heavy burden. However, every anaesthesiological society recommends that an anaesthesiologist should at least conclude this process.^{2,12-17}

Assessment of patients should consist of review of available medical records, patient interview(s) and history collection, and physical examination which should include airway, pulmonary (including auscultation of the lungs), and cardiovascular examination.² Assessment of anaesthesia history can be facilitated by a structured, ad hoc questionnaire²³; its use is strongly encouraged by the Italian¹⁴ and British¹⁶ society guidelines.

There is no evidence of any influence of the timing of anaesthesia evaluation (performed either before or on the day of surgery) on outcome of anaesthesia. In clinical practice, the timing is influenced by customs, professional habits, regulations (for instance, in France it has to be performed at least the day before surgery), and type of practice (prevalence of day surgery, which strongly favours assessment on the day of surgery). It is generally recommended^{2,16} that the timing would be at minimum influenced by the invasiveness, and hence the risk, of the surgical procedure.

Only after the assessment of the patient should preoperative tests be ordered, and then only those relevant to the particular case.²⁴⁻²⁶ In the United Kingdom the National Institute for Clinical Excellence (NICE) very recently published an exhaustive evaluation of the available evidence on the subject.²⁷ It is suggested that in preoperative test ordering anaesthesiologists keep in consideration the patient's age, physical status

Table 1. American society of anesthesiologists (ASA) physical status classification.

1	A normal healthy patient
2	A patient with mild systemic disease
3	A patient with severe systemic disease
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive without the operation
6	A declared brain-dead patient whose organs are being removed for donor purposes

Adapted from ASA (2005, *Relative Value Guide*. <http://www.asahq.org/clinical/physicalstatus.htm>) with permission.

(Table 1), extent of the planned procedure (Table 2), and presence of comorbidity (particularly from cardiovascular, respiratory and renal disease).

Comorbidity, particularly from cardiovascular disease, is a great concern to the clinical anaesthesiologist, leading to the preparation of specific recommendations.²⁸ However, any coexisting disease or alteration of health status (e.g. acute respiratory illness) should be carefully evaluated in order to assure the maximum safety for the patient with the minimum disruption of surgical activity.^{2,12–17} Different age groups, and particularly children, need specific attention. If there is little available evidence for adult preoperative evaluation, even less can be found on paediatric settings.^{14,29}

The abridged version of the NICE guidance³⁰ presents possible combinations of the four dimensions (patient age, physical status, grade of surgery and coexisting disease) as a series of tables in which appropriateness of a number of tests (plain chest radiograph; resting electrocardiogram; full blood count; haemostasis—including prothrombin time, activated partial thromboplastin time and international normalized ratio; renal function—including tests for potassium, sodium, creatinine and/or urea levels; random blood glucose; urine dipstick tests—for pH, protein, glucose, ketones, blood/haemoglobin; blood gases; lung function—peak expiratory flow rate, forced vital

Table 2. Classification of surgical interventions in different intensity (and risk) categories; some examples for each category.

Grade 1 (minor)	Excision of lesion of skin; drainage of breast abscess; carpal tunnel release; nasal septum correction
Grade 2 (intermediate)	Primary repair of inguinal hernia; excision of varicose vein(s) of leg; tonsillectomy/adenotonsillectomy; knee arthroscopy; endoscopic bladder procedures; eye lens substitution
Grade 3 (major)	Total abdominal hysterectomy; endoscopic resection of prostate; lumbar discectomy; thyroidectomy; diaphragmatic hernia repair; operations on trachea; prosthetic femora head replacement
Grade 4 (major +)	Total joint replacement; lung operations; colonic resection; radical neck dissection; organ transplantation

Neurosurgery

Cardiovascular surgery

Adapted from National Institute for Clinical Excellence (2003, *Preoperative Tests. The use of routine preoperative tests for elective surgery. Appendices, Guidelines and Information* http://www.nice.org.uk/pdf/PreopTests_Apps.pdf) with permission.

capacity and forced expiratory volume) is evidenced, using the metaphor of the traffic light. The document is very compact, and is of invaluable help not only to the individual anaesthesiologist but also in preparing clinical pathways for categories of patients and of type of surgery, an approach to the preoperative evaluation which is favoured by a number of anaesthesia societies^{2,14–16} in order to assure consistency and quality control to the process.

Practice points

- all patients subject to anaesthesia should undergo anaesthesia preoperative evaluation
- patient assessment should consist of review of available medical records, patient's interview(s), physical examination, and necessary additional testing
- any assessment should be concluded by an anaesthetist, but initial screening—and in many cases most of a patient's work-up— could be conducted by nurses or primary care physicians
- the ideal timing of the assessment is not defined; however, it should be performed earlier in the process when the patient is more compromised and/or the procedure more invasive, in order to allow time for further necessary investigations
- additional tests should be ordered, weighing the benefits of obtaining more detailed information about the health status of a single patient against the cost of performing the tests and the potential harm stemming from false-negative or false-positive results; in any case the extent of additional testing should be guided by the patient's age, physical status and comorbidity, and by the invasiveness of the planned procedure

Research agenda

- the value of the participation of nurses and primary care physicians in the process of preoperative assessment should be better defined
- further investigation is needed in defining the ideal timing of patient assessment
- ways for better decision-making in ordering additional tests should be investigated, in order to reach a viable algorithm for the preparation of correct clinical pathways for specific patient age groups and surgery class groups

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Risk reduction: Perioperative smoking intervention

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Smoking is a well-known risk factor for perioperative complications. Smokers experience an increased incidence of respiratory complications during anaesthesia and an increased risk of postoperative cardiopulmonary complications, infections and impaired wound healing. Smokers have a greater risk of postoperative intensive care admission. Even passive smoking is associated with increased risk at operation. Preoperative smoking intervention 6–8 weeks before surgery can reduce the complications risk significantly. Four weeks of abstinence from smoking seems to improve wound healing. An intensive, individual approach to smoking intervention results in a significantly better postoperative outcome. Future research should focus upon the effect of a shorter period of preoperative smoking cessation. All smokers admitted for surgery should be informed of the increased risk, recommended preoperative smoking cessation, and offered a smoking intervention programme whenever possible.

Key words: smoking intervention; surgery; operation; risk reduction; postoperative complications; impaired wound healing; smoking cessation.

Smoking is known to be a significant risk factor for perioperative morbidity.¹ About one third of the patients presenting for surgery are smokers, although the proportion of smokers in the general population of Western countries is lower and declining by about 1% per year. Cigarette smoke contains more than 1000 components with wide-ranging effects on pulmonary, cardiovascular, and immune functions, healing of wounds and bones, haemostasis, drug metabolism and patient psychology, all of which influence the outcome after operations. Smokers have increased rates of postoperative

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complications and increased risk of postoperative intensive care admission.² Cessation of smoking would be an obvious step for risk reduction. The preoperative period seems to be a suitable time for smoking intervention, with effects on postoperative complication rates and patients' smoking habits.³

The aim of the current review is to describe the effects of smoking on organ systems and on the development of clinical complications, as well as the effects of preoperative smoking interventions.

CARDIOPULMONARY FUNCTION

The relationship between smoking and postoperative pulmonary complications (PPC) was first described by Morton in 1944.⁴ In a retrospective trial, Morton studied the incidence of PPC in abdominal surgery and found a six-fold increase in the risk of bronchitis, bronchopneumonia and atelectasis in smokers who smoked more than 10 cigarettes a day. Wightman⁵ found an overall incidence of 6.2% of PPC in a general surgical population, significantly more frequent in smokers (14.8%) compared to non-smokers (6.3%). The increased incidence of postoperative pulmonary complications in smokers has been shown many times since then. The topic has recently been reviewed by Moores.⁶

The effects of smoking on the respiratory system are mainly on ciliary function, mucus hypersecretion, changed mucus rheology, and narrowing of the small airways. Ciliary function is decreased in smokers. In vitro experiments show that ciliary movement stops or slows down significantly when exposed to cigarette smoke.⁷⁻¹² Smoke also changes the composition of tracheal mucus. Mucus rheology is important for ciliary function and the ability of the trachea to clear the fluids, and changes in the mucus composition will slow transportation of mucus from the lungs.^{11,13-15} As a net effect, smoking leads to a decrease in mucociliary transport.

Small airway narrowing is seen even in young, otherwise healthy smokers.¹⁶ Smokers with normal gross spirometry may still have significant small airway disease¹⁷, specifically in closing capacity.¹⁸⁻²⁰ Other effects of smoking on the respiratory system are an increase in non-specific bronchial reactivity^{21,22}, an increase in pulmonary epithelial permeability²³, and alteration in pulmonary surfactant.^{24,25}

Smokers experience an increased incidence of respiratory complications during anaesthesia and after operations due to multiple defects.

The pulmonary dysfunction is reversible to some degree after cessation of smoking; however, the time for the reversibility seems longer than for other smoking-related organ dysfunctions.

The effects of smoking on the cardiovascular system can be divided in short-term and long-term effects. The short-term effects are due mainly to the content of carbon monoxide (CO) and nicotine in tobacco smoke. The two major effects of CO-haemoglobin are a decrease in oxygen binding capacity, resulting in a reduced oxygen content and a shift of the oxygen dissociation curve to the left.²⁶ Both effects result in a decrease in oxygen delivery to the tissues. The myocardium is specifically sensitive to a high CO-haemoglobin rate, due to the high O₂ extraction rate in these cells²⁷ and the negative inotropic effect exerted by CO.²⁷ Smokers tend to compensate for the decline in oxygen concentration by increasing the amount of red blood cells, thus bringing the overall oxygen content up to normal. This, however, is at the expense of an increase in blood viscosity, a decrease in tissue perfusion, and an increase in the risk

of thrombosis.²⁸ Nicotine increases the sympathetic nervous system, thereby increasing heart rate, blood pressure and peripheral vasoconstriction.²⁹ The net effect of CO and nicotine is a decrease in oxygen delivery combined with an increase in oxygen consumption, so that smokers suffer from varying degrees of oxygen deficit and hypoxaemia. The effects of CO and nicotine are short-term, and recede within 24–48 hours after cessation of smoking.^{1,30}

The long-term effects of smoking on the cardiovascular system are accelerated atherosclerosis³¹, an increased risk of vasospastic angina³², and sudden cardiovascular death.³³ Smokers suffering from myocardial infarction or cardiac death are younger, have fewer cardiac risk factors and less severe underlying cardiac disease compared to non-smokers.

IMMUNE SYSTEM

Active and passive smoking both increase the risk of infection. Cigarette smoking affects the immune response in many ways.³⁴ Cigarette smokers exhibit impaired natural killer cytotoxic activity in peripheral blood and unbalanced systemic production of pro- and anti-inflammatory cytokines.^{35,36} White cell count is generally increased.^{37,38} These changes may be predisposing factors for respiratory and systemic infections in the postoperative period³⁹, bacterial as well as viral.⁴⁰ Immunoglobulin levels are influenced by smoking.⁴¹ Mean IgC and IgM have been shown to be lower, whereas IgE levels are increased. The effects are superimposed by the immune system suppression effect of anaesthesia and surgery itself.⁴² Some evidence indicates that at least parts of the immune response will be normalized by 6 weeks after cessation of smoking.³⁴

TISSUE HEALING

The most frequent complications over-represented in smokers are those related to tissue-healing problems. The increased incidence is probably caused by a combination of the effects of smoking on the vascular system⁴³, the effect on the healing process⁴⁴, and the impaired immune system seen in smokers.^{34,39} The effect of smoking on wound healing was first described by Mosely and Finseth⁴⁵ who in 1977 described the impaired healing of a hand wound in a smoker with arteriosclerosis.

Nicotine inhibits the proliferation of red blood cells, fibroblasts and macrophages⁴⁶, all of which must be present in order to heal injured tissue. Nicotine has also been associated with increased platelet adhesiveness, which causes micro-clots and decreases microperfusion.⁴⁵ This eventually leads to clot formation and reduced blood flow.⁴⁷ Finally, nicotine produces cutaneous vasoconstriction because of the release of catecholamine.⁴⁸ The overall effect of CO is decreased tissue oxygenation (see above). Hydrogen cyanide, another constituent of cigarette smoke, is responsible for impaired enzyme formation.⁴⁵ The enzyme systems are necessary for oxidative metabolism and oxygen transport at the cellular level. Another factor influencing the healing process is collagen production, which is significantly reduced in smokers.⁴⁴ Mature collagen is the main determinant of strength of an operative wound.

Several studies have shown that smokers have increased wound problems. Siana et al performed a controlled study of 120 women undergoing laparotomy sterilization⁴⁹ and found that scarring was unsatisfactory in 25% of the smokers compared to none of

the non-smokers. Manassa et al⁵⁰ retrospectively analysed 132 cases of abdominoplasty and found that 47.9% of the smokers had wound healing problems needing medical intervention compared to 14.8% of the non-smokers. Padubidri et al performed a retrospective analysis of 155 smokers and 517 non-smokers undergoing postmastectomy breast reconstruction and found an overall complication rate of 39.4% in smokers compared to 25.9% in the non-smokers; 76 smokers who had stopped smoking at least 3 weeks before surgery had complication rates comparable with those of the non-smokers.⁵¹ In orthopaedic surgery, smoking is implicated in impeding bone metabolism and fracture repair and in increasing the rate of postoperative infection and incidence of non-union.⁵² Postmenopausal women who smoke lose significantly more cortical bone and have a higher incidence of spinal osteoporosis and hip fractures than non-smoking women.^{53–55} In an animal study, Lau et al⁵⁶ found that the incidence of delayed union or non-union was doubled in rabbits exposed to cigarette smoke. This has been shown in humans as well: Kyro et al reported a 50% non-union rate among smokers compared to 32% in non-smokers.⁵⁷

Delayed wound healing with unsatisfactory scarring is a problem after plastic surgery in smokers.^{58–60} Reports show that smoking increases both incidence^{61,62} and recurrence of gastric and duodenal ulcers^{63,64} and also delays ulcer healing.⁶⁵ Dentists have known for a long time that oral wounds heal more slowly in smokers^{66,67}, and this is further influenced by the more pathological oral bacteria in smokers.⁶⁸

Overall, smokers suffer from impaired wound healing^{60,69}, impaired bone healing^{70,71}, and an anastomotic dehiscence in bowel and vascular surgery.⁷²

Some prospective results indicate that cessation of smoking for 4 weeks reduces the risk of wound infection to the levels of those who have never smoked.⁷³

DRUG METABOLISM

In clinical day-to-day life, the anaesthesiologist may find that smokers require higher doses of anaesthetics in the operating theatre.

Only a small number of the constituents of tobacco smoke have been investigated for their pharmacological or toxicological effect on the body.⁷⁴ Smoking does, however, affect drug metabolism by both pharmacokinetic and pharmacodynamic mechanisms.⁷⁵ The most important effect seems to be the induction of the hepatic enzymes, thus accelerating the metabolism of several drugs used in anaesthesia and postoperative care (such as opioids and benzodiazepines). Other drugs whose metabolism is affected in smokers include theophylline, caffeine, tacrine, imipramine, haloperidol, pentazocine, propranolol, flecainide, oestradiol and warfarin.⁷⁶ It is likely that these effects are of clinical importance and that 6–8 weeks of abstinence from smoking is needed for reversal.^{77–79}

PASSIVE SMOKING

Passive smoking seems to influence the course of anaesthesia for adults as well as children. Dennis et al (1994) studied 120 adults undergoing elective surgery in general anaesthesia and found an increased risk of respiratory complications in both active and passive smokers.⁸⁰ Lyons et al (1996) found an increased risk of postoperative respiratory events in children exposed to passive smoking. This was related to

the cumulative number of cigarettes smoked by individuals to whom the child was exposed.⁸¹ Skolnick et al (1998) also demonstrated a dose relationship between the risk of airway complications in children receiving general anaesthesia and the urinary cotinine concentration in 602 children.⁸² In 2003, Drongowski et al demonstrated an increased risk of respiratory complications during and after anaesthesia in children exposed to passive smoking.⁸³ Passive smoking apparently also affects drug metabolism. Reisli et al (2004) evaluated the effect of environmental smoke on onset and recovery time after a single dose of rocuronium in children, and found that passive smokers consumed less rocuronium than non-smokers during similar anaesthesia.⁸⁴

Some evidence demonstrates a dose relationship between the magnitude of passive smoking and the overall risk of respiratory complications in children and adults. Furthermore, passive smoking also seems to influence drug metabolism. More research is needed within this field.

PREOPERATIVE SMOKING INTERVENTION

In order to reduce smoking-related complications, it seems obvious to stop smoking before surgery, and several authors have focused upon the duration of preoperative abstinence necessary to reduce the increased postoperative morbidity in smokers.

Observational studies

The first observational studies hypothesized that cessation of smoking for 1–2 months preoperatively could be more dangerous than just to continue smoking. Another hypothesis was that reduction of smoking, rather than complete cessation, could be effective. However, later studies rejected both these hypotheses.

In 1984, Warner et al⁸⁵ published a retrospective study on 500 cardiopulmonary bypass patients, 456 of whom were smokers. All smokers had been advised to stop smoking preoperatively. Of these, 124 never stopped, 84 stopped less than 2 weeks before surgery, 44 stopped 2–4 weeks before surgery, 28 stopped 4–8 weeks before surgery, and 176 more than 8 weeks before surgery. The patients who stopped smoking more than 8 weeks before surgery had significantly fewer pulmonary complications than the patients who smoked or stopped smoking less than 8 weeks before surgery. These results were confirmed in a prospective, descriptive study in 1989, where 200 patients were evaluated.⁸⁶ Patients who stopped smoking more than 6 weeks before surgery had a pulmonary complication rate of 14.5% compared to 57.1% in those who did not. Patients who had stopped smoking more than 6 months before surgery had rates similar to those who had never smoked (11.1 versus 11.9%).

Nakagawa has evaluated the optimal duration of preoperative smoking abstinence⁸⁷ in patients undergoing pulmonary surgery. In this retrospective cohort study, 288 patients were evaluated. The results of this study indicate that the risk of pulmonary complications after pulmonary surgery is significantly reduced in smokers who were abstinent for more than 4 weeks before surgery. Padubidri et al found in 2001 that smokers who had stopped at least 3 weeks before surgery had complication rates comparable with those of non-smokers.⁵¹

Some clinicians have feared an increased incidence of pulmonary complications in recent quitters because of physiological studies indicating an increased mucociliary clearing. Barrera et al⁸⁸ performed a prospective cohort study on patients with lung

cancer undergoing pulmonary resection who were divided in four subgroups: smokers, never smokers, quitters who stopped more than 4 weeks before surgery, and quitters who stopped less than 4 weeks before surgery. There was no evidence of a paradoxical increase in pulmonary complications among those who quit smoking within 2 months of undergoing surgery.⁸⁸ This is confirmed by a recent randomised clinical study of 1–3 weeks of preoperative smoking intervention.⁸⁸

Randomised clinical trials

Only two randomised clinical trials evaluating the effect of preoperative smoking intervention on postoperative complications have been published, even though more than 50 years have passed since the association between smoking and increased postoperative morbidity was first documented.

Møller et al in 2002³ evaluated 120 patients who were randomly assigned to either a smoking intervention programme or standard care before hip and knee replacement surgery. The intervention started 6–8 weeks preoperatively and consisted of individual counselling by a specially trained project nurse. The patients were offered weekly consultations and free, individualized nicotine replacement therapy. The data were analysed on an intention-to-treat basis. The study showed an overall reduction in complication rates from 52% in the intervention group compared to 18% in the controls. The most significant effect was seen in the risk of wound-related complications, where the incidence was reduced from 31% in the control group to 5% in the intervention group. Significantly more patients in the control group had secondary surgery (15 versus 4%); most procedures related to wound complications. Some of the patients in the intervention group had reduced their cigarette consumption by at least 50%, but were still everyday smokers. A per-protocol analysis showed that the risk of postoperative complications in these patients was not reduced but stayed at the same level as that in patients in the control group who continued to smoke.

Sorensen and Jorgensen in 2003⁸⁹ also performed a clinical randomised trial on preoperative cessation of smoking 1–3 weeks before colorectal surgery. In total, 81 patients were untraditionally randomised to either stop or continue smoking, instead of randomisation to either intervention or control group. In the latter group, many patients withdrew their consent (21 versus 3 in the former group), while 15 of 30 others staying in the continued-smoking group stopped or reduced smoking. The patient was offered weekly individual counselling by a specially trained project nurse and free, individualized nicotine replacement therapy. The intention-to-treat analysis showed no difference between the two groups, who experienced a complication rate >40%. The authors have described their problems in the publication, and call for more research to clarify the effect of short-term smoking cessation before surgery.

New evidence will be gathered in the next few years from ongoing research groups evaluating the effect of preoperative intervention programmes for 4 weeks and 2 days before surgery, respectively. Today, there is no doubt that smoking is closely related to the development of significantly increased complications at surgery. Furthermore, smoking intervention—even short-term before operation—is not associated with danger. Finally, cessation of smoking 6–8 weeks before surgery reduces the complication rate significantly; however, the effect of shorter preoperative abstinence from tobacco remains to be evaluated.

IMPLICATIONS FOR PRACTICE

In general, risk reduction and uncomplicated operations have top priority for patients, staff, hospital organization and community. The development of preventable complications is associated with tremendous consequences, for the individual as well as economically. Therefore, all smokers admitted for operation should be informed about their increased risk at surgery, recommended smoking cessation, and offered a preoperative intervention programme in due time before the operation (Table I) as an integrated part of the preoperative procedures. Though the focus is on prevention of complications, the long-term effect of smoking intervention should be kept in mind.

In case of acute surgery, the preoperative activities should of course depend on the circumstances. However, if patients need subacute surgery, or in case of a short preoperative waiting list, the patients should be able to make their own decisions about preoperative smoking intervention based upon evidence for and against given by the clinicians.

The establishment of new routines for the preoperative period is necessary, and medical doctors and nurses must receive short education programmes. To support the smoking cessation process, the patients should not be confronted with smoke in the hospital area or among the staff.

According to the law of patients' rights in many Western countries, the patients have a legal right to be informed about the risk of complications and possibility of prevention in relation to treatment. Furthermore, responsibility for giving information is stronger in some countries than others, especially in relation to surgery, and smoking patients developing complications would complain if there were insufficient preventive procedures. Therefore, the recommendations or local guidelines should include smoking as a risk factor and smoking intervention as a risk reduction, remembering that

Table I. Preoperative cessation of smoking for patients admitted to surgery

When	What
At admission to surgery from GP, specialist or others	Include history of present smoking (yes/no daily smoking) If yes, recommend smoking cessation and give information about smoking intervention programmes in the hospital/community
At first contact with the surgeon/anaesthesiologist	Obtain smoking history (yes/no) if not done yet If yes, give information (oral and written) about the increased risk at surgery and the effect of smoking intervention before surgery Recommend cessation of smoking and offer smoking intervention programme, if not done already Motivate the unmotivated patient
At decision to operate	Include smoking as a risk factor in the dialogue between surgeon, anaesthesiologist and patient, in the same way as for severe heart disease, unstable diabetes etc.
At discharge	Register the intervention and present smoking habits in the discharge letter
At follow-up for quality improvement	Include a few indicators in the quality management programme (choose among screening for smoking, information and recommendation, smoking intervention, smoking rate preoperatively)

in the end the surgeon and hospital are responsible for the information, preventive procedures, and informed consent before operating, whereas the anaesthesiologist and the hospital are responsible for the information and preventive procedures in relation to anaesthesia.

IMPLICATIONS FOR FUTURE RESEARCH

The effect of shorter preoperative abstinence from tobacco on the complication rate remains to be evaluated, and evidence of the effect of smoking invention on the clinical outcome of other types of surgery and groups of patients is needed.

Furthermore, intervention studies are highly desirable in relation to stopping exposure to passive smoking prior to surgery, especially because so many children are exposed to passive smoking and therefore develop postoperative complications, which should be preventable.

Evaluation of drug metabolism in smokers and the changes during the smoking intervention process are clinically relevant, not only in relation to operations and intensive care, but also for non-surgical smokers who often require life-long medication due to chronic disease.

Practice points

- active and passive smoking is a major risk factor for intra- and postoperative complications
- the effect of short-term cessation of smoking remains unclear, but it does not increase the risk of pulmonary complications
- smoking intervention 6–8 weeks before surgery is effective in reducing the complication rate

Research agenda

- the effect of short-term smoking intervention
- the effect of smoking intervention on different types of surgery and in different patient categories
- interventions for prevention of passive smoking
- evaluation of drug metabolism in smokers

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Regional anaesthesia versus general anaesthesia, morbidity and mortality

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The regional versus general anaesthesia debate is an age-old debate that has brought about few clear answers. Most concur that multiple factors including the patient, the surgery, the method of regional and general anaesthesia, and the quality of perioperative care, all influence surgical outcome. In this age of evidence-based medicine, the heterogenous data available need to be reconciled with the advances in perioperative care and the significant decline in complications associated with the surgical process as a whole. This review considers general issues such as the type of available evidence, and its limitations, particularly with regard to the relatively broad question of neuraxial versus general anaesthesia. It then assesses current evidence on regional versus general anaesthesia for specific scenarios such as hip fracture surgery, carotid

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endarterectomy, Caesarean section, ambulatory orthopaedic surgery, and postoperative cognitive dysfunction in elderly patients after non-cardiac surgery.

Key words: regional anaesthesia; general anaesthesia; heterogeneity; meta-analysis; randomised controlled trial; hip fracture; carotid endarterectomy; Caesarean section; ambulatory surgery; postoperative cognitive dysfunction.

INTRODUCTION

At the end of the nineteenth century, barely 50 years after ether anaesthesia was first demonstrated in 1846, and rapidly became utilized throughout the Western world, August Bier discovered that a class of drugs (local anaesthetics) could stop neural transmission and halt sensation in the area of supply of the affected nerves. Regional anaesthesia thus became an alternative to general anaesthesia. And since that time, the debate over the relative safety of the two techniques has persisted. There have been phases in this history where one has achieved popularity over the other, and vice versa. Nowadays we strive to assess safety and efficacy on the basis of valid scientific evidence rather than on personal experience, expert opinion and anecdotal evidence. However, we cannot expect evidence to make broad generalizations for us—that would be as absurd as asking whether rainy days are better than sunny days. In evidence-based medicine, we need focused questions that apply to the patient population, the treatment and the standards of care that are relevant to the issue of interest. In the case of the regional versus general anaesthesia debate, the broader issue of whether one is safer than the other will not be answered: what we must ask is in which circumstances one anaesthetic choice has advantages over another.

With different surgical procedures and patient populations, an effect or side effect of anaesthesia can be favorable or unfavorable. For example, sympathectomy, vasodilatation and venous pooling from neuraxial blockade reduce venous return to the heart, which compounds the hypotension. Profound hypotension and reduced preload can be devastating for a frail elderly patient. The same phenomena can reduce intraoperative blood loss by reducing local blood flow to the surgical site—usually an advantage. Some advantages of the regional anaesthesia option are simply related to avoidance of general anaesthesia. For example, the high risk of acid regurgitation and aspiration during general anaesthesia for Caesarean section makes this a procedure for which regional anaesthesia is likely to be beneficial. Using regional rather than general anaesthesia for carotid endarterectomy has the advantage of the patient being awake during carotid artery clamping. This may reduce morbidity and mortality by early detection of the onset of intraoperative stroke. The choice of anaesthetic and its advantages and disadvantages will inevitably be influenced by the patient's comorbidities and the surgery itself. Accordingly, it is necessary to consider different procedures and patient populations separately. For this review, we have selected those comparisons that are studied with sufficient frequency in the literature to warrant review.

Neuraxial versus general anaesthesia—general

When reviewing this question, any analysis, meta-analysis or systematic review is made difficult, sometimes even irrational, by the heterogeneity of the patient populations and of the treatments themselves. In some studies, neuraxial anaesthesia is used in conjunction with general anaesthesia, in others not. The surgical

procedures for which the two techniques are indicated may be distinctly different. Sole neuraxial anaesthesia is commonly used for extremity, body surface surgery, and non-extensive intraabdominal and pelvic procedures, whereas adjunctive neuraxial anaesthesia is more commonly used for major intraabdominal and intrathoracic procedures and for postoperative analgesia. The dense sympathetic blockade provided by intraoperative neuraxial anaesthesia results in improved lower extremity blood flow, lesser incidence of hypercoagulability, and reduced cardiac work. Hence, the incidence of deep venous thrombosis, pulmonary embolism, and cardiac events may be reduced. On the other hand, postoperative epidural analgesia, using low dose local anaesthetics with opioids, likely has different benefits, largely related to superior analgesia, continuous low-dose local anaesthetic effects, and avoidance of systemic opioids. Thus postoperative neuraxial analgesia is likely to result in improved bowel mobility, improved coughing and breathing, earlier ambulation, and consequently a lower incidence of thrombosis. The many studies that utilize intra- and postoperative epidural therapy do not allow any separation between the likely benefits arising from intraoperative epidural anaesthesia versus those arising from postoperative epidural analgesia.

A meta-analysis published by Rodgers et al in 2000¹ strongly supported a reduction in mortality associated with use of neuraxial anaesthesia. Yet this meta-analysis assessed the effect of neuraxial blockade with or without general anaesthesia, and whether or not the treatment was continued postoperatively. Their overall conclusion was that neuraxial anaesthesia reduced postoperative mortality by about one third (33, 95% C.I., 0.54–0.9; $P=0.006$). The authors recommended more widespread use of neuraxial anaesthesia. Yet they drew this conclusion from a meta-analysis that included various patient populations using different anaesthesia techniques and undergoing different surgical procedures. They included studies of spinal and epidural anaesthesia, thoracic or lumbar catheter placements, regardless of whether spinal or epidural anaesthesia was used in combination with general anaesthesia or not. Their subgroup analyses show, however, that significant reduction in mortality occurred only in specific patient populations with specific types of regional anaesthesia such as spinal anaesthesia for hip fracture surgery and spinal or epidural anaesthesia for vascular surgery. Both populations seemed to do better in older studies, with no difference shown by newer studies. Therefore, applying their overall conclusion to every patient can be misleading. Benefit versus risk assessment should always be population and practice specific.

Another important issue in the discussion of neuraxial versus general anaesthesia is the issue of changes in anaesthetic and surgical practice, and whether these have changed the relative benefits of neuraxial versus general anaesthesia. In 1987, Yeager et al² found that epidural anaesthesia and postoperative epidural analgesia significantly reduced mortality and major morbidity in high-risk surgical patients when compared to sole general anaesthesia with postoperative parenteral opioid analgesia. But more recent large randomised controlled trials failed to reproduce the Yeager findings.^{3,4} Was this because improvements in perioperative management have increased the safety of the operative course to the extent that benefits attributable to any anaesthetic or surgical intervention are no longer obvious? Such improvements might include the use of shorter acting drugs, high dependency on intensive care units, improved standards of monitoring and vigilance, better preoperative optimization, and less invasive surgical techniques. Improved deep venous thrombosis prophylaxis with

Table I. Summary of evidence supporting benefits of intraoperative neuraxial blockade.

Outcome	Summary of evidence	Type of evidence	References
Decrease in mortality	Not supported	Large RCTs and observational studies	3-6
	Note: supported in older studies, but confined to fractured hip and vascular surgery patients, and with high mortality in general anesthesia group	RCTs and meta-analyses	1,2,7-9
Fewer cardiac events	Supported for thoracic epidurals in high risk patients	RCTs	3,2,10-12
	Not supported for a wider population	RCTs, including large RCTs, and meta-analyses	3-5,13,14
Less thrombo embolism	Not supported when modern thromboprophylaxis used	RCTs, including large RCTs	3,15
	Note: supported in older studies, but thromboprophylaxis used was non-aggressive	RCTs, meta-analyses and observational studies	1,7-9,16
Improved graft survival-vascular surgery	Supported	RCTs	14,17
Reduced blood loss	Supported	RCTs and meta-analyses	1,18
Reduced metabolic stress response	Supported	RCTs and observational studies	2,19

newer drugs and a focus on early mobilization may have had an important role in improving surgical outcome, and may have undermined the traditionally quoted benefits of epidural anaesthesia and analgesia in terms of improvement in serious morbidity. Moreover, even large trials may not have enough power to detect differences, as adverse events become increasingly rare for both surgical and anaesthetic outcomes.

In the following discussion, various outcomes of neuraxial versus general anaesthesia are reviewed. Meta-analysis and systematic reviews are cited where available, and emphasis has been given to randomised controlled trials (RCTs). Observational studies are cited when randomised controlled trials are not available, or not suitable for the research question and/or target population. A summary of the evidence is presented in [Table I](#).

Mortality

While it is true that the earlier studies showed a clear decrease in mortality when neuraxial techniques were compared to general anaesthesia^{1,2,7-9}, more recent studies have not shown statistical differences in the mortality rate.³⁻⁶ The narrowing of the difference in mortality in newer versus older studies could be based on improvements in perioperative care that have improved mortality overall (at least in equivalent risk groups). The fact that potent thromboprophylaxis was not available or used for patients enrolled in earlier studies is probably an important factor. On close scrutiny, studies that were able to show significant improvements in mortality involved patients considered high risk at baseline for general anaesthesia, and

the mortality rate in the general anaesthesia groups was markedly higher than today's mortality rates (for example, 30 versus 8% after fractured hip surgery). It would not be rational to state that neuraxial or general anaesthesia have a better outcome in terms of mortality across all patients and for all surgical procedures is again not possible because the question can only be logically assessed for specific procedures and specific patient populations.

Cardiac events

The use of neuraxial anaesthesia in patients with coronary artery disease undergoing major cardiac or vascular surgery has been shown to reduce the incidence of perioperative cardiac event.^{2,3,10–12} This benefit appears to be more pronounced for thoracic epidurals when compared to lumbar, and the epidurals must be used in the postoperative period. Other studies assessing more general populations and broader techniques have demonstrated little or no benefit in terms of cardiac morbidity, and no significant difference in cardiac mortality.^{3–5,13,14,20,21}

Thromboembolic events

Perhaps one of the most important contributors to statistical difference in outcomes with neuraxial anaesthesia has been the lower incidence of thromboembolic events when compared to general anaesthesia.^{1,7–9,16} But the patients enrolled in these studies did not receive venous thromboembolism prophylaxis, unlike patients in newer studies^{3,15}, which did not show an appreciable difference. The use of potent pharmacological thromboprophylaxis, compression boots and venous stockings and early ambulation are now an established part of standard care, and it would not be possible now to study this aspect versus neuraxial anaesthesia alone. In fact, neuraxial anaesthesia in the setting of new or established potent thromboprophylaxis is now a topic of some concern.

Risks associated with neuraxial anaesthesia

Risks associated with neuraxial anaesthesia may be forgotten in the context of evidence synthesis because complications are rare and may not arise during the conduct of a trial. However, two complications cannot be ignored in the risk/benefit analysis for neuraxial anaesthesia—spinal headache and epidural hematoma. Spinal headache arises in an estimated 0.16–8% of patients undergoing neuraxial procedures, with subsequent headache in 16–18%. While post-dural puncture headache is considered a mild and self-limiting complication, nevertheless, the patient suffering this complication in a postoperative setting may find this complication devastating. The rate of epidural haematoma occurring after epidural or spinal injection or catheterization is much lower—estimated at fewer than 1/500 000, even in the presence of potent antithrombotic agents²²—yet the possible consequence of paraplegia after missed epidural haematoma is obviously catastrophic. These complications must be weighed carefully against the benefits of neuraxial interventions in the surgical setting. New and untested antithrombotic agents, with a potency that is often unclear until they are used in a wide patient population, enter the clinical arena frequently. Often true risk assessment in respect of epidural hematoma cannot be carried out before disastrous outcomes have occurred, and we are left having to write protocols on the basis of these drugs' known pharmacokinetic profile.^{23–25} There is an urgent need to reassess the risk

of epidural hematoma and the true benefits of neuraxial interventions in a changing clinical climate.

Practice points

- by present day standards of anaesthesia and surgical practice, evidence suggests that there is no difference between neuraxial and general anaesthesia in terms of safety or surgical outcome when considering surgical populations overall
- there are, however, some benefits to neuraxial anaesthesia in isolated circumstances (see Table 1)
- epidural haematoma and subsequent paraplegia is rare but catastrophic

Research agenda

- RCTs based on current practices are needed and need to clearly state what kind of thromboprophylaxis is used
- a key issue for future research is that of catastrophic outcome due to epidural haematoma. Advantages of neuraxial anaesthesia in terms of reduced thromboembolism may have been superseded by modern thromboprophylaxis. Since modern thromboprophylaxis is known to increase the risk of haematoma (possibly to an extent not yet realized), how can we quantify and rationalize current risks and benefits?

Neuraxial versus general anaesthesia for hip fracture surgery

A systematic review⁷ compared mortality and morbidity after hip fracture surgery between regional anaesthesia (spinal or epidural anaesthesia without general anaesthesia) and general anaesthesia. Findings are summarized in Table 2. The primary outcome was mortality. Pooled results from eight trials^{8,9,26–31} showed regional anaesthesia to significantly decrease mortality at one month (Risk ratio: RR 0.69, 95% Confidence interval: CI 0.50–0.95). At three months, mortality was also smaller in the regional anaesthesia group, but the result was not statistically

Table 2. Summary of evidence from Parker et al, Cochrane review.⁷

Outcome	Finding	Risk ratio	Difference	95% CI
1 month mortality	Reduced by neuraxial	0.69		0.5–0.95
3 month mortality	No difference	0.92		0.71–1.21
DVT	Reduced by neuraxial	0.64		0.48–0.96
Blood loss	Decreased by neuraxial		85 ml ^a	9–162 ml
Post-op confusion	Reduced by neuraxial	0.5		0.26–0.95

NOTES: CI—confidence interval, DVT, deep vein thrombosis.

^a Weighted mean difference.

significant (RR 0.92, 95% CI 0.71–1.21). Only two trials evaluated one-year mortality, which was not significantly different between regional and general anaesthesia groups. Regional anaesthesia was associated with a reduced risk of deep venous thrombosis (RR 0.64, 95% CI 0.48–0.96), a decrease in operative blood loss (weighted mean difference –85 ml, 95% CI –162 to –9 ml), and a reduced risk of acute postoperative confusion (RR 0.50, 95% CI 0.26–0.95).

However, as the authors suggested, a weakness of this meta-analysis was that many of the included trials were old (seven out of eight studies were more than 15 years old). They may not represent current practice nor account for the advances in safety in the field of anaesthesia today. With the benefit of interventions such as pharmacological thromboprophylaxis and beta-blockade^{32,33} the benefit of neuraxial anaesthesia in terms of improvement in serious morbidity seems to become less important. When the authors excluded the oldest trial with very high mortality in the general anaesthesia group⁸, the difference in one-month mortality was no longer significant.

There are several reports suggesting that better management of surgical patients contributes to improved surgical outcome. Parker et al³⁴ prospectively observed 2846 patients who had acute hip fracture over a 11-year period to evaluate the effectiveness of their hip fracture service, in which they designated specific staff to treat hip fracture patients and encouraged early discharge with community nursing service. Mortality at 30 and 120 days after fracture decreased from 21 and 35% (year 1986) to 7 and 15% (year 1997). Unfortunately, they did not present data on the anaesthetic technique used or whether they used any method of thromboembolism prophylaxis.

According to a multicenter audit published in 1995⁶, only 46% of 580 patients admitted for femoral neck fracture received pharmacological thromboembolic prophylactic agents. A significant reduction in fatal pulmonary emboli was identified among patients who received thromboembolic prophylaxis. One of the hospitals included in this audit showed a higher survival rate. This was thought to be due to the multidisciplinary team based care, which utilizes early assessment and surgery, routine prophylaxis and early mobilization plans for discharge began almost immediately after surgery.

Conducting large randomised controlled trials on a long-term basis is difficult. Carefully designed observational studies are valuable because they allow for the inclusion of larger numbers of patients for longer time periods. Gilbert et al³⁵ prospectively observed the effect of anaesthetic technique (spinal versus general anaesthesia) on long-term (two years) morbidity and mortality in a large cohort ($n=741$) of elderly (over 65) patients with acute hip fracture who had surgery from January, 1990 to June, 1991. After controlling for the effect of demographics and baseline medical and surgical factors, there was no significant difference in mortality between patients who received spinal anaesthesia or general anaesthesia, or in the incidence of serious morbidity (pulmonary embolism, myocardial infarction, bowel obstruction or pneumonia).

Current aggregated evidence suggests that intraoperative neuraxial anaesthesia reduces mortality and morbidity after hip fracture surgery during the first month after surgery. Yet the weight of evidence supporting this conclusion is old, and the overall conclusion may not be true of present-day practice. There is less support for improved morbidity and mortality in terms of long-term outcome. Randomised controlled trials based on current standard of practice are needed. Such trials

Practice points

- a comprehensive meta-analysis finds improvements in 1-month mortality, incidence of DVT, blood loss and cognitive function with neuraxial anaesthesia⁷
- close scrutiny of this meta-analysis, and additional information from a large observational study³⁵ suggests that these benefits may no longer apply in an era of improved overall outcome
- benefits seem to be short-term rather than long-term

Research agenda

- same as neuraxial versus general anaesthesia—general

should clearly state what kind of thromboprophylaxis is used, and observe patients on a longer-term basis.

Neuraxial versus general anaesthesia for Caesarean section

A large prospective review of obstetric anaesthesia between 1993–2003 including 377 159 deliveries in England was published recently.³⁶ It showed a significant increase in the Caesarean section rate from 13.6% (1993) to a high of 26.0% (2000). If the choice of anaesthesia affects outcome after Caesarean section, it can therefore affect many pregnant women and their babies. Both regional anaesthesia and general anaesthesia are used for Caesarean delivery with different advantages and disadvantages. Advantages and disadvantages must be considered both for the mother and the fetus.

The maternal risks of general anaesthesia include increased incidence of pulmonary aspiration of gastric contents and failed endotracheal intubation (the incidence was 1:238 in the previously mentioned prospective review³⁶). They are the major causes of maternal morbidity and mortality. Of course, maternal changes as the result of such outcomes as hypoxia and hypotension affect the outcome of the fetus. Use of halogenated volatile agents may be associated with a greater risk of maternal blood loss.³⁷ On the other hand, the advantage of general anaesthesia would be faster induction than regional anaesthesia in an emergency situation when fetal distress prompts urgent delivery.

The chief disadvantages of spinal and epidural anaesthesia are the potential for profound hypotension, and post-dural puncture headache. Among parturient women, the risk of accidental dural puncture with epidural insertion is estimated as approximately 1.5%, of which half will result in post-dural puncture headache (PDPH). For spinal anaesthesia, the estimated incidence of PDPH is 1.7%.³⁸ From 1993 to 2003, significant decreases in the use of general anaesthesia for both elective (24.7–3.7% of total Caesarean sections) and emergency (43.6–11.1%) Caesarean sections were observed in the previously mentioned prospective review.³⁶

There are not many randomised trials of general versus regional anaesthesia for Caesarean section. A published meta-analysis therefore chose to include both randomised and non-randomised trials.³⁹ They conducted a meta-analysis on the effects of different anaesthesia methods (general, spinal or epidural) on fetal/neonatal

outcome. Their primary aim was to compare spinal anaesthesia with general anaesthesia. They performed two analyses: an analysis including all the trials, and an analysis including only randomised controlled trials. Umbilical artery pH was significantly lower and base deficit significantly higher in the group receiving spinal anaesthesia compared to the group receiving general anaesthesia in both analyses. This systematic review concluded that choice of spinal anaesthesia might not add advantage on fetal/neonatal outcome. Although significant heterogeneity and inclusion of non-randomised trials interfere with drawing solid conclusions, consistency between results from both randomised and non-randomised trials was seen, which strengthen the evidence. As they suggested, it is difficult to obtain consent from patients to randomly allocate them to very different anaesthesia methods- for example, sleeping or awake during the procedure. Careful evaluation of non-randomised trials therefore was inevitable and important in this situation.

Maternal outcome was not evaluated in the above systematic review. The advantage of spinal anaesthesia for maternal outcome may outweigh its possible advantage or disadvantage toward the fetus. A Cochrane systematic review is underway, which plans to evaluate both maternal and neonatal outcomes between using regional versus general anaesthesia.⁴⁰

Practice points

- large observational studies^{41–42} suggest both advantages (lower risk of aspiration and avoidance of airway difficulties) and disadvantages (profound hypotension, PDPH) of neuraxial anaesthesia for the mother
- conclusion from a published meta-analysis of fetal and neonatal outcome finds no difference between neuraxial and general anaesthesia³⁹

Research agenda

- a Cochrane systematic review is underway to evaluate both maternal and neonatal outcomes

Regional versus general anaesthesia for carotid endarterectomy

Debate on the anaesthesia method for carotid endarterectomy raises several specific points. The advantage of regional anaesthesia is that it enables accurate neurological assessment during carotid clamping. Early detection and reversal of intraoperative brain ischemia may improve postoperative morbidity and mortality. However, being conscious during surgery may be stressful for both patients and surgeons, and the incidence of myocardial ischemia may increase as a result of increased distress and pain. Currently, most surgeons prefer general anaesthesia.⁴³

Rerkasem et al⁴⁴ performed a systematic review on this topic. Their results are summarized in Table 3. They included both non-randomised trials and randomised trials, since not many randomised trials were found. They analyzed randomised and non-randomised trials separately. The results from 41 non-randomised trials

Table 3. Summary of evidence from Rerkasem et al Cochrane Systematic Review.⁴⁴

Outcome	Finding	Odds ratio	95% CI
Results from randomised trials			
No differences			
Results from non-randomised trials			
Mortality	Lower with regional	0.67	0.46–0.97
Perioperative stroke rate	Lower with regional	0.56	0.44–0.70
Myocardial infarction rate (30 days)	Lower with regional	0.55	0.39–0.79

NOTE: CI-confidence interval.

showed better outcomes among patients who received regional anaesthesia; significantly lower mortality (OR 0.67, 95% CI 0.46–0.97), significantly lower perioperative stroke (OR 0.56, 95% CI 0.44–0.70) and significantly lower risk of myocardial infarction within 30 days (OR 0.55, 95% CI 0.39–0.79). However, these results may overestimate the benefit of regional anaesthesia. Many of the trials were retrospective, and consecutive patients were not always included. Such trials are susceptible to publication bias and patient selection bias. On the other hand, the results from randomised controlled trials were underpowered. Only seven randomised trials including 554 operations were identified. None of the outcomes above were significant in the meta-analysis of randomised trials, and the results had wide 95% confidence intervals. Because of the remaining uncertainty, a large multicenter randomised controlled trial of 5000 patients is underway to determine whether the choice of anaesthesia (regional versus general) influences post-operative mortality and morbidity after carotid endarterectomy.⁴⁵

Practice points

- meta-analysis of non-randomized trials finds lower mortality, lower perioperative stroke rate and lower myocardial infarction rate with regional⁴⁴
- however, these findings are not reproduced in meta-analysis of RCTs⁴⁴

Research agenda

- large multicenter RCT of 5000 patients is underway to assess differences in outcome between regional and general anaesthesia⁴⁵

Regional versus general anaesthesia for ambulatory orthopaedic surgery

Improvements in surgical and anaesthesia techniques over the past several years have led to an increase in the number and types of surgeries being performed in outpatient settings. Seventy percent of all surgical procedures performed in the United States are currently done on an ambulatory basis.⁴⁶ In ambulatory orthopaedic surgery, regional anaesthesia techniques are utilized extensively.⁴⁷ Regional anaesthesia provides

excellent analgesia with reduced risk of opioid side effects such as nausea, vomiting and drowsiness, which can frequently delay discharge or result in the patient being admitted.^{48,49}

Orthopaedic surgery has been shown to be one of the most painful procedures performed in ambulatory settings.⁵⁰ A recent study by Watt-Watson et al⁵¹ reported that 55% of ambulatory shoulder surgery patients had severe pain 7 days after discharge. The use of outpatient peripheral nerve blocks is frequently criticized because intense pain may follow after the analgesic effect diminishes at home.⁵² It is also suggested that long-acting peripheral nerve blockade results in elevated risk of injury as the result of loss of proprioception and the protective reflex of pain. In ambulatory surgery, substantial pain with limited function can still be a problem seven days after discharge.⁵³ As Klein et al reported, a large percentage of patients (17–27%) who receive regional anaesthesia with long acting local anaesthetics, still used opioids at seven days following upper or lower ambulatory orthopaedic surgeries.⁴⁷

Whether the type of anaesthesia affects long-term postoperative outcome such as pain and function after discharge is still unknown. Future study should look at outcomes after discharge from ambulatory surgery, with long-term basis.

Practice points

- regional anaesthesia has obvious advantages in the ambulatory care setting because of less immediate pain and nausea, with consequent early hospital discharge
- however, preliminary data on resolution of pain and recovery of function suggest no advantage to regional anaesthesia

Research agenda

- studies are needed to assess outcomes after discharge from ambulatory surgery, as well as long term outcomes and complications

Regional versus general anaesthesia -postoperative cognitive dysfunction in elderly patients after non-cardiac surgery

Postoperative cognitive dysfunction is common in elderly patients. Moller et al prospectively observed 1218 elderly patients who underwent non-cardiac major surgery under general anaesthesia. They found that long-term cognitive dysfunction after surgery was common; the prevalence was 25.8 and 9.9%, respectively, at one week and three months after surgery.⁵⁴ They also suggested that long-term cognitive dysfunction correlated with decreased levels of activities of daily living.

It is believed that acute postoperative confusion and disorientation are less common after regional anaesthesia than after general anaesthesia. However, studies suggest that this advantage pertains only in the first few hours after surgery, and is not prolonged into the later postoperative period.^{26,55–58} Parker et al⁷ showed a significant reduction

in acute (up to one week) postoperative confusion in the regional anaesthesia group compared to the general anaesthesia group (RR 0.50, 95 CI 0.26–0.95) in their meta-analysis of hip fracture patients. Current evidence does not support significant differences in longer-term cognitive dysfunction^{26,56,57,59,60}. Rasmussen et al⁶¹ studied 438 patients over 60 years old undergoing major non-cardiac surgery. Participants were randomised to receive either general or regional anaesthesia (spinal or epidural, light sedation with propofol was permitted). The majority of participants underwent orthopaedic (hip and knee) and gynecological procedures. The incidence of postoperative cognitive dysfunction was greater in the general anaesthesia group at one week after surgery. The difference was marginally significant. However, the difference did not exist after three months. A low recruitment rate and poor adherence to the allocated anaesthetic by surgeons and anaesthetists underpowered and obscured the results.

For other trials, the sample size (30–57) was small^{26,56,57,59,60}. They used different methods for evaluating the level of cognitive dysfunction (use of different neuropsychological tests, comparing two treatment groups rather than looking at score change in individuals), which precluded combining data quantitatively. Moreover, the study population in these trials was almost exclusively orthopaedic, making it difficult to apply the result to other patient populations. Further study should predefine postoperative cognitive dysfunction and include patients with various types of surgery.

Practice points

- while immediate postoperative cognitive function may be better after regional anaesthesia, no evidence exists to support a role for avoidance of general anaesthesia in terms of later cognitive function

Research agenda

- future studies should predefine postoperative cognitive dysfunction, and include patients with various types of surgery

CONCLUSION

Regional anaesthesia is an anaesthetic option that not only provides an alternative to general anaesthesia, but can also be used to supplement general anaesthesia or to provide postoperative analgesia. Postoperative analgesia is produced through prolongation of intraoperative effects, or through continued pharmacotherapy via a catheter. Some regional drug effects produce benefits and adverse effects through mechanisms that are neither anaesthesia- nor analgesia-related: for example, hypotension due to sympathectomy. Thus, the analysis of regional anaesthesia advantages and disadvantages compared to general anaesthesia becomes immensely complicated. As can easily be imagined, the secondary effects of both regional and

general anaesthesia are varied, and realistically, they must be considered for each and every patient, since each patient presents a unique clinical profile. Evidence based medicine inevitably uses generalization and studies questions across relatively broad patient populations. It is the job of practicing physicians to apply the evidence to the individual patient, combining as many sources of information as are relevant to that particular patient. We do not need to look for broad answers to broad questions because the complexity of our patients matches the complexity of the issues.

ACKNOWLEDGEMENTS

We would like to thank Tina Toland for her editorial assistance.

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Fluid therapy for the surgical patient

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Perioperative fluid therapy is the subject of much controversy, and the results of the clinical trials investigating the effect of fluid therapy on outcome of surgery seem contradictory. The aim of this chapter is to review the evidence behind current standard fluid therapy, and to critically analyse the trials examining the effect of fluid therapy on outcome of surgery. The following conclusions are reached: current standard fluid therapy is not at all evidence-based; the evaporative loss from the abdominal cavity is highly overestimated; the non-anatomical third space loss is based on flawed methodology and most probably does not exist; the fluid volume accumulated in traumatized tissue is very small; and volume preloading of neuroaxial blockade is not effective and may cause postoperative fluid overload. The trials of 'goal-directed fluid therapy' aiming at maximal stroke volume and the trials of 'restricted intravenous fluid therapy' are also critically evaluated. The difference in results may be caused by a lax attitude towards 'standard fluid therapy' in the trials of goal-directed fluid therapy, resulting in the testing of various 'standard fluid regimens' versus 'even more fluid'. Without evidence of the existence of a non-anatomical third space loss and ineffectiveness of preloading of neuroaxial blockade, 'restricted intravenous fluid therapy' is not 'restricted', but rather avoids fluid overload by replacing only the fluid actually lost during surgery. The trials of different fluid volumes administered during outpatient surgery confirm that replacement of fluid lost improves outcome. Based on current evidence, the principles of 'restricted intravenous fluid therapy' are recommended: fluid lost should be replaced and fluid overload should be avoided.

Key words: fluid therapy; third space loss; perioperative fluid therapy; goal-directed fluid therapy; fluid volume; outcome of surgery.

In order to maintain a patient's physiological functions and to replace fluid lost, intravenous fluid resuscitation is a key component in the treatment of surgical patients. The determination of the optimal fluid volume to be given is not simple, however, because both the lost volume and physiological parameters depend on preconditions that are not always fulfilled, i.e. (1) that lost fluid can be accurately measured, and (2) that changes in physiological parameters with adequate sensitivity are proportional to changes in blood volume.

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In daily clinical practice a combination of measured lost volume and physiological changes is used for the assessment of the fluid status in the surgical patient, and a typical protocol for postoperative fluid management will include frequent monitoring of blood pressure, heart rate, blood pH, urinary output, fluid balance, and body weight measurements. However, during and after surgery, blood pressure is decreased by anaesthetic and analgesic drugs, urinary output is decreased by the release of stress hormones, and acidosis may be inflicted on the patient by the very administration of saline-containing fluids.^{1–3} Moreover, movement of fluids between body compartments, with a disappearance of intra-vascular volume into a third space, would make the replacement of only measured losses inadequate.

There is little doubt that hypovolaemia leads to poor tissue perfusion, suboptimal organ function, organ failure, and death. Fluid overload, on the other hand, may be just as harmful as hypovolaemia, but the effects of fluid overload have not attracted the same scientific attention as have the effects of hypovolaemia. Iatrogenic fluid overload has been shown to decrease pulmonary function^{4,5}, to hamper gut motility^{6,7}, and to decrease subcutaneous oxygen tension.⁸ Pulmonary oedema has been described as a consequence of fluid overload^{9,10}, even in patients without pre-existing cardiac disease.^{11–15} Associations have been shown between intra-operative fluid overload and complications^{16–19} as well as mortality following major surgical procedures²⁰, and recently clinical randomised trials have shown fluid overload to cause a poor outcome following gastrointestinal surgery.^{7,11} Currently, the volumes of fluid administered during surgery far exceed the volumes lost. The observed postoperative body weight increase of 3–7 kg following major surgery reflects this.^{6,21–23}

In order to determine the optimal fluid volume to be administered during surgery, randomised trials examining the possible effects of fluid volume on outcome of surgery have been performed. The theoretical and therapeutic approaches of the trials have, however, been contradictory. The trials of 'goal-directed fluid therapy' test the effects of standard fluid therapy versus standard fluid plus extra fluid given to obtain central haemodynamic parameters on target values that are thought to be beneficial for outcome (typically maximal stroke volume, oxygen delivery or oxygen consumption). The trials examining 'restricted fluid therapy' claim that all fluid administered in excess of measured losses (and thus increasing body weight) will result in fluid overload and may be harmful; these trials may be regarded as goal-directed trials where the goal is not maximal stroke volume but normal body weight.

This chapter reviews the existing (or missing) evidence behind the current standard fluid therapy, as well as the literature concerning the influence of administered intravenous fluid volumes on outcome of surgery.

CURRENT FLUID THERAPY IN MAJOR SURGERY: EVIDENCE AND IMPLICATIONS

Standard fluid therapy includes replacement of fluid lost (by basal fluid requirements, perspiration through the surgical wound, loss to the third space, and blood loss and exudation through the surgical wound) and maintenance of physiological functions ('preloading' of neuroaxial blockade).

It is generally agreed that fluid lost by the basal fluid requirements, perspiration through the surgical wound, blood loss, and exudation should be replaced. Any disagreement regarding these losses is about the timing, the route of administration,

and the type of fluid used for replacement. However, replacement of the so-called 'loss to the third space' and the 'preloading of neuroaxial blockade' are subject to much controversy, and doubts have been raised about the very existence of the third space loss.²⁴ Replacement of such a third space loss, as well as the preloading of neuroaxial blockade, will inevitably cause a postoperative body weight gain, i.e. a postoperative fluid overload.

Fluid lost during surgery

The insensible perspiration

The *insensible perspiration* is approximately 10 mL/kg/day in normal conditions, and this does not change much during surgery. About two thirds of the volume is lost through the skin and one-third from the airways. The loss through the airways depends on the humidity of the inhaled air. Inhalation of (or ventilation with) 100% water-saturated air causes a loss close to zero, while inhalation of (or ventilation with) dry air causes a loss of approximately 0.5 mL/kg/hour.²⁵ Patients are allowed to drink until 2 hours before elective surgery and should therefore be well hydrated.²⁶ Unfortunately this is not always the case. For determination of the volume lost during fasting, an obvious approach would be to record or ask the patient about the intake. The deficit may then be replaced with approximately 80 mL/fasting hour.

Both perspiration and deficit from fasting primarily involve the loss of water, and replacement with a water preparation seems therefore logical (i.e. glucose 5%). Surgery- and disease-induced stress, however, causes a rise in blood glucose, and to avoid an enhancement of this, preoperative or intra-operative glucose infusion has previously been discouraged. However, clinical trials have shown that preoperative glucose administration—either intravenous or oral—reduces the postoperative cellular insulin resistance^{27,28}, increases well-being²⁹, and improves postoperative muscle strength.³⁰ Preoperative rehydration with glucose-containing fluids is therefore both logical and beneficial for the fasting patient. Intra-operative glucose administration is controversial, mostly due to lack of evidence and concerns about hyperglycaemia. Two clinical randomised trials have investigated the effect of intra-operative glucose administration during outpatient gynaecological laparoscopy, with contradictory results: one trial showed intra-operative glucose infusions to improve recovery³¹, but the other trial could not confirm this.³²

Urine

Urine in large volumes cannot be expected during surgery, both because the release of stress hormones reduces the excretion of salt and water, and because the anaesthesia may cause hypotension. It is, however, important to distinguish between the anaesthesia-induced hypotension and hypovolaemia. The first is caused by vasodilatation and may reduce the glomerular filtration rate (GFR) but not the arterial blood supply to the renal stoma. Hypovolaemia, on the other hand, reduces both GFR and renal blood supply and may cause renal failure. It is not at all evident that a large urinary output is necessary to prevent postoperative renal failure, or that a small urinary output is associated with renal failure in the absence of hypovolaemia.^{33,34} A small diuresis is therefore acceptable during surgery as long as hypovolaemia is not the cause.

The evaporative loss

The evaporative loss from the surgical wound depends on both the size of the incision and the exposure of the intestines³⁵.

- in minor incisions with slightly exposed but non-exteriorised viscera it is 2.1 g/hour;
- in moderate incisions with partly exposed but non-exteriorised viscera it is 8.0 g/hour;
- in major incisions with completely exposed and exteriorised viscera it is 32.2 g/hour.

Note that the loss is given in grams per hour, and is independent of the body weight of the patient.

The loss from completely exteriorised viscera decreases by 50% after 20 minutes³⁵, and wrapping the exteriorised viscera in plastic reduces the evaporation loss by 87.5%.³⁶ There is no reason to believe that the loss from incisions in other anatomical regions is very different.

The loss to third space

The 'loss to the third space' can be divided into an anatomical and a non-anatomical loss.^{37,38} The anatomical third space loss represents pathological accumulations of fluid in the extracellular volume (ECV), and may be named as such to avoid confusion.

Pathological fluid accumulations. Before, during, or after surgery the disease and/or trauma may cause fluid to accumulate in a transcellular or interstitial space and cause an expansion of the ECV. Examples of this are ascites in the peritoneal cavity, pleural exudation, or other transcellular fluid sequestrations, as well as accumulations of blood or oedema in the interstitial space of traumatized tissues. A volume of ascitic or pleural fluid emptied through drains or during surgery can be accurately measured, and will cause a postoperative weight loss. In patients who are allowed to drink, regeneration of such fluid postoperatively will cause a return to preoperative weight. In case of doubt the loss may be quantified, for example by ultrasound imaging.

The volume of fluid accumulated in the interstitial space of traumatized tissue is more difficult to assess, and is highly influenced by the administration of intravenous fluid. In a study of rabbits, it was found that the formation of a small bowel anastomosis caused an increase of water in the surrounding tissue of 5–10% if no intravenous fluid was administered. The oedema doubled when 15 mL/kg/hour of intravenous fluid was given.³⁸ If equivalent changes occur in humans, 2.5–5 mL may accumulate around a large bowel anastomosis if no fluid is administered, and 5–10 mL may accumulate if 15 mL/kg/hour fluid is given. If one imagines the entire colon to be oedematous, the accumulation would be 150–300 mL, depending on the volume of intravenous fluid administered.

The non-anatomical third space loss (or deficit in functional extracellular volume). It is believed that the surgical trauma per se causes a contraction of the ECV, with a volume of extracellular fluid sequestered in a compartment where it is not available for measurement with a tracer or for the regeneration of lost plasma.³⁹ This phenomenon was first described in 1960 in a trial of dogs subjected to haemorrhagic shock⁴⁰; compared with the ECV before bleeding, the ECV measured during shock was much smaller than anticipated from the volume of lost blood. A year later the same

observation was made in patients undergoing abdominal surgery: despite correction for external losses, the measured ECV during surgery was found to be largely diminished (up to 28% or -3.7 L) compared to similar measurements before surgery.⁴¹ The severity of the trauma seemed to correlate with the ECV lost⁴², so that the larger the trauma, the larger the 'loss of ECV'. The anatomical location of the missing fluid was not clear. Sequestration in the intracellular compartment was suggested, but was not confirmed by later investigations including measurements of total body water.^{43–46} Sequestration in the intestinal lumen was suggested, but this hypothesis was later rejected.⁴⁷ A last hypothesis—that the fluid was sequestered in traumatized tissue—could not be confirmed by measurement of ECV changes in American soldiers with extensive trauma and severe shock during the armed conflict of Vietnam.^{48,49}

A systematic review of the literature concerning measurements of ECV changes in surgery or haemorrhagic shock reveals that only trials utilizing the SO³⁵ tracer and a very short equilibration time (20–30 minutes) have demonstrated this non-anatomical third space loss.²⁴ All other studies—utilizing various different tracers, multiple sampling techniques, and longer equilibration times—have not been able to find a contraction of the ECV neither during surgery nor during haemorrhagic shock.^{43–86} Furthermore, investigators utilizing the labelled bromide tracer have found the opposite of a third space loss: corrected for the lost blood, an expansion of the ECV instead of a contraction was found following surgery.^{44,46,54–56,73–76}

In my opinion, a phenomenon that can only be demonstrated with one specific method of measurement is not evident, in particular not when the method used implies serious weaknesses^{46,78,87,88} and all other methods of measurement contradict the finding. Nevertheless, the loss to the third space is replaced according to algorithms.^{39,89,90} Volumes up to 15 mL/kg/hour are recommended in the first hour of abdominal surgery, with decreasing volumes in subsequent hours.⁹⁰

Replacement of lost blood

Replacement of lost blood with a crystalloid demands infusion of double or triple volume because crystalloid is dispersed throughout the entire extracellular space. This causes an expansion of the interstitial space, with postoperative oedema formation and body weight gain. This may be desirable if the surgical trauma causes a contraction of the ECV (a third space loss, see above) that needs replacement. Indeed, it was the firm belief in the third space loss that started the 'crystalloid era'. If surgery, on the other hand, does not cause a contraction of the ECV, a colloid that stays in the vascular space for a longer time seems to be a more expedient choice for replacement of lost blood. Trials of colloid versus crystalloid have shown diverging results, and the literature has been reviewed in several publications. However, none of the trials of crystalloids versus colloids have used what is perhaps the most important beneficial potential of resuscitation with a colloid: avoiding postoperative fluid overload (body weight increase). Therefore, all the trials may have investigated the effects of fluid overload with a colloid versus fluid overload with a crystalloid.

Exudation from surgical wound

Exudation from the surgical wound is often lost in the surgical dressings, and its volume is therefore based on an estimate, but it will show as a postoperative weight change. In abdominal surgery with exteriorised viscera in a plastic bag, however, the loss can be

measured rather accurately. The exudate contains protein, and manipulation of the intestines increases the protein loss.⁹¹

The maintenance of physiological functions

Neuroaxial blockade causes a relaxation of the vascular bed innervated by the affected segments of the spinal cord.⁹² This causes a decrease in peripheral vascular resistance with a decrease in arterial blood pressure (BP). Despite the fact that cardiac output and peripheral blood flow may be unaltered, it is common to respond to this decrease in BP by giving either 500 mL of colloid or 1000 mL of crystalloid intravenously. However, this treatment has not been shown to be effective. The earliest non-randomised trials and retrospective investigations^{93–95} suggested fluid preloading to reduce the incidence of hypotension in 20–35% of patients, but this has not been confirmed in clinical randomised trials of preloading versus no preloading.^{96–104} Neither the decrease in blood pressure nor the need for pressor substances was significantly altered by the fluid preloading of the neuroaxial blockade.

TRIALS OF GOAL-DIRECTED FLUID REGIMENS (STANDARD FLUID VERSUS EXTRA FLUID)

The trials of goal-directed therapy fall into two categories: trials of fluid loading alone, and trials investigating the effect of fluid therapy in addition to different medications.

Six trials were found examining the effect of fluid therapy alone.^{105–110} The trials of good methodological quality (see below) are shown in Table I. The goal of the fluid therapy was to obtain a maximal stroke volume (SV) output determined by oesophageal Doppler or a target CVP, from the theoretical point of view that maximal stroke volume is also optimal for the patient (i.e. it is optimal that the patient's heart is working on 'the top of the Starling curve'). As seen from the table, the study populations of these trials are small, reflecting that power was not calculated to show a difference in postoperative morbidity or mortality, but in intestinal pH¹⁰⁷ or length of hospital stay. With the possible exception of the trial by Gan and colleagues¹¹¹, who registered gastric emptying time (see below), none of the trials defined by protocol a primary endpoint of a specific complication or group of complications that may be 'fluid-related'. Moreover, the difference in fluid volume between the groups was very small. With no control or registration of postoperative fluid therapy, it is not at all obvious that the fluid therapy is actually responsible for the differences observed. Only one trial¹¹¹ attempted blinded registration of outcome measures, but none of the trials followed the patients after discharge. Even though 'standard fluid therapy' varies enormously between centres and doctors, none of the investigators presented a view of what the right 'standard fluid therapy' is, but tested 'standard therapy' versus 'standard fluid plus more fluid'. As seen from Table I, the absolute volumes given during surgery varied from 1000 mL¹⁰⁹ to 5252 mL.¹⁰⁶ This is, in my opinion, the greatest weakness of these trials.

The trial by Gan and colleagues¹⁰⁶ found a shorter duration of postoperative nausea and earlier return to solid food in the intervention group. The difference in intra-operative fluid volume between groups compared was, however, only 595 mL, and pre- or postoperative fluid therapy was not recorded. The results of this trial are contradicted by those of two other trials with a much larger fluid difference between

Table 1. Trials of goal-directed fluid therapy with extra hydroxyethyl starch (HES) to maximal stroke volume.

Authors	Surgery	Number of patients	Intervention	Preoperative fluid	Intraoperative fluid	Postoperative fluid	Results
Sinclair et al, 1997	Orthopaedic surgery	40 in two groups	HES to maximal SV evaluated by ED	Unknown	1475 mL (ED) versus 1000 mL	Unknown	Hospital stay shorter in the intervention group No difference for complications Mortality: 1 in intervention group, 2 in control group
Mythen et al, 1999	Thoracic surgery	60 in two groups	HES to maximal SV evaluated by ED	Unknown	2100 mL (ED) versus 1800 mL	Unknown	More patients with complications in the control group (6 versus 0) Mortality: 1 in the control group
Venn et al, 2002	Orthopaedic surgery	90 in three groups	HES to maximal SV evaluated by ED or CVP	2051 mL (ED) 1850 (CVP) 2000 mL	2300 mL (ED) versus 2300 (CVP) versus 1700 mL	Volumes include fluid given in the recovery room. Unknown on the surgical ward	Hospital stay shorter in the intervention group No difference in complications Mortality: 9 in the intervention groups and 2 in the control group
Conway et al, 2002	Abdominal surgery	57 in two groups	HES to maximal SV evaluated by ED	Unknown	4522 mL (ED) versus 3864 mL	Unknown	No differences for complications or hospital stay Mortality: 1 in the control group
Gan et al, 2002	General, urological or gynaecological surgery	100 in two groups	HES to maximal SV evaluated by ED	Unknown	5252 mL (ED) versus 4657 mL	Unknown	Hospital stay shorter in the intervention group No difference for complications Mortality not reported

SV, stroke volume; ED, oesophageal Doppler; CVP, central venous pressure.

the groups (close to 3 L) on the day of surgery and adequate recording of postoperative administered fluid volume.^{6,7} In both these trials liberal fluid therapy was found to significantly delay gastric emptying time and increase postoperative complications.

The three trials of patients with fractures of the hip have been analysed in a Cochrane review.¹¹² One trial was excluded due to methodological problems¹⁰⁸, but two trials were included in the meta-analysis.^{109,110} The conclusion of the Cochrane review was that the number of trials and patients included were few, and that fluid optimization regimens tended to increase the administered fluid volume and may have a benefit in shortening hospital stay but also a possible adverse effect of increased mortality (control versus intervention: 3/50 versus 10/80; Peto's odds ratio 1.44, 95% CI: 0.45–4.65).

TRIALS OF AN OPTIMIZATION PROGRAMME WITH FLUID AND ADDITIONAL DRUGS

Eleven trials were found which tested 'standard fluid therapy' versus 'extra fluid, inotropic, and other-drug therapy'.^{113–123} Even though fluid therapy was the first treatment of choice, the fluid volume administered is described in only four trials.^{113,115,116,122}

In the trial by Wilson and colleagues¹²², 138 patients undergoing major abdominal surgery were randomised into three groups. The two intervention groups received preoperative intravenous fluid in addition to intra-operative dopexamine or adrenaline. The dopexamine group had a reduction in postoperative morbidity, while the mortality was significantly reduced in both the intervention groups. It is difficult to interpret the importance of the fluid therapy for the results of this trial, mainly because all patients in the intervention groups received pressor substances.

In the trial by Boyd and colleagues¹¹⁶ 107 patients undergoing major surgery were randomised either to an optimization programme or to a control group. The intravenous volume difference between the groups was, however, only 183 mL, and postoperative fluid administration was not controlled.

Two trials of patients undergoing vascular surgery were found. In the trial by Bender and colleagues¹¹³, 104 patients were randomised either to a control group or to an optimization programme including fluid, dopamine, nitroprusside, and/or diuretics administered to obtain physiological goals measured with a pulmonary artery catheter (PAC). The control group received a PAC only if judged to be clinically necessary. The volume difference between the two groups was 1348 mL (intervention versus control: 5137 versus 3789 mL). Thirteen patients in the intervention group developed a complication versus seven patients in the control group, but the result was not significant. One patient in each group died.

In the trial by Bonazzi and colleagues¹¹⁵, 100 male patients younger than 75 years and free of cardiac diseases were randomised into two groups. The patients in the treatment group were transferred to the ICU the day before surgery, and fluid, dobutamine and nitroglycerine were administered to obtain physiological goals measured with a PAC. For the two first postoperative days the optimization programme was continued on the ICU for the patients in the intervention group but not for the control group; 4500 mL fluid was given to the intervention group versus 3250 mL to the control group on the day of surgery. The differences between groups

on the first and second postoperative days were 580 and 170 mL. No significant differences in clinical outcome or hospital stay were found.

The effect of the administered fluid for the results of these trials is difficult to interpret, because it is impossible to separate effects of the fluid therapy from the effects of the additional therapy. Moreover, only one trial registered the postoperative fluid administration¹¹⁵, blinding of outcome measures was not attempted, and the patients were not followed after discharge in any of the trials.

Sandham and colleagues¹¹⁹ have recently performed the most exhaustive trial of goal-directed therapy. In a multi-centre design, 1999 ASA group 3–4 patients undergoing urgent or elective surgery were randomised to a goal-directed optimization programme using a PAC or 'standard therapy'. The goal was optimal oxygen delivery and cardiac index in the PAC group, and the first drug of choice was intravenous fluid, but the administered fluid volumes are not given. The optimization programme, however, did not reduce postoperative mortality, morbidity or time in hospital, but the use of a PAC had significant adverse effects.

TRIALS ON RESTRICTED INTRAVENOUS FLUID THERAPY

As discussed above, current standard fluid therapy is not at all evidence-based; the existence of a non-anatomical third space loss is not convincing, and no effect of the preloading of the neuroaxial blockade has been shown. The postoperative weight gain of 3–7 kg in patients undergoing major elective surgery therefore seems to represent a genuine fluid overload. For a thorough review of the physiological (adverse) effects of fluid overload see Holte et al.¹²⁵

We therefore designed a clinical randomised assessor-blinded multi-centre trial to answer the following questions¹¹:

1. Can a restricted fluid protocol improve tissue healing?
2. Can a restricted fluid protocol prevent cardiopulmonary complications?

Patients planned for colorectal resection were randomly allocated to either a restricted (R) or a standard (S) intra- and postoperative intravenous fluid regimen (86 in each group). The R regimen was designed to replace measured fluid losses but without a postoperative weight gain. During surgery, fluid preloading of the epidurals and fluids for the non-anatomical third space loss were omitted. Blood was replaced with hydroxyethyl starch (HES) 6% volume for volume (with allowance for a maximum of 500 mL extra). The same principles were followed postoperatively, and a body weight increase of more than 1 kg was treated with furosemide. The administered fluid volume on the day of surgery was a median of 2740 mL in the R group versus 5388 mL in the S group, and on the first postoperative day R versus S was 500 versus 1500 mL. Administered fluid on postoperative days 2–6 was similar. Complications were registered after 30 days of follow-up by both an unblinded (clinical) and a blinded assessment.

Postoperative complications were significantly reduced by the restricted fluid therapy (R versus S, ITT-analysis: 28 (33%) versus 44 (51%), $P=0.013$; per-protocol analysis: 21 (30%) versus 40 (56%), $P=0.003$). The two hypotheses were confirmed (R versus S: tissue healing complications 11 (16%) versus 22 (31%), $P=0.040$; cardiopulmonary complications 5 (7%) versus 17 (24%), $P=0.007$). A dose-response relation between administered fluid volume and postoperative complications was found ($P<0.001$). Four patients in the standard group died, but there were no deaths in the restricted group (absolute risk

reduction 5.6, 95% CI: 0.3–10.9%). In all cases, the cause of death was a cardiopulmonary complication. Adverse effects were lower diuresis and higher creatinine (but not urea) on the day of surgery in the R group. On the other hand, patients in the S group had lower arterial pH, a lower concentration of bicarbonate, and negative base excess in the immediate postoperative period ($P < 0.01$).¹²⁶ Furthermore, the S regimen caused haemodilution, with lower concentrations of serum albumin and total protein. The restricted regimen did not cause haemodynamically unstable patients; no significant differences in intra- and postoperative arterial blood pressures were found, and the administration of pressor substances was similar.¹²⁶

The results of our trial confirm the results of Lobo and colleagues⁶ who randomised 20 patients undergoing colonic resection to either a restricted postoperative fluid regimen or a standard regimen to investigate the effects on gastric emptying time and complications. The restricted group received no more than 2 L intravenous fluid and 77 mmol sodium daily. The control group received at least 3 L water and 154 mmol sodium daily. Even though the intervention did not include the intra-operative fluid therapy, the administered fluid volume between the groups on the day of operation was 3000 versus 5700 mL. Significantly shorter solid- and liquid-phase gastric emptying times and a significant reduction in postoperative complications were found in the restricted group (R versus S: 1 versus 7, $P < 0.05$).

Recently, the results of both the above trials have been confirmed by Nisanevich et al.⁷ who randomised 156 patients undergoing various major gastrointestinal procedures to either a restricted intravenous fluid protocol (R: 4 mL LR/kg/hour) or a liberal intravenous fluid protocol (L: 12 mL LR/kg/hour). In both groups lost blood was replaced by lactated Ringers solution (LR) by 1:3. Low diuresis, low blood pressure, or increased heart rate initiated the administration of a fluid bolus. The mean administered intra-operative volume was (L versus R) 3871 versus 1408 mL, and the rest of the day of operation (L versus R) 2012 versus 2170 mL was given. Thus, the total volume administered on the day of surgery was very similar to the volumes given in the two previous trials. On postoperative days 1 and 2 a similar fluid volume was given to the two groups. Blinded registration of outcome was performed. The trial showed that significantly fewer patients in the restricted group had a postoperative complication (R versus L: 13 versus 23, $P < 0.05$). Patients in the restricted group had significantly shorter time to first flatus and stool ($P < 0.001$), and hospital stay was significantly reduced. The trial has the weakness that the patients were not followed after discharge, with the consequence that late complications (for example wound infections) may have been overlooked.

In conclusion, restricted intravenous fluid therapy has consistently been shown to improve outcome in patients undergoing major gastrointestinal surgical procedures. No trials exist, however, testing the effects of restricted fluid therapy on other types of surgery.

TRIALS OF OUTPATIENT SURGERY

Nine randomised trials were found testing different intravenous fluid volumes on outcome of outpatient surgery (see Table 2).^{31,32,127–133} The outcome assessed included thirst, dizziness, drowsiness, well-being, and for some of the trials nausea, vomiting and overnight stay in hospital. Intravenous fluid was found to improve self-reported drowsiness and dizziness in seven of the trials^{31,127–131,133}, and in three of the trials postoperative nausea was less in the groups receiving fluid.^{128,130,131} The volume

Table 2. Trials of outpatient surgery.								
Author	Surgery	Number of patients	Blinding	Duration of surgery (minutes)	Intervention	Fast (hours)	Postoperative oral fluid intake	Results
Keane and Murray, 1986	Mixed outpatient surgery	212 in two groups	No	18	1000 mL Hartman's solution + 1000 mL DW versus no fluid	?	?	Fluid reduces thirst, drowsiness and increases well-being No effect on nausea
Spencer, 1988	Minor gynaecological surgery	100 in two groups	No	8	1 L CSL versus no fluid	?	?	Fluid reduces dizziness and nausea
Cook et al, 1990	Gynaecological laparoscopy	75 in three groups	Yes	20	CSL 20 mL/kg versus CSL + DW 20 mL/kg versus no fluid	11–16	?	Fluid reduces dizziness and drowsiness Hospital stay reduced in dextrose group
Yogendran et al, 1995	Mixed outpatient surgery	200 in two groups	Yes	28	Plasmolyte 20 mL/kg (1215 mL) versus plasmolyte 2 mL/kg (164 mL)	8–13	?	Fluid reduces thirst, dizziness and drowsiness No effect on nausea
Elkahim et al, 1998	Day case termination of pregnancy	100 in two groups	Yes	12	1 L CSL versus no fluid	9.66	1.5–2	Fluid reduces nausea and vomiting
Bennet et al, 1999	Dent-alveolar surgery	90 in two groups	Yes	?	NS 16 mL/kg versus NS 1 mL/kg	8–13	?	Fluid reduces dizziness and drowsiness No effect on nausea
McCaul et al, 2003	Gynaecological laparoscopy	108 in three groups	Yes	22	CSL 1.5 mL/kg/feeding hour (1115 mL) versus CSL + DW 1.5 mL/kg/feeding hour (1148 mL) versus no fluid	11.5	?	No significant differences between the groups

(Continued on next page)

Table 2 (continued)

Author	Surgery	Number of patients	Blinding	Duration of surgery (minutes)	Intervention	Fast (hours)	Postoperative oral fluid intake	Results
Magner et al, 2004	Gynaecological laparoscopy	141 in two groups	Yes	20	CSL 30 mL/kg versus CSL 10 mL/kg	13	?	Fluid reduced nausea and vomiting No effect on dizziness or thirst
Holte et al, 2004	Laparoscopic cholecystectomy	48 in two groups	Yes	68	LR 15 mL/kg (998 mL) versus 40 mL/kg (2928 mL)	2	Mean 600 mL	Fluid reduces thirst, nausea, dizziness, drowsiness, improves well-being and pulmonary function and shortens hospital stay

DW, dextrose in water 5%; CSL, compound sodium lactose (Na: 131, K: 5, Ca: 2, Cl: 111, lactate: 29 mmol/L); NS, normal saline 0.9%; LR, lactated Ringer's solution.

administered, however, equates very well with the patient's deficit from fasting, and may even be small if the fasting lasted more than 12–24 hours. Thus, the results confirm that fluid losses should be replaced, but do not assess the problem of fluid administration in excess of external losses during surgery.

Practice points

- preoperative glucose-containing fluid by the oral or intravenous route improves outcome; a deficit due to fasting should not exist
- fluid preloading of neuroaxial blockade has not been shown to prevent or lessen the decrease in blood pressure or the need for pressor substances, but may cause fluid overload
- the fluid volume needed for maintenance is not altered much by surgery
- evaporation from the surgical wound is small: 2.1–32.2 mL/hour, depending on the exposure of the intestines
- pathological fluid accumulation in the traumatized tissue is small in elective surgery
- the non-anatomical third space loss is based on flawed methodology and most probably does not exist
- the logical choice for replacement of lost blood is a colloid given on a volume-for-volume basis
- a small urinary output during surgery is acceptable as long as vasodilatation and not hypovolaemia is the cause
- in major surgery, trials of 'goal-directed fluid therapy' aiming at maximal stroke volume have shown diverging results, but not a convincingly improved outcome, most probably because the 'standard fluid therapy' has not been questioned or modified, causing some of the trials to test fluid overload versus even more fluid, because the volume difference between the groups have been small, and because the fluid therapy in the surgical ward has not been controlled
- also in major surgery, trials of 'restricted intravenous fluid therapy' or 'goal-directed fluid therapy' aiming at normal body weight have improved outcome in gastrointestinal surgery; the principles have not been tested during other surgical procedures
- in outpatient surgery, replacement of the deficit due to fasting with approximately 1000 mL of intravenous fluid increases postoperative well-being

Research agenda

- the role of glucose-containing fluid during surgery is not known
- possible transfer of fluid between compartments during surgery is unknown, if it occurs at all
- the goal of intravenous fluid therapy aiming at normal body weight—i.e. 'restricted intravenous fluid therapy'—needs testing in areas other than gastrointestinal surgery
- central haemodynamic changes during 'restricted intravenous fluid therapy' are unknown
- the goal of fluid to maximal stroke volume has not been tested against 'restricted intravenous fluid therapy'

One trial examined the effect of a mean volume of 1 versus 2.9 L LR in 48 patients undergoing laparoscopic cholecystectomy.^{1,32} Measured 2 and 4 hours postoperatively, it was found that thirst, dizziness, drowsiness, nausea, and fatigue were decreased, while well-being, pulmonary function and exercise capacity was increased in the group receiving liberal fluid therapy. However, the fluid was not the only difference between the groups in this trial: in the recovery room significantly more patients in the low-volume group received an opiate ($P=0.01$) in significantly larger doses ($P<0.04$) than did the patients in the high-volume group. As all the above outcome measures are well-known morphine side-effects, not controlling the postoperative opiate administration is a major weakness, and the result of the trial is therefore difficult to interpret. Moreover, in two previous trials (one by the same group of investigators), 3 L intravenous fluid has been shown to hamper pulmonary function.^{4,5}

The last trial—of gynaecological laparoscopy—found no significant benefits of fluid therapy compared to no fluid at all.³²

RECOMMENDATIONS

With no evidence of the existence of a non-anatomical third space loss and no effect of fluid preloading of neuroaxial blockade, the 'restricted intravenous fluid therapy' is not at all 'restricted', but based on current evidence. The principle is that loss should be replaced, but fluid overload (recognized as a postoperative body weight gain) should be avoided.

This principle should be continued *postoperatively* (in the recovery room and in the surgical ward), with replacement of the daily requirements for nutrition, electrolytes, glucose, and water. The patients should be fed.

Body weight measurements are the most reliable tool for estimation of fluid balance in surgical patients and should consequently guide the *quantity* of perioperative fluid administration. Registration of fluid losses on the fluid chart should guide the *quality* of fluid replacements. However, clinical judgement is indispensable: body weight changes do not recognize internal loss of vascular volume. Careful examination of patients with hypotension or low diuresis should be performed and the cause treated. If the cause is loss of volume, intravenous fluids should be supplemented; if the cause is vasodilatation (e.g. due to large doses of epidural analgesia or habitual anti-hypertensive medication), the treatment is not fluid but dose adjustment of the provoking factor or vasoconstricting agents (e.g. ephedrine). If the cause is development of a surgical complication (e.g. anastomotic leakage with sepsis), action should be taken to treat the complication, etc.

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Benefits and harms of perioperative beta-blockade

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Cardiac events in patients undergoing surgery may have serious consequences for both short- and long-term postoperative prognosis. Recently conducted trials have not demonstrated beneficial effects of perioperative beta-blockade, although originally small trials with methodological flaws did suggest this. We evaluate the evidence for using perioperative beta-blockade in both cardiac and non-cardiac surgery, and conclude that there is no statistically significant effect on mortality and insufficient evidence for a reduction of the incidence of myocardial infarction in meta-analyses of all randomized trials. However, confidence intervals of the intervention effects in the meta-analyses are wide, leaving room for both benefits and harms. The largest observational study performed suggests that perioperative beta-blockade is associated with higher mortality in patients with low cardiac risk or diabetes, and with lower mortality in patients with high cardiac risk undergoing non-cardiac surgery. Larger randomized trials are needed to determine dosage, optimal duration, and safety of therapy, and to identify populations in whom—and how—perioperative beta-blockade may be beneficial.

Key words: beta-blockers; adrenergic; perioperative care; surgery; perioperative procedures; surgical procedures; cardiac surgical procedures; postoperative; mortality; myocardial infarction.

Beta-blocker therapy after myocardial infarction (MI)^{1,2} and for congestive heart failure^{3–5} are well-documented pharmacological interventions. The beneficial effects of beta-blockers for these conditions comprise reduced mortality^{4,2}, reduced morbidity^{1,5}, improved life quality⁶, and ability to work after MI.⁷ As there is both pathological and angiographic evidence that the aetiology of MI resembles that in the non-surgical

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setting, it seems logical that perioperative beta-blocker administration could be beneficial during the period of perioperative stress.⁸ Until 1996, only observational studies and very small randomized trials with surrogate outcomes had investigated the effects of a preoperatively initiated perioperative beta-blockade in patients with cardiac risk factors, and only for short-term outcomes. This applied to both non-cardiac and cardiac surgery. Consequently the reports from the randomized trials of perioperative atenolol⁹ and bisoprolol¹⁰ for patients with or at risk for cardiac disease undergoing non-cardiac surgery were received internationally with great expectations. Both trials, at first sight, suggested a beneficial effect on mortality and postoperative cardiac morbidity. The trials, however, have serious flaws. Since the appearance of the initial reports of the small randomized trials on perioperative beta-blockade, a meta-analysis of the randomized trials performed up to 2003¹¹, two larger randomized trials on the effect of metoprolol in patients undergoing vascular surgery (MAVS trial)¹² and in diabetic patients undergoing major non-cardiac surgery (DIPOM trial)¹³, and a small trial in patients undergoing infrarenal vascular surgery (POBBLE trial)¹⁴, have been conducted. Further, a large retrospective cohort study¹⁵ analysing the association of perioperative beta-blockade and postoperative mortality has been performed. Moreover, Devereaux et al¹⁶ recently summarized the strength of the evidence for the use of perioperative beta-blockers in non-cardiac surgery in a cumulative meta-analysis of all randomized trials conducted before April 2003. These trials and meta-analyses profoundly challenge the widely held belief that nearly all patients scheduled for non-cardiac surgery benefit from perioperative beta-blockade. Furthermore, a thorough search reveals that the evidence for perioperative beta-blockade in cardiac surgery is virtually non-existent. The net result is that the recommendations launched by three American societies need major revisions and updating. This review aims to integrate and reach conclusions on the entire evidence produced up to August 2005 on perioperative beta-blockade.

DOES PERIOPERATIVE BETA-BLOCKADE PROTECT SURGICAL PATIENTS AGAINST POSTOPERATIVE COMPLICATIONS?

The most dreaded postoperative complications are death, postoperative MI, stroke, congestive heart failure, severe sepsis, and respiratory failure. At present nearly all trials and observational studies on perioperative beta-blockade have focused on cardiac complications and cardiac mortality, and a few have focused on stroke. From a narrow physiological and pathophysiological point of view, with the hypothetical assumption that beta-blockers have a cardioprotective effect, this might have been reasonable. However, severe sepsis and respiratory failure may eventually result from translocation of endotoxins from the intestinal lumen to the circulation due to long-lasting hypotensive periods. Hypotension needing treatment is precisely one of the documented adverse effects of perioperative beta-blocker intervention.¹⁶ The beta-blocked patient is at significant risk of hypotension and bradycardia needing treatment, which may stress the need to use overall mortality as the ultimate outcome measure in trials testing perioperative beta-blockade. The effect of perioperative beta-blockade on the incidence of atrial fibrillation and stroke in cardiac surgery has been addressed in a systematic review from the Cochrane Collaboration¹⁷ and is currently being tested in the PeriOperative Ischaemia Evaluation Trial (POISE trial).

Trials estimating the effect of perioperative beta-blockade on postoperative mortality in non-cardiac surgery

The trial by Mangano and colleagues⁹ indicated a substantial long-term postoperative mortality among patients with or at risk of coronary artery disease (CAD) undergoing non-cardiac surgery. Two hundred male patients undergoing elective major non-cardiac surgery were randomized to 7 days perioperative atenolol or placebo treatment. The patients had either CAD or at least two of the following cardiac risk factors: age above 65 years, hypertension, current smoking, serum cholesterol > 6.2 mmol/L, or diabetes mellitus. Event-free survival after discharge from hospital at 2 years was 83% in the atenolol group versus 68% in the placebo group ($P=0.008$). They reported a relative risk reduction in all-cause mortality of 55% after 2 years. Patients who were already receiving beta-blockers had them discontinued on entry to the study and were thereafter randomized to beta-blockade or placebo. The patients receiving placebo were, therefore, at risk of beta-blocker withdrawal symptoms.^{18,19} Deaths and adverse events in hospital were ignored in the analyses, and it appeared that the statistically significant effect of beta-blockade on survival analysis disappeared when outcomes were assessed on an intention-to-treat analysis where both in-hospital and long-term outcomes were included.⁸

The trial by Poldermans and colleagues¹⁰ added evidence for the preventive effect of perioperative beta-blockade on postoperative cardiac mortality and morbidity. A total of 112 patients undergoing high-risk vascular surgery were randomized to bisoprolol or standard perioperative care (i.e. where beta-blockers were used if symptoms or signs of perioperative myocardial ischaemia accompanied by tachycardia developed). Fifty-nine patients received bisoprolol and 53 patients received the standard treatment. Beta-blocker treatment was initiated a minimum of 1 week before surgery and lasted for 30 postoperative days. The patients were a high-risk subpopulation with abnormal results on stress echocardiography with dobutamine chosen among 1351 patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction. All included patients received a minimum of 7 days beta-blocker therapy preoperatively, but there was no information on patient compliance. The number of deaths and cases of MI in the group receiving bisoprolol treatment was 2 (3.4%) compared to 18 (34%) in the group receiving standard treatment 30 days postoperatively. After the first interim analysis a relative risk reduction in cardiac events of 91% in 30 postoperative days was reported. The trial was stopped at this point.²⁰ The effect may have been overestimated, as the trial selected a subgroup of extremely high-risk patients, had unclear randomization, was not blinded, and was stopped early.²¹

The implications of the two randomized trials^{9,10} are confusing. It seems appropriate that patients undergoing major surgery and having evidence of inducible myocardial ischaemia on stress testing should receive beta-blockers perioperatively, but we do not know if patients with a history of CAD presenting for major surgery should be given beta-blockers on the basis of this history alone. Mangano and colleagues studied patients who either had a history of CAD or who had two or more cardiac risk factors. Thus, the patients in this study could be subject to intermediate or high risk of adverse cardiac events. And what is the optimal duration and dosage of perioperative beta-blocker treatment? Is it a short-term treatment beginning immediately prior to surgery, as in the Mangano trial, or must the therapy be initiated at least 1 week before surgery and continued for 30 postoperative days as in the Poldermans trial? It is not clear what degree of

sympathetic blockade is required to offer cardiac protection. In addition, the perioperative introduction of beta-blockers and the associated adverse effects have not been extensively studied, and the safety of the deliberate addition of beta-blocker shortly before surgery needs to be established. For example, both the Mangano and the Poldermans trials were carried out in intensive care environments where adverse effects could easily be detected and corrected, but this may not be the case in an ordinary ward. And the abrupt interruption after perioperative beta-blockade also poses an additional risk as withdrawal of beta-blockers may lead to adrenergic hypersensitivity and may possibly worsen outcomes.^{18,19} Nevertheless, due to the results of these trials, both the American College of Physicians and the American College of Cardiology/American Heart Association have recommended the use of perioperative beta-blockade in patients with CAD.^{22,23} However, they also state that further research is needed, and this suggestion has been followed.

In 2004 Yang et al reported results from the MAVS trial¹², including 497 patients undergoing abdominal aortic, infrainguinal, or extra-anatomical revascularization surgery. The MAVS trial was adequately randomized and double-blinded, and included beta-blocker-naïve patients; the primary outcome measure was a 30-day postoperative composite outcome of cardiac death, non-fatal MI, unstable angina, new atrial, or ventricular dysrhythmia requiring treatment. The MAVS¹² trial randomized 497 patients undergoing vascular surgery to either a maximum of 5 days perioperative beta-blockade or placebo. The primary outcome was 30-day composite incidence of postoperative cardiac morbidity and mortality. The intervention, 100 mg metoprolol or equivalent intravenous dose, was started just prior to surgery and anaesthesia and continued until discharge from hospital for a maximum of 5 days. Yang and colleagues did not find a significant difference in the 30-day primary composite outcome measure: 25/247 patients (10.1%) on metoprolol versus 30/250 (12.0%) patients on placebo ($P=0.40$). Further, there was no statistically significant difference between the incidence of cardiac death, MI, or any other of the components of the composite outcome measure.

The MAVS findings are in accordance with the results of the DIPOM trial.²⁴ The DIPOM trial, including 921 diabetic patients undergoing non-cardiac surgery lasting more than 1 hour, is comparable to the Mangano et al trial⁹ regarding intervention (dosage and duration), the inclusion of intermediate- and high-risk patients, types of surgery, outcome measures, and follow-up. The effect of metoprolol 100 mg daily was compared with placebo on mortality and cardiovascular morbidity in beta-blocker-naïve diabetic patients above the age of 39 years undergoing non-cardiac surgery. The study drug was given during hospitalization to a maximum of 8 days, beginning the evening before surgery. The primary outcome measure was a composite of all-cause mortality, acute MI, unstable angina, or congestive heart failure. The median follow-up was 18 (range 6–30) months. The incidence of the primary outcome measure was 99/462 (21%) in the metoprolol versus 93/459 (20%) in the placebo group. The all-cause mortality frequency was 16% (74/462) in the metoprolol group and 16% (72/459) in the placebo group (log-rank test, $P=0.88$). A similar reduction of HR in the intervention group was obtained, 72²⁴ and 75⁹ beats per minute, respectively. Both intention-to-treat and per-protocol analyses were performed. Only diabetic patients were randomized, as this patient group seemed to benefit most from the treatment according to a subgroup analysis in the Mangano trial.⁹ In addition, 496 of all randomized diabetic patients also met the inclusion criteria of the Mangano trial.⁹ An analysis of this subgroup with the proportional hazards model could not reproduce anything similar to the favourable

effect of perioperative beta-blockade previously reported.²⁴ Fewer primary outcomes in the DIPOM trial were experienced than anticipated. This may be a reflection of the facts that some of the patients in the DIPOM trial may have been low-risk patients without CAD or diabetic complications, and that some patients underwent low-risk surgical procedures. Furthermore, patients undergoing emergency surgery and patients unable to give written informed consent were not randomized. Thus, a group of patients with high baseline risk and high event rate were excluded. As a consequence, the 95% CI of 0.82–1.46 in the multivariate analysis is wide. A beneficial effect of 18% or less or a detrimental effect of 46% or less of metoprolol cannot be excluded. However, a relative risk reduction of 50% or more, as reported by Mangano et al and Poldermans et al, can be ruled out. A daily dose of 100 mg metoprolol CR/XL during a mean of 4 1/2; days may not have been the optimal duration and dosage of therapy to ensure sufficient beta-blockade in all patients. However, the duration of treatment in the DIPOM trial seems to be longer than in most of the trials included in the meta-analysis by Stevens and colleagues¹¹, and certainly comparable to the duration of treatment in the trial by Mangano et al. Moreover, the dose regimen matches the dose regimen of Mangano and colleagues. A number of patients in the DIPOM trial only tolerated half the target dose or no dose at all due to hypotension and/or bradycardia. As a result, initiating beta-blockade with a dose of metoprolol higher than 100 mg in cardiac risk patients prior to surgery may jeopardize the patients. Administering the trial drug after discharge from hospital also causes difficulties in ensuring that the safety criteria are met.

Recently, the POBBLE trial investigators reported the results from their trial in 103 patients undergoing infrarenal vascular surgery of the effects of metoprolol 100 mg daily versus placebo on the primary composite outcome of 30-day postoperative cardiac events.¹⁴ The trial could not discern any statistically significant difference between the incidence of death or cardiac events in the intervention group (34%) and in the placebo group (32%). However, the POBBLE investigators found a statistically significant decrease between the groups concerning time from surgery to discharge ($P < 0.02$).

Also recently Lindenauer et al¹⁵ reported the results from a cohort study of 663 635 patients analysing whether beta-blocker intervention in the first two hospital days in patients undergoing non-cardiac surgery was associated with benefit or harm. They identified two groups of patients with a Revised Cardiac Risk Index (RCRI) of 3 and 4 that seemed to benefit from perioperative beta-blocker intervention, with an adjusted odds ratio for death in hospital of 0.71 (95% CI 0.63–0.80) and 0.58 (95% CI 0.50–0.67), respectively. However, patients with a RCRI of 0 and 1 seemed to be harmed, with odds ratios for death in hospital of 1.36 (95% CI 1.27–1.45) and 1.09 (95% CI 1.01–1.19), respectively. Moreover, in patients with diabetes perioperative beta-blocker intervention also seemed to be harmful, with an odds ratio of 1.28 (95% CI 1.10–1.50). This huge observational study with data from patients in 329 hospitals throughout the United States may suggest that patients with the highest RCRI scores benefit from perioperative beta-blocker intervention; however, it also suggests that patients with the lowest RCRI scores may be harmed from exactly the same intervention.¹⁵

From analyses of single randomized trials and one big cohort study it is still impossible to tell which types of patients would definitely benefit from perioperative beta-blockade.

The association between perioperative beta-blockade and mortality or morbidity in cardiac surgery

The effect of peri- or preoperative beta-blockade on postoperative mortality and MI in cardiac surgery has not been assessed as the primary outcome measure in any randomized clinical trials. However, the association between preoperative beta-blocker use and mortality and morbidity has been analysed in a large observational study²⁵ of 629 877 patients undergoing coronary artery bypass graft (CABG) between 1996 and 1999 from the Society of Thoracic Surgeons National Adult Cardiac Surgery Database (NCD). In this large north American observational analysis, preoperative beta-blocker therapy was associated with a small but consistent survival benefit for patients undergoing CABG, except among patients with a left ventricular ejection fraction of less than 30%. A much smaller Belgian retrospective cohort study of 1586 patients undergoing CABG has demonstrated a similar association.²⁶ Despite the lack of grade I and II evidence for the use of beta-blockers in order to prevent death and MI, an argument could be made for the use of perioperative beta-blockade to prevent the common postoperative atrial fibrillation in open heart surgery. In a recent published Cochrane systematic review¹⁷ the authors demonstrated in a meta-analysis including 4074 patients that perioperative beta-blockade was able to prevent atrial fibrillation when tested against placebo, and had a larger intervention effect than amiodarone and sotalol.¹⁷ Beta-blockers, however, were not compared with the other interventions, but solely to placebo. Furthermore, there were no statistically significant effects on the incidence of stroke or length of stay in hospital, which were clinically the most important outcome measures in this systematic review.¹⁷ As long as the effects on mortality and substantial postoperative morbidity of perioperative beta-blockade in cardiac surgery are unknown, it seems to us hazardous to use this intervention solely on the indication of preventing atrial fibrillation.

Perioperative beta-blockade: beneficial effects

The mechanisms of the potential beneficial effects of perioperative beta-blockade remain to be established. Sympatholytic effects of beta-blockade may reduce the incidence of perioperative cardiac complications. Several trials have demonstrated that perioperative beta-adrenergic blockade reduces the incidence of perioperative myocardial ischaemia.²⁷⁻²⁹ Perioperative cardiac events may be a result of a supply/demand imbalance in the delivery of oxygen to the myocardium; thus a reduction in heart rate produced by beta-blockers could minimize this imbalance. However, perioperative MI could also be a result of an acute coronary event precipitated by the rupture of an atheromatous plaque.³⁰ Beta-blockers may reduce the shear stress across atheromatous plaques by inducing haemodynamic changes, thereby reducing the incidence of plaque rupture and consequent acute coronary thrombosis.³¹ Another possible mechanism of perioperative beta-adrenergic blockade is a reduction in the neuroendocrine stress response to surgery. Beta-blockers may also improve myocardial metabolism independently of their effects on heart rate (HR), by reducing myocardial contractility or overall oxygen consumption of the heart.^{32,33}

Perioperative beta-blockade: harmful effects

The most common adverse effects of beta-adrenoceptor blockers are bradycardia, hypotension, congestive heart failure, and bronchospasm. In the cumulative meta-analysis of all randomized trials up to April 2003 recently published by Devereaux et al¹⁶

bradycardia and hypotension needing treatment were increased in the group receiving beta-blockers, with a relative risk of 2.27 (95% CL 1.53–3.36) and 1.27 (95% CL 1.04–1.56). In this meta-analysis all the included trials still monitored the patients during the postoperative period in a setting of an intensive care or intermediate care unit. However, this finding is based on relatively small trials, and most of them have been carried out in intensive care wards where adverse effects are easily detected and corrected. In an ordinary ward intensive monitoring of these patients may cause logistical problems, and the risk of experiencing serious adverse events may increase. The patients included in the DIPOM trial were discharged from the recovery room to an ordinary ward on usual discharge criteria. In the DIPOM trial bradycardia (HR below 65) or hypotension (systolic blood pressure below 100 mmHg) necessitating halving or stopping the study medication was increased by 15% in the metoprolol compared to the placebo group ($P < 0.05$). This problem may be even greater, as the HR and blood pressure in DIPOM patients were only assessed regularly immediately prior to administration of study medication, and there was a statistically insignificant tendency towards a higher incidence of serious adverse events.²⁴

The use of perioperative beta-blockade may also pose an additional risk as withdrawal of beta-blockers may lead to adrenergic hypersensitivity and possibly worsen outcomes.¹⁸ A particular concern is how long the treatment should last to avoid withdrawal effects. Neither Mangano and colleagues⁹, who treated patients with beta-blockers for a maximum of 7 days, nor Poldermans and colleagues¹⁰, who treated patients for a minimum of 37 days, have reported adverse effects from discontinuing beta-blockade. However, it remains possible that larger trials with increased power may detect adverse effects when the beta-blockers are withdrawn.

TYPES OF PERIOPERATIVE BETA-BLOCKADE

So far atenolol⁹, bisoprolol¹⁰, metoprolol^{12–14} and esmolol^{34,35} have been used in trials of perioperative beta-blockade in a daily dose equivalent to 100 mg of atenolol. The drug most often used is metoprolol; esmolol has been used in only a few trials of patients undergoing cardiac surgery, administered either as an infusion³⁴ or in cardioplegic solutions³⁵ to control HR.

The pharmacodynamic and pharmacokinetic profiles of atenolol and metoprolol are quite similar.³⁶ The absorption and coverage of a controlled release formulation (CR/XL) of 50 mg metoprolol given the day before surgery, and a second 100 mg metoprolol given between one and several hours before surgery on the day of surgery, is parallel to the regimen using 50 mg of atenolol twice a day. A bioequivalence study of two metoprolol CR/XL formulations, including assessment of day-to-day variability³⁷, and of metoprolol CR/XL in young subjects³⁸ have shown that the bioavailability and pharmacodynamic effects of 100 mg metoprolol CR/XL dosed once within 24 hours on HR and blood pressure is equal to a total of 200 mg traditional metoprolol administered as 100 mg metoprolol twice during 24 hours. The studies have also shown that the concentration of metoprolol in plasma was within therapeutic ranges 22–24 hours of the time with one dose every 24 hours. Furthermore, a tolerability study with 50 mg controlled-release metoprolol compared with 100 mg conventional metoprolol in hypertensive patients³⁹ has shown that 50 mg metoprolol CR/XL given as one dose in 24 hours has equal effects and improved tolerability compared with 100 mg conventional metoprolol in hypertensive patients.

An intravenous administration of the study drug has been used for the initial dose⁹ and in patients with pre- or post-operative ileus as in the DIPOM trial.¹³ But the use of individual intravenous titration must be extremely cautious because of the possible interaction between beta-blockade and epidural anaesthesia, with ensuing profound sympathetic blockade and hypotension after induction of general anaesthesia. This might also be a problem postoperatively¹⁶, as well as being preoperatively time-consuming.

In all the trials, except for that by Poldermanns et al¹⁰, the perioperative beta-blockade has been short-term use of a beta-blocker starting immediately prior to surgery and ending at up to 1 week postoperatively. In the trial by Poldermanns et al, bisoprolol was administered 30 days preoperatively and targeted to reduce HR to 60 beat/min.¹⁰

All the beta-blockers tried are without intrinsic sympathomimetic effects, and none of them have been compared to each other in terms of clinical postoperative outcome, as none possesses unequivocal benefits compared to placebo.¹⁶ In treatment of patients with chronic heart failure, carvedilol⁴⁰ reduces mortality compared to metoprolol, although short-acting metoprolol was given in a dose of 100 mg daily, a lower dose than now recommended. However, we still have to await the conclusion on perioperative beta-blockade compared to placebo before trials are launched to compare one beta-blocker with another in perioperative beta-blockade.

IS PERIOPERATIVE BETA-BLOCKADE EFFECTIVE IN DIABETIC PATIENTS FOR MAJOR NON-CARDIAC SURGERY?

Long-term postoperative mortality among diabetic patients is substantial. An observational study at Herlev Hospital⁴¹ indicated a 12-month overall postoperative mortality of 24% (95% CI 17–31%). One third of the fatalities occurred within 30 postoperative days. Concurrent ischaemic heart disease diagnosed before surgery was associated with an overall postoperative mortality of 44% (95% CI 29–58%), which was significantly higher ($P < 0.03$) than in diabetic patients without a history of ischaemic heart disease. Diabetic patients have an increased risk of developing ischaemic heart disease and are also more often in need of surgery compared to non-diabetic patients. Diabetes mellitus was a major predictor of postoperative mortality in the trial by Mangano and colleagues.⁹ The results of the trial showed that perioperative beta-blocker treatment of patients with diabetes had survival rates similar to those of patients without diabetes, whereas diabetic patients receiving placebo had a fourfold increase in mortality. However, diabetic patients constituted only a subgroup in the study ($n = 63/200$ patients). The trial by Poldermanns and colleagues¹⁰ included only 17 diabetic patients and did not specify the course of this subpopulation. No data concerning quality of perioperative metabolic control or autonomic neuropathy status were presented in any of the trials. In the Mangano trial patients were characterized by having a minimum of two risk factors of CAD, including diabetes. Furthermore, a subgroup analysis in the trial by Mangano and colleagues indicated that diabetic patients in particular would benefit from the treatment (hazard ratio = 0.25, no confidence interval provided). The trials by Mangano et al⁹ and Poldermann et al¹⁰ did not provide enough data from which to draw firm conclusions or recommendations for diabetic patients.

The effects of metoprolol in diabetic patients undergoing major non-cardiac surgery was tested in the DIPOM trial.²⁴ This trial was an investigator-initiated and -controlled, centrally randomized, placebo-controlled, blinded, multicentre trial. Thirteen centres in the Copenhagen area participated. The effect of metoprolol 100 mg CR/XL daily was compared with placebo on mortality and cardiovascular morbidity in beta-blocker-naïve diabetic patients above the age of 39 years undergoing non-cardiac surgery. The study drug was given during hospitalization to a maximum of 8 days, beginning the evening before surgery. The primary outcome measure was a composite of all-cause mortality, MI, unstable angina, or congestive heart failure. Follow-up involved re-examination of patients at 6 months and collection of data by linkage to the Danish National Hospital Register and the Centralized Civil Register. In the DIPOM trial 921 patients were randomized: 462 to metoprolol and 459 to placebo. Baseline patient characteristics were similar in the two groups. Patients received metoprolol for a mean of 4.6 days versus placebo 4.9 days. Metoprolol significantly reduced the mean HR by 11% and mean arterial blood pressure by 3%. The primary outcome measure frequency was 21% in the metoprolol versus 20% in the placebo group. Intention-to-treat analysis demonstrated a hazard ratio of 1.10 (95% CI 0.82–1.46). The all-cause mortality was 16% in both the intervention group and the placebo group. Per-protocol and secondary outcomes analyses showed similar results. The proportion of reported serious adverse events in the metoprolol group was 7.8% (36/462 patients) versus 5.7% (26/459 patients) in the placebo group ($P=0.20$). Although the long-term mortality of diabetic patients undergoing non-cardiac surgery is substantial, short-term perioperative metoprolol did not significantly affect mortality and cardiac morbidity or adverse events in diabetic patients undergoing non-cardiac surgery.

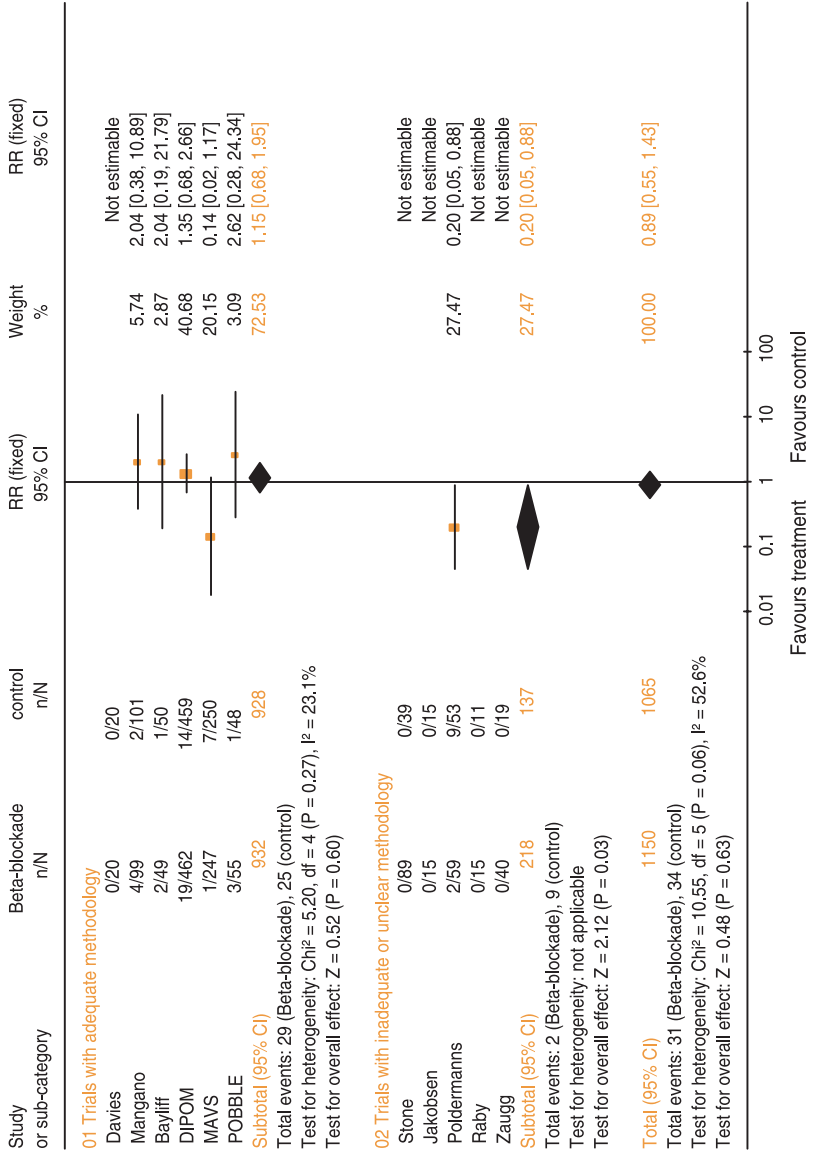
In the cohort study by Lindenaier et al¹⁵ analysing beta-blocker intervention during the first two hospital days in 663 635 patients undergoing non-cardiac surgery, a subgroup of 79 431 diabetic patients had an odds ratio of 1.28 (95% CI 1.10–1.50) for the occurrence of death in hospital.

On the basis of the evidence provided, use of perioperative beta-blockade on the indication of diabetes does not seem to be indicated.

CURRENT EVIDENCE OF THE EFFECT OF PERIOPERATIVE BETA-BLOCKADE ON 30-DAY MORTALITY AFTER NON-CARDIAC SURGERY

We combined the data from the DIPOM trial²⁴, the MAVS trial¹², and the POBBLE trial¹⁴ with the data in the meta-analysis by Stevens and colleagues¹¹ on 30-day postoperative mortality. The meta-analysis included data from eight trials assessing the effect of beta-blockade on 30-day postoperative cardiac morbidity and mortality in patients undergoing non-cardiac surgery (386 patients in the beta-blocker group versus 308 patients in the placebo group).^{9,10,12,24,27,29,42–46} Perioperative beta-blockade versus placebo did not significantly affect 30-day postoperative all-cause mortality (RR 1.15; 95% CI 0.68–1.95)^{10,14,27–29,42,46} among the trials having adequate methodology (Figure 1).^{21,47,48} There was only modest heterogeneity ($I^2=23.1\%$). Among the trials having inadequate or unclear methodology, the effect of perioperative beta-blockade versus placebo on 30-day postoperative all-cause mortality was significant (RR 0.20; 95% CI 0.05–0.88) (Figure 1)^{10,27–29,42,46}, but such trials may be biased.²¹ Only the trial by Poldermans and colleagues¹⁰ provided data. Even when we added the trials having one or more inadequate quality components to the adequate

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 Outcome: 01 Perioperative beta-blocker versus placebo/no intervention



trials, there was no significant effect of beta-blockade on mortality (RR 0.89; 95% CI 0.55–1.43). Now there was more heterogeneity among the trial results ($I^2=52.6\%$)(Figure 1),^{10,27,42,46} and the test of interaction between the intervention effect in trials with adequate and inadequate methodological quality was statistically significant ($P=0.0001$).

CURRENT EVIDENCE OF THE EFFECT OF PERIOPERATIVE BETA-BLOCKADE ON LONG-TERM MORTALITY AFTER NON-CARDIAC SURGERY

The only trials so far addressing long-term mortality have been the trial by Mangano et al⁹ and the DIPOM trial. In the trial by Mangano and colleagues⁹ event-free survival after discharge from hospital at 2 years was 83% in the atenolol group versus 68% in the placebo group ($P=0.008$), indicating that short-term (7 days) perioperative beta-blocker treatment could reduce the long-term postoperative mortality and cardiac morbidity in patients with or at risk of CAD. But as already pointed out, this way of summarizing the results does not include the fatalities during the intervention with beta-blockers, and if deaths in the postoperative period during hospitalization are included in the analysis the statistical significance disappears.

In the DIPOM trial²⁴, which included 921 diabetic patients, the long-term mortality (median 18 months observation) was 16% in both the metoprolol and the placebo group (log rank test, $P=0.88$). Also, in the subgroup of patients fulfilling the criteria for inclusion in the trial by Mangano and colleagues⁹, there was no statistically significant effect of perioperative metoprolol CR/XL 100 mg on long-term mortality.

CURRENT EVIDENCE OF THE EFFECT OF PERIOPERATIVE BETA-BLOCKADE ON POSTOPERATIVE MYOCARDIAL INFARCTION AFTER NON-CARDIAC SURGERY

The benefits of perioperative beta-blockade in reducing perioperative myocardial ischaemia in cardiac risk patients undergoing vascular surgery have been demonstrated in non-randomized studies^{46,49} as well as in randomized trials.^{27,28} There is also evidence from several randomized trials that perioperative beta-blockade in cardiac risk patients undergoing non-cardiac surgery reduces the occurrence of perioperative cardiovascular morbidity, as determined by blood pressure and HR responses as well as ECG changes associated with ischaemia.^{28,29,50,51} However, these are surrogate outcome measures. We combined the data from the DIPOM trial²⁴, the MAVS trial¹², and the POBBLE trial¹⁴ with the data in the meta-analysis by Stevens and colleagues¹¹ on 30-day postoperative MI. Among the

Figure 1. Meta-analysis of 30-day all-cause mortality in randomized trials comparing perioperative beta-blocker versus placebo/no intervention included in the meta-analysis by Stevens et al¹¹ plus the data from the DIPOM trial²⁴, the MAVS trial¹², and the POBBLE trial.¹⁴ Trials were subdivided into those with adequate methodology (i.e. with adequate generation of the allocation sequence, adequate allocation concealment, and adequate blinding) and those being inadequate or unclear regarding one or more of these components. The test of interaction between the intervention effect in trials with adequate and inadequate methodological quality was statistically significant ($P=0.0001$).

Review: Perioperative beta-blockade
 Comparison: 02 Perioperative non-fatal myocardial infarction
 Outcome: 01 Beta-blocker versus placebo/no intervention

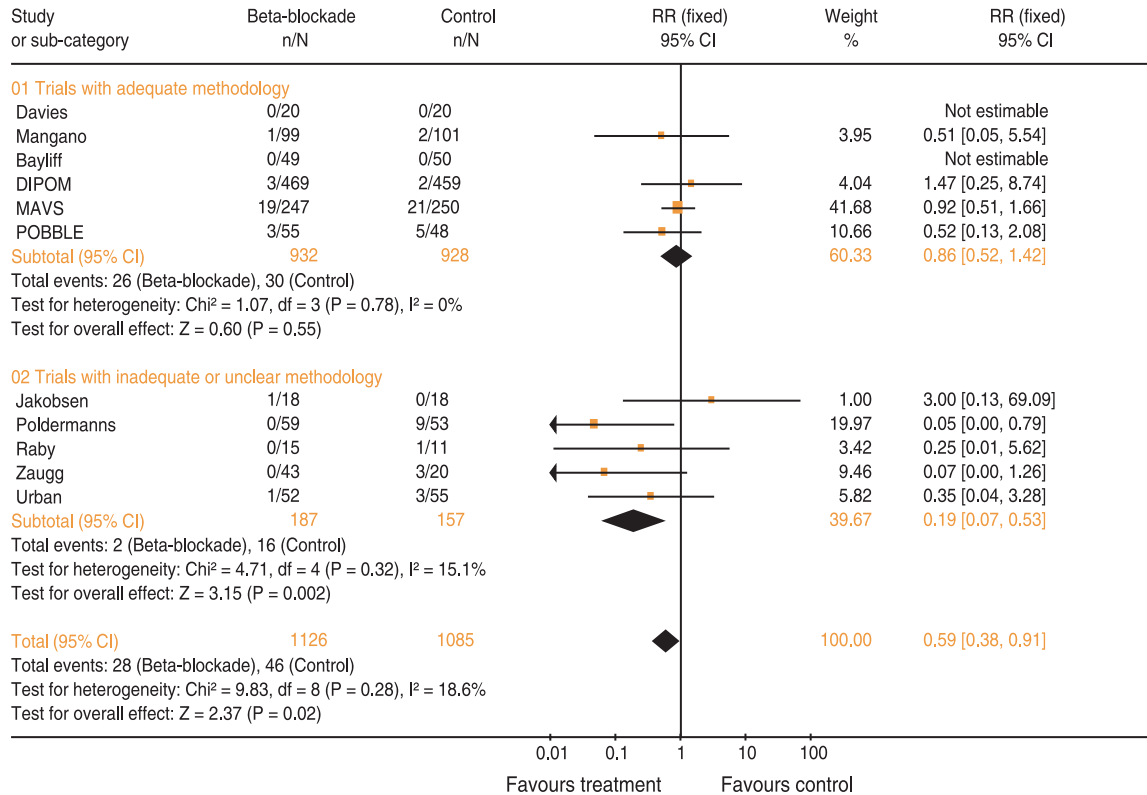


Figure 2. Meta-analysis of perioperative non-fatal myocardial infarction (MI) in randomized trials comparing perioperative beta-blocker versus placebo/no intervention

trials having adequate methodology, the effect of perioperative beta-blockade versus placebo on 30-day postoperative MI was not significant (RR 0.86; 95% CI 0.52–1.42) (Figure 2).^{10,14,27–29,42,43,46} There was no heterogeneity ($I^2=0\%$). Among the trials having inadequate or unclear methodology, the effect of perioperative beta-blockade was significant (RR 0.19; 95% CI 0.07–0.53) (Figure 2)^{10,27–29,42,46}, but again this may be due to bias.²¹ There was no substantial heterogeneity ($I^2=15.1\%$). When combining the results of the trials having one or more inadequate quality component to the adequate trials, we also observed a significant effect of beta-blockade on non-fatal MI (RR 0.59; 95% CI 0.38–0.91). But now the heterogeneity among the trial results ($I^2=18.6\%$) (Figure 2) was bigger, and the CL considerably larger, and the test of interaction⁵² between the intervention effect in trials with adequate and inadequate methodological quality was statistically significant ($P<0.0001$). Caution should be exercised in interpreting these results because of the inherent differences in patient population, types and dosages of beta-blocker used, time of initiation, duration of treatment^{10,27,42,43,46}, and most importantly the inclusion of trials with unclear or inadequate methodological quality.²¹

CURRENT EVIDENCE OF THE EFFECT OF PERIOPERATIVE BETA-BLOCKADE ON POSTOPERATIVE MORTALITY AND MYOCARDIAL INFARCTION AFTER CARDIAC SURGERY

There is no grade I or II evidence on the effect of peri- or preoperative beta-blockade on postoperative mortality and MI in cardiac surgery. Two observational studies, one large²⁵ and one small²⁶, have suggested that patients already preoperatively in beta-blocker therapy for reasons other than the forthcoming surgery and anaesthesia have a small but consistent survival benefit when undergoing CABG. This, however, did not apply to patients with a left ventricular ejection fraction of $<30\%$. Evidence for perioperative beta-blockade is virtually non-existent.

SUMMARY

Implications for clinical practice

A possibly beneficial effect of perioperative beta-blockade in high-risk patients having evidence of myocardial ischaemia on stress testing cannot be excluded.¹⁰ However, the DIPOM²⁴, the MAVS¹², and the POBBLE¹⁴ trials did not find any significant beneficial effects from perioperative beta-blockade in cardiac risk patients. In addition, the meta-analyses were unable to demonstrate a statistically significant difference in fatal events (Figure 1) or in non-fatal MI (Figure 2) when trials with inadequate or unclear methodology were excluded. On the basis of the DIPOM results a beneficial effect of

Figure 2. Meta-analysis of perioperative non-fatal myocardial infarction (MI) in randomized trials comparing perioperative beta-blocker versus placebo/no intervention included in the meta-analysis by Stevens et al¹¹ plus the data from the DIPOM trial²⁴, the MAVS trial¹², and the POBBLE trial.¹⁴ The trials were subdivided into those with adequate methodology (i.e. with adequate generation of the allocation sequence, adequate allocation concealment, and adequate blinding) and those being inadequate or unclear regarding one or more of these components. The test of interaction between the intervention effect in trials with adequate and inadequate methodological quality was statistically significant ($P<0.0001$).

18% or less of perioperative beta-blockade on our primary outcome in diabetic patients cannot be excluded. This is also the case with a detrimental effect of 46% or less. Thus, there is no valid evidence to recommend perioperative beta-blocker treatment on the sole indication of diabetes mellitus. These figures are supported by our meta-analyses taking methodological quality into consideration. Also the observational study by Lindaenauer et al¹⁵ casts considerable doubt upon the benefits of using perioperative beta-blockade in low- and intermediate-risk patients as well as in diabetic patients undergoing non-cardiac surgery. Therefore, considering the design flaws in the two randomized clinical trials first advocating the use of perioperative beta-blockade in non-cardiac surgery^{9,10}, and the virtually non-existent high-grade evidence in cardiac surgery, there is not sufficient evidence to recommend perioperative beta-blockade in any beta-blocker-naive patients. International, national, and local guidelines therefore need to be updated accordingly.

Practice points

- there is insufficient evidence to recommend perioperative beta-blockade in beta-blocker-naive patient in any type of surgery for the prevention of death, myocardial infarction or stroke
- perioperative beta-blockade prevents atrial fibrillation in cardiac surgery, but evidence is inconclusive for an effect on stroke and length of stay in hospital
- perioperative beta-blockade in non-cardiac surgery may be associated with a higher mortality in low-risk cardiac and diabetic patients (evidence grade III)
- perioperative beta-blockade in non-cardiac surgery may be associated with a lower mortality in high-risk cardiac patients (evidence grade III)
- national and international recommendations need major revision and updating

IMPLICATIONS FOR RESEARCH

Short-term perioperative metoprolol (100 mg/day) does not significantly affect mortality and cardiac morbidity in patients undergoing non-cardiac major surgery. However, possibly a larger dose and/or longer treatment duration with beta-blockers may provide a beneficial effect on important clinical outcomes, although possible harm cannot be excluded.

Until now the use of perioperative beta-blockade has not been associated with significant risk as long as the treatment is withheld in cases of relative bradycardia or hypotension. However, this conclusion is based on small trials with patients observed postoperatively in intensive care wards. In future trials a larger number of patients may have to be treated to prevent one non-fatal MI or fatal event, and the treatment may have to be continued after discharge from the intensive care ward or hospital. This makes heavy demands on the examination of the safety of the treatment, and it is extremely important to weigh the benefits of perioperative beta-blockade against any risk of harm, both in ordinary wards and after discharge from the hospital.

The design flaws in the first clinical trials advocating the use of perioperative beta-blockade in non-cardiac surgery^{9,10} make it very likely that these results are false.⁵³ Future trials must be adequately powered, as it is very likely that the effect of

perioperative beta-blockade in cardiac risk patients has been overestimated. The size of intervention effects is often overestimated in early, small trials compared with later, equally rigorous but larger trials.^{53,54} This pattern may arise from bias⁵³, but it may also be related to a shift in setting from trials testing efficacy under ideal condition to those assessing effectiveness in daily clinical practice.⁵⁵ In long-term prevention trials on beta-blockade for survivors of MI⁵⁶, a relative risk reduction of 22% can be calculated in non-fatal reinfarction or for fatal events. It is probably more realistic to expect this effect size from short-term perioperative beta-blocker treatment.^{57,58} To detect a 20% relative risk reduction in the primary composite outcome with a 5% type I error rate, 80% power, and a control outcome rate of 10%, we need a sample size of at least 6626 patients, as stressed by Devereaux et al¹⁶. Our meta-analyses—including data from the DIPOM, MAVS and POBBLE trials (Figures 1 and 2) on peri- and postoperative mortality and non-fatal PMI—included only about 20% of this minimal sample size. The evidence from the meta-analyses is therefore inconclusive. This is even more true if we adjust the sample size for heterogeneity among the included trials^{59–61} to detect a relative risk reduction of approximately 20% in a meta-analysis or an equally powered randomized trial. Large randomized trials using larger dose and/or longer duration of treatment than were used in the DIPOM and the MAVS trial are therefore needed to answer questions regarding optimal duration and dosage, and to investigate the incidence and degree of adverse reactions to perioperative beta-blockade, thereby identifying populations in which beta-blocker use is beneficial and safe. Such a trial, conducted by the PeriOperative ISchemic Evaluation study (POISE) investigators, is currently under way.^{57,58,62}

Research agenda

- the evidence from the meta-analyses to detect a relative risk reduction of approximately 20% is highly inconclusive when the necessary sample size is adjusted for heterogeneity among included trials
- large randomized trials using larger doses and/or longer duration of treatment than used hitherto are needed
- the PeriOperative ISchemic Evaluation study (the POISE trial), which is aiming for inclusion of 10 000 patients for perioperative beta-blockade, is currently under way and needs international support

ACKNOWLEDGEMENTS

We want to thank the DIPOM Trial Group without whom this review would have been impossible.

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6

Acupuncture and anaesthesia

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Acupuncture and related techniques are increasingly practised in anaesthesia. This paper reviews the current evidence and applicability of acupuncture and related techniques for anaesthetic procedures and postoperative nausea and vomiting. Recent evidence suggests that manual acupuncture is effective for reducing preoperative anxiety and for postoperative pain relief. Current available data do not support the use of acupuncture as an adjunct to the general anaesthetic in the intraoperative setting. There are extensive and good quality data to support the use of P6 acupoint stimulation techniques for preventing postoperative nausea and vomiting in combination with or as an alternative to conventional anti-emetics. The use of acupuncture for labour pain management appears promising but requires further research. Patient selection, acupoint selection, needling techniques, and mode of acupuncture need to be considered when applying acupuncture and related techniques in the perioperative setting. There are guidelines for the conduct and reporting of acupuncture research, and these should be followed to improve the quality of studies.

Key words: evidence-based medicine; acupuncture; perioperative care; postoperative nausea and vomiting; pain.

Acupuncture is an integral part of an ancient Chinese system of medicine that has been used for more than 2500 years to treat diseases and relieve pain.¹ The process of acupuncture involves the use of small needles placed at specific points along the energy meridians in the body to regulate the flow of *qi* (vital energy) along these pathways to help restore the patient to health. Non-invasive techniques of acupuncture include manual acupressure, acupressure wristbands, transcutaneous electrical stimulation, moxibustion, and laser stimulation. Compared to invasive manual acupuncture,

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non-invasive stimulation techniques require less practitioner time spent directly with the patient and facilitates standardization of acupoint stimulation.

Official reviews conducted in the United States, United Kingdom, Europe and Canada suggest that acupuncture appears to be effective for postoperative dental pain, postoperative nausea and vomiting (PONV), and chemotherapy-related nausea and vomiting.² For chronic pain and neck pain, the evidence is considered inconclusive and difficult to interpret.² In the last decade, there has been growing interest in the use of acupuncture and related techniques in anaesthesia. Although there is increasing evidence that acupuncture evokes changes via the nervous system¹, there is much scepticism among anaesthetists about its effectiveness.

This paper reviews the current evidence and applicability of acupuncture and related techniques for anaesthetic procedures and PONV using an evidence-based approach. For detailed background, theory, mechanism of action of acupuncture, and perioperative studies of acupuncture published to the end of 2003, the reader is referred to a review by Chernyak and Sessler.¹

IS THERE GOOD EVIDENCE?

Methodological quality of primary acupuncture and related technique studies

One of the arguments for not supporting the use of acupuncture in anaesthetic practice is that the methodological rigour of clinical trials of acupuncture and related techniques is generally poor.² Some of the methodological flaws in clinical trials of acupuncture and related techniques are similar to randomised controlled trials in conventional medicine: inadequate allocation concealment, no blinding, and loss to follow-up. In addition to these flaws, specific problems unique to acupuncture randomised controlled trials are treatment effects³, matching sham control, and heterogeneity of acupoints. These issues are discussed in more detail below.

Treatment effects of complex non-pharmacological interventions

In a conventional drug trial, diagnosis determines the eligibility for the trial and occurs before the drug intervention. Talking and listening to the patient are separate from the drug intervention. In comparison, treatment factors that are characteristic of acupuncture include, in addition to the needling, the diagnostic process and aspects of talking and listening to the patient (which may be different at each acupuncture session).³ Therefore, it has been suggested that the use of placebo- or sham-controlled trial designs for acupuncture interventions may lead to false-negative results.³

Matching sham control

There is considerable controversy as to the appropriate placebo as a control intervention in acupuncture studies. 'Sham acupuncture' (acupuncture at random points on the body surface that are thought to be inactive and are not located in the meridian) is often used. A recent functional magnetic resonance imaging showed

that acupuncture at Hegu LI4, a major analgesia acupoint, evoked specific activation in the middle temporal gyrus and cerebellum, along with deactivation areas in the middle frontal gyrus and inferior parietal lobule, compared with the effects of sham acupuncture.⁴ These findings suggest that real acupuncture induces specific patterns of brain activity different to sham acupuncture, which may explain the therapeutic effects of real acupuncture.

Recent evidence suggests that the Streitberger needle is promising as a valid and convincing placebo needle for use in acupuncture trials.⁵ As the needle is pushed against the skin, it causes a pricking sensation, but as increased pressure is applied, the shaft of the needle disappears into the handle, giving the impression that the needle is actually entering the skin.⁵ Most patients were unable to discriminate between the real acupuncture needle and the Streitberger needle by penetration; however, only 60% found similarities between real acupuncture and placebo acupuncture.⁵ The authors concluded that further work on inter-tester reliability and standardization of technique is needed before the Streitberger needle is valid and reliable as a placebo needle.

Heterogeneity of acupoints

Many different acupoints can be stimulated to treat the same disease or syndrome. For example, for PONV the Neiguan P6 is the most common single acupoint studied, although there are more than 30 classic acupoints described as being effective for nausea and vomiting. Such simplification may not always be appropriate and may result in the treatment failure seen in many studies.¹ The selection of acupoints is discussed in more detail in the latter part of this chapter.

A recent guideline on design, implementation and reporting of clinical research on acupuncture and related techniques has been published and may improve the quality of trials conducted in the future.⁶ Several complementary medicine journals have now adapted the STRICTA guidelines to improve standards for reporting interventions in controlled trials of acupuncture.⁷ These guidelines may lead to greater ease in interpreting the results of trials and systematic review of acupuncture and related techniques.

METHODOLOGICAL QUALITY OF SYSTEMATIC REVIEWS OF ACUPUNCTURE AND RELATED TECHNIQUE STUDIES

Anaesthetists are increasingly using systematic reviews for patient management. Are systematic reviews of acupuncture and related techniques in the anaesthetic setting reliable? The answer is unclear as there are no data. However, a recent study showed that the quality of reporting complementary and alternative medicine systematic reviews (acupuncture, homeopathy, cognitive behaviour therapy) is at least as good as that found for conventional medicine, and is not affected by inclusion or exclusion of language other than English.⁸ Publication bias may be problematic in systematic review of acupuncture, as one study found that all primary trials originating in China, Japan, Hong Kong and Taiwan were all positive.⁹ The implication of this is that the efficacy of acupuncture may be over-estimated. As more systematic reviews of acupuncture and related techniques are published in anaesthesia, the quality of these systematic reviews and consideration of publication bias should be assessed.

FINDING THE EVIDENCE

In order to apply the evidence on acupuncture and related techniques, anaesthetists must know how to obtain this information efficiently. Good sources of information about acupuncture and related techniques include electronic searching of MEDLINE, EMBASE, the Cochrane Library and CISCOM database. The CISCOM database was developed by the United Kingdom Research Council for Complementary Medicine and contains articles on complementary and alternative medicine published in the medical literature.¹⁰ Apart from the mainstream anaesthetic journals, the following journals have published acupuncture and related techniques in the anaesthesia setting and may be useful sources of evidence to consider: *Acupuncture in Medicine*, *Journal of Alternative and Complementary Medicine* and *Evidence-based Complementary and Alternative Medicine*.

EVIDENCED-BASED INTERVENTIONS

Convincing evidence from randomised controlled trials and systematic reviews of perioperative applications of acupuncture and related techniques are available in anaesthesia. Below is a selection of current evidence published in the last 2 years (2004 to September 2005). For earlier studies, refer to the review by Chernyak and Sessler.¹

PREOPERATIVE INTERVENTIONS

Several randomised controlled trials of auricular acupuncture at 'master cerebral point', 'tranquilizer point' and 'relaxation' suggest that it is effective for treatment of preoperative anxiety in surgical patients.¹ More recently, auricular acupuncture has been extended to parents of children undergoing surgery.¹¹ Mothers of children undergoing general anaesthesia for outpatient surgery were randomised to auricular acupuncture or sham acupuncture (auricular press needles at the shoulder, wrist and extraneous auricular point). After induction, maternal anxiety in the acupuncture group, as measured by the State Trait Anxiety Inventory, was slightly lower than that in the sham group (42.9 ± 10 versus 49.5 ± 11 , respectively; $P=0.014$). An important outcome of the study was that children whose mothers received the acupuncture intervention were significantly less anxious on entry to the operating room and during introduction of the anaesthesia mask. No side-effects were reported in the study.¹¹

More recently, the same group of investigators examined the effect of acupressure on the Yintang point (midpoint between the two eyebrows) on preoperative parental anxiety.¹² Parents were randomised to an acupressure bead with occlusive tape covering at the Yintang point or sham acupressure above the lateral border of the left eyebrow (same dermatomal distribution as the Yintang point) for 20 minutes in the preoperative holding area. Parents in the acupressure group had significantly less anxiety at 20 minutes post-intervention compared with parents in the sham group (37 ± 10 versus 45 ± 13 , respectively, $P=0.03$). The main advantage of acupressure over auricular acupuncture at the Yintang point for preoperative anxiety was that there was less discomfort.¹²

In contrast, there was no difference in the reduction of preoperative anxiety levels in a randomised controlled trial of acupuncture versus sham acupuncture at the Yintang point in patients undergoing minor or moderate surgery.¹³ The differences in results

between these studies^{11–13} may be due to different techniques and the way in which anxiety was measured (State Trait Anxiety Inventory^{11,12} and verbal score scale¹³). In general, the results appear to be favourable for the use of acupuncture and related techniques for preoperative anxiety.

INTRAOPERATIVE ACUPUNCTURE-ASSISTED ANAESTHESIA

Interest in the role of acupuncture for anaesthesia grew following the reports of surgery being performed with only acupuncture as an anaesthetic in China by Western physicians more than 30 years ago.¹⁴ However, it became clear from subsequent research that acupuncture does not provide true anaesthesia or unconsciousness but rather provides analgesia and sedation.¹ Nevertheless, on the basis of the involvement of endogenous opioid peptides along the pain pathway proposed by Pomeranz and Chiu¹⁵, focus has shifted towards the role of acupuncture in reducing intraoperative anaesthetic and opioid requirements.

In a recent review, Chernyak and Sessler¹ concluded that although acupuncture may reduce the anaesthetic requirement in some volunteer studies, the reduction was not clinically important. In addition, intraoperative acupuncture stimulation did not alter the analgesic requirement.¹ This has been supported by the findings of another recent systematic review¹⁶ where real acupuncture was not significantly different from placebo acupuncture as an adjunctive analgesic during surgery. This conclusion was later supported by a recent well-designed randomised controlled trial by Usichenko et al.¹⁷ Although the German group had demonstrated a significant reduction in postoperative analgesic requirement and pain score in patients after total hip arthroplasty with auricular acupuncture, the intraoperative fentanyl requirement and duration of general anaesthesia were similar in both acupuncture and control groups.¹⁷ Hence, the currently available data do not support the use of acupuncture as an adjunct to the general anaesthetic in the intraoperative setting.

POSTOPERATIVE INTERVENTION

Postoperative pain control

Recent evidence¹ suggests that acupuncture may be effective for postoperative pain relief, but it probably requires a high level of expertise and training of the practitioner. In a recent randomised controlled trial¹⁷ patients in the acupuncture group received press steel needles at several points (hip joint, shenmen, lung and thalamus of the ipsilateral ear) compared to the control group receiving sham needles on the non-acupuncture points of the helix, fixed with flesh-coloured adhesive tape. Compared with the control group, the acupuncture group required significantly less analgesia (32%) during the first 36 hours after surgery and had a longer time to first request for analgesia.¹⁷ Also patients in the acupuncture group had a significantly lower pain score at all time intervals compared with sham controls.¹⁷ The success of blinding was confirmed in this study as more than 80% of patients from both acupuncture and control groups believed that they had received true acupuncture.¹⁷

Postoperative nausea and vomiting (PONV)

The overall incidence of PONV is reported to be about 38% and may reach 79% in high-risk patients.¹⁸ The current consensus strategy is to identify high-risk patients, avoid emetogenic stimuli, and use multimodal therapy.¹⁹ Acupuncture and related techniques were identified as important non-pharmacological interventions to consider.¹⁹

Several reviews have confirmed the effectiveness of acupuncture and related techniques in preventing PONV at the P6 acupoint.^{1,20–23} Although the earlier review suggested that acupuncture is ineffective for PONV in children²², it became clear in a subsequent review²³ that acupuncture for PONV is as effective in children as in adults. A plausible explanation is that acupuncture was administered after induction of anaesthesia which failed to elicit the anti-emetic effect of acupuncture.¹ The effectiveness of acupuncture-related techniques for the prevention of PONV in children has been reaffirmed by recent studies.^{24,25} Two acupuncture-related techniques were recently compared with anti-emetics in paediatric patients: laser acupuncture versus metoclopramide versus sham laser²⁴ at P6 acupoint, and acustimulation with capsicum plaster versus ondansetron versus sham plaster at P6 acupoint.²⁵ In these randomised placebo-controlled trials, it was found that these acupuncture-related techniques significantly reduced the incidence of PONV and were as effective as the anti-emetics.^{24,25} In a separate randomised controlled trial of transcutaneous electrical acupoint stimulation versus ondansetron versus control (no treatment), acupoint stimulation was effective for prevention of PONV.²⁶ Moreover, its effect is comparable to ondansetron.²⁶ The application of these acupuncture-related techniques was initiated prior to induction of anaesthesia in all three paediatric studies, and there were very few side-effects.

However, there is a recent conflicting report on the timing of acupuncture stimulation in relation to the induction of anaesthesia. In a randomised placebo-controlled patient- and observer-blinded trial, Streitberger et al.²⁷ showed no difference between applying acupuncture before or after induction of anaesthesia. The main finding was that acupuncture significantly reduced the incidence of postoperative vomiting, but not nausea, in patients undergoing gynaecological or breast surgery. One plausible explanation for this conflicting result is that, as the authors also suggested, Neiguan P6 is hardly the only point to prevent PONV, and that other acupuncture points may be required to supplement the P6 effect.²⁷

In a study to evaluate the efficacy of transcutaneous electrical acupoint stimulation in combination with ondansetron, the device was most effective for reducing PONV when applied after plastic surgery rather than before surgery.²⁸ Unlike many previous studies of acupuncture and related techniques for prevention of PONV, patient satisfaction was measured. Patients receiving peri- or postoperative acustimulation therapy had significantly higher satisfaction with the quality of recovery and anti-emetic management than patients receiving preoperative acustimulation.²⁸ As there is a paucity of well-designed studies with direct comparisons of the timing of acupoint stimulation^{27,28}, the question of when to apply acupoint stimulation remains unclear.

Other postoperative complications

The use of acupuncture for postoperative laryngospasm and cardiovascular resuscitation has been reviewed, and the evidence does not support its use in these settings due to conflicting results or insufficient data.¹

In a randomised double-blind sham-controlled study, Park et al.²⁹ showed that capsicum plaster on the Korean hand acupuncture point K-A20 significantly reduced the incidence of postoperative sore throat compared with sham and placebo control groups (0 versus 16 and 19%, respectively). Although further evaluation is required, this early result appears to be promising and may be considered in patients with a high risk of developing postoperative sore throat, such as in patients with anticipated difficult airway intubation.

LABOUR PAIN MANAGEMENT

A systematic review of three randomised controlled trials of women in labour³⁰ suggests that acupuncture alleviates pain and reduces analgesic consumption compared with control groups (relative risk 0.36, 95% confidence interval 0.24–0.54). Common acupoints used during labour in all three trials included in the systematic review were: Baihui GV20 (tension), Taichong LV3 (cervix rigidity), Kunlun UB60 (back pain in early labour), Ciliao UB32 (back pain later in labour) and Hegu LI4 and Sanyinjiao SP6 (strong pain during contractions). No adverse events were reported in any of the trials included in the review.³⁰ The authors concluded that the effectiveness of acupuncture for labour pain is promising but uncertain, mainly due to paucity of primary trials in the area.³⁰

Following the publication of the systematic review³⁰, acupressure at the SP6 acupoint for 30 minutes was effective for decreasing labour pain for up to 60 minutes after the acupressure intervention—mean pain score in acupressure group versus sham (SP6 touch) group were 7.7 ± 1.5 versus 8.9 ± 1.7 , respectively—but there was no difference in the use of analgesia ($P=0.20$).³¹ The total labour time (3 cm cervical dilatation to full dilatation) was significantly shorter ($P<0.01$) in the Sanyinjiao SP6 acupressure group (108 ± 52 minutes) than in the sham group (146 ± 61 minutes).³¹ Based on these findings^{30,31}, acupuncture and related techniques are promising interventions to consider for labour pain management.

GENERAL PRINCIPLES OF APPLYING ACUPUNCTURE AND RELATED TECHNIQUES

Although a thorough understanding of the theory of traditional Chinese medicine is advisable, there are several factors which should be considered when applying acupuncture in the perioperative setting, including patient selection, acupoint selection, needling techniques, and mode of acupuncture.

Patient selection

Chernyak and Sessler¹ have summarized some of the important aspects of patient selection for perioperative acupuncture and related techniques. Acupuncture in young adults is generally more effective than in elderly patients, with the exception of small children who would normally be uncooperative with needling.¹ Furthermore, a better result is expected from patients with a good attitude towards and faith in acupuncture, and acupuncture is less effective in severely ill patients. Moreover, approximately 10% of population are 'non-responders' in whom typical physiological responses cannot be

elicited with acupuncture stimulation, and hence test needling prior to treatment is recommended.

Acupuncture point selection

The detailed prescription of acupoint selection based on traditional Chinese medicine is beyond the scope of this article. Nevertheless, the point selection in patients presenting for anaesthesia would depend on the purpose of the acupuncture (such as analgesia or PONV), the patient's overall condition, and the type of operation.

Yintang point^{12,13} and auricular Shenmen³² are common points used for preoperative anxiolysis. For PONV, Neiguan P6 is commonly employed.^{1,20–28} However, one should note that due to the variation in patients' conditions, different aetiologies for the same symptoms, and other factors, it would be inappropriate to assume that one single or specific set of acupoints for the treatment of a disease condition will always be effective. For example, PONV may be drug-induced or surgery-related, and would have a different management approach, as in the case of strabismus surgery. Neiguan P6 acupressure prior to induction of anaesthesia was shown to be ineffective in children undergoing strabismus surgery.³³ However, the incidence of PONV was significantly reduced after strabismus surgery in a randomised controlled trial using acupoints for meridians associated with the eyes.³⁴ These results suggested that PONV in strabismus surgery may be surgery-related rather than drug-induced.

The points chosen for acupuncture and related techniques can be considered at three levels³⁵: the local points, the distant points, and the points along the course of the affected meridian. Local points refer to the acupoints located near the affected area. Wushu GB27, Weidao GB28, Qixue KI13 and Siman KI14 (acupoints located at the lower abdomen and groin, respectively) have been used as acupuncture anaesthesia during inguinal hernia repair in a small study.³⁶ Some reactive acupoints, usually below the elbows and knees, are helpful for painful conditions at remote body regions.³⁵ For example, Hegu LI4 (located between the thumb and index finger) is traditionally used for facial and oral pain; Zusanli ST36 (near the proximal tibia) is used for abdominal pain; Lieque LU7 (near the wrist at the radial side) is used for head and neck discomfort; and Weizhong BL40 (situated at the popliteal fossa) is helpful for back pain.³⁵ Acupoints from the meridian that passes through the surgical area or the meridian strongly associated with the organ undergoing surgery (the 'organ phenomenon') can be selected for postoperative pain control.¹ Moreover, back shu points of the viscera are located bilaterally 1.5 cun (about 2.5–3 cm) lateral to the posterior midline (the bladder meridian) and may be useful for postoperative deep visceral pain.¹

In addition, the patient's comfort and convenience have to be taken into account when selecting the acupoints. Therefore, acupoints located at the limbs and auricular points are usually preferable to those at the trunk. Nevertheless, preoperative intradermal needle to the back shu points have been successfully used for postoperative analgesia as an adjunct to epidural morphine in patients undergoing abdominal surgery.³⁷

Needling technique

In order to achieve a good effect of acupuncture, it is crucial to obtain *De-qi* during needling. *De-qi* (which means arrival of *qi*) refers to a specific sensation of soreness, numbness, distension or heaviness around the acupoint after the needle is inserted to a

certain depth. At the same time, experienced acupuncturists may also feel tenseness and tightness around the needle.³⁵ If the *De-qi* sensation cannot be obtained at needle insertion, manual manipulation of the needle by twirling, rotating, lifting or thrusting is performed until it is achieved. The *De-qi* sensation experienced by healthy volunteers has been verified and is different from the pain sensation from needle pricking.^{38,39} Indeed, increased skin blood flow to Hegu LI4 and Quchi LI11 (near the elbow) is associated with *De-qi* sensation during acupuncture stimulation of Hegu LI4 in volunteers.⁴⁰

Mode of acupuncture

Acupuncture-related techniques include: acupressure, electroacupuncture, transcutaneous electrical acustimulation, laser acustimulation, and more recently, capsicum plaster acustimulation. Compared with manual acupuncture, these techniques have the following advantages: (1) they are less painful and hence are more acceptable to patients, especially small children; (2) they require less specialist training; (3) they are less labour-intensive; and (4) they provide better analgesia when electroacupuncture is used.¹ In a recent review, Rowbotham²¹ concluded that various acupuncture-related techniques are effective for the prevention of PONV, and as these techniques are not time-consuming and do not require specially trained personnel, he has advocated their widespread use.

The analgesic effect of electroacupuncture was reported to be different according to the frequency of stimulation used, suggesting that different neurotransmitters are involved.¹ High frequency (100 Hz) was reportedly to provide better postoperative pain control in patients undergoing abdominal surgery compared with low frequency (2 Hz).⁴¹ Acupressure and transcutaneous electrical acustimulation have a long history and a favourable safety profile. Laser acustimulation (with the precaution of eye protection) was advocated for use in paediatric patients for the prevention of PONV.⁴² Capsicum plaster developed in Korea was found to be effective in PONV when applied to the Korean hand acupoint⁴³ or at the Neiguan P6²⁵, and also for treatment of postoperative sore throat.²⁹ As capsicum plaster is not readily available, the widespread use of this simple technique has yet to be determined.

SUMMARY

Manual acupuncture requires specialist training and is labour-intensive and time-consuming, which limits its applicability in many units. However, recent evidence suggests that manual acupuncture is effective for reducing preoperative anxiety and for postoperative pain relief. Current available data do not support the use of acupuncture as an adjunct to the general anaesthetic in the intraoperative setting. The results from recent studies of non-invasive techniques and systematic reviews of acupoint stimulation techniques suggest that they are effective for preventing postoperative nausea and vomiting in combination with—or as an alternative to—conventional antiemetics. The use of acupuncture for labour pain management appears promising but requires further research. Patient selection, acupoint selection, needling techniques and mode of acupuncture are important factors to consider when applying acupuncture and related techniques in the perioperative setting.

Practice points

- guidelines to improve standards for reporting interventions in controlled trials of acupuncture and related techniques exist and should be followed in future studies
- current available data do not support the use of acupuncture as an adjunct to the general anaesthetic in the intraoperative setting
- there is extensive and good evidence to support the use of acupuncture and related techniques for the prevention of postoperative nausea and vomiting
- patient selection, acupoint selection, needling techniques, and mode of acupuncture need to be considered when applying acupuncture and related techniques in the perioperative setting

Research agenda

- the quality of systematic reviews of perioperative applications of acupuncture and related techniques is unknown
- further research is warranted to evaluate the optimal timing (preoperative, postoperative, perioperative) of acupuncture and related techniques
- the value of acupuncture and related techniques for treating postoperative complications needs to be determined
- the efficacy of capsicum plaster acustimulation appears favourable but requires further research
- the role of acupuncture for labour pain needs to be defined more clearly

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Postoperative cognitive dysfunction: Incidence and prevention

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Postoperative cognitive dysfunction (POCD) is a decline in cognitive function for weeks or months after surgery. Due to its subtle nature, neuropsychological testing is necessary for its detection. The interpretation of literature on POCD is difficult because of numerous methodological limitations, particularly the different definitions of POCD and the lack of data from control groups. POCD is common after cardiac surgery, and recent studies have now verified that POCD also exists after major non-cardiac surgery, although at a lower incidence. The risk of POCD increases with age, and the type of surgery is also important because there is a very low incidence associated with minor surgery. Regional anaesthesia does not seem to reduce the incidence of POCD, and cognitive function does not seem to improve after carotid surgery as has previously been suggested.

Key words: cognitive; postoperative; complication; neuropsychological test.

After surgery and anaesthesia, many elderly patients notice a decline in cognitive function, especially memory. This condition is called postoperative cognitive dysfunction (POCD), and it is present for weeks or months after surgery. Due to its subtle nature, neuropsychological testing is necessary for its detection. The condition may occur after anaesthesia and surgery that otherwise seemed to have been uncomplicated, and can occur even after minor procedures.

For more than 30 years, it has been well known that brain complications are common after cardiac surgery, and one of these complications is POCD. The reported incidence of POCD, however, varies enormously depending on the definition, composition of the test battery, and time of postoperative assessment. Accordingly, the incidence is reported to be 30–80% a few weeks after cardiac surgery and 10–60% after 3–6 months.^{1–6} The primary focus of this chapter is POCD after non-cardiac surgery; POCD after cardiac procedures has been well covered in a recent review.⁷

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It has been much more difficult to verify that POCD exists after non-cardiac surgery, and many patients have probably not been taken seriously when they described a cognitive decline after such surgery, especially if this was a minor procedure. Most scientific studies have focused on the comparison between regional and general anaesthesia, and in studies using the methods from cardiac surgery it has not been possible to document any difference in neuropsychological test results between the two types of anaesthetic management.⁸⁻¹⁰ This may not be surprising since deficits are less pronounced after non-cardiac surgery. Therefore, it has not been possible to detect a postoperative deterioration or a difference between groups when neuropsychological tests with low sensitivity have been used, even though these tests have proved useful in cardiac surgery patients.

INCIDENCE OF POCD AFTER MAJOR SURGERY WITH GENERAL ANAESTHESIA IN THE ELDERLY

Several studies have tried to answer the question of whether cognitive deterioration occurs after non-cardiac surgery in elderly patients. In 1955, Bedford reported that 7% (18/251) of elderly patients over the age of 65 years became demented after undergoing general anaesthesia.¹¹ This was based on his observations and questioning of relatives, care-givers, and others, but no neuropsychological testing was performed. Subsequently, Simpson et al reported in 1961 that there was no significant connection between anaesthesia and decreased mental performance in 681 patients (620 had anaesthesia) aged 65 and over.¹² In contrast, Blundell found that in 6/12 tests a significant deterioration was found after surgery in 51 patients aged 70 and over.¹³ The time interval and type of surgery and anaesthesia were not specified. In a control group consisting of 16 subjects moving to a nursing home, deterioration was seen in one test, but this could clearly represent type 2 error. During subsequent years, a number of studies used cognitive function as an outcome measure in comparisons between types of anaesthesia (see later), but no accurate definition of POCD was used and no incidence could be calculated. The inability to find a statistically significant deterioration was interpreted as documentation that POCD did not exist. In 1995, however, POCD was reported in 5% of 231 patients aged ≥ 65 years 6 months after knee replacement.¹⁰ The definition of POCD was based on a consensus in a panel defining 'a clinically important deterioration'. However, an important problem was that no control group was included for comparison.

In the International Study of Postoperative Cognitive Dysfunction (ISPOCD1) study 1218 elderly patients undergoing major non-cardiac surgery were included, and an incidence of POCD of 25.8% was found after 1 week and 9.9% after 3 months.¹⁴ This was significantly higher than in a control group of 176 healthy volunteers in whom the diagnostic criteria based on Z-scores were fulfilled in only 3.4 and 2.8%, respectively.¹⁵ In another study, it was reported that POCD occurred in 45% of 29 patients with a mean age of 60 years at 6-12 weeks after thoracic or vascular surgery.¹⁶ The definition was based on detection of a 20% deterioration in 20% of the tests (11 test variables considered), but no control group was included. In a study published in 2001, POCD at 3 months was found in 56% of patients with a mean age of 73 years.¹⁷ In total, 140 patients were recruited, but testing after 9 days and 3 months was completed in only 133 and 98, respectively. Of the

28 variables considered, deterioration (regardless of magnitude) was seen in at least one variable in 71% after 9 days and in 56% of patients after 3 months. This way of defining POCD is very sensitive and not standardized, and the results must be interpreted cautiously, especially as no control group was included.

Several limitations must be discussed in the estimation of incidence. Only patients without brain disease can be included, and accordingly patients with dementia could not participate. The participation also required cooperation and interest. It must therefore be assumed that the included patients represent a group of well-functioning subjects where the expected incidence of POCD is lower than in the general patient population at that age. Patients undergoing emergency procedures cannot be included since it is not possible to obtain a reliable evaluation of baseline. Also, such patients would be considered at risk of cognitive deterioration already at baseline.

In 10–30% of patients, no late follow-up test was performed, and it is likely that reluctance to follow up examination could be explained by a wish to conceal cognitive deficits. The incidence of POCD in all elderly patients undergoing major surgery with general anaesthesia is therefore likely to be at least at the level detected in the ISPOCDI study.

INCIDENCE OF POCD AFTER MAJOR SURGERY WITH GENERAL ANAESTHESIA IN MIDDLE-AGED PATIENTS

Few studies of POCD have included younger patients. In one study, 85 patients were included, and it was found that age was significantly related to relative deterioration in three tests administered before and 2 days after surgery.¹⁸ Shaw et al reported that in 48 patients aged 41–68 years, 15 (31%) deteriorated by at least 1 SD (13 on one test, two on two tests) 1 week after vascular surgery.¹⁹ No patients deteriorated in more than two tests, and the incidence of improvement in the 10 test variables was 2–50% compared with an incidence of deterioration of 0–13%. Treasure et al reported that in 24 major non-cardiac surgery patients (mean age 60 years) the incidence of POCD was 50% when defined as deterioration of 1 SD in two or more tests (out of eight tests) at 8 days, and this was unchanged at 8 weeks.⁶ In a study of 508 middle-aged patients (40–59 years) and 185 control subjects of similar age undergoing major surgery with general anaesthesia, POCD was found in 89/463 (19.2%).²⁰ At the 3-month test, POCD was identified in 26/422 (6.2%) of the patients. In the control population, the criteria for cognitive dysfunction were fulfilled in 7/176 (4.0%) of the subjects at 1 week and in 7/169 (4.1%) at 3 months. The difference in incidence of cognitive dysfunction between patients and controls is statistically significant ($P=0.001$) at 1 week but not at 3 months ($P=0.33$).

In middle-aged patients, the risk of POCD is lower 1 week after surgery when compared to that in elderly patients and at 3 months the incidence of deterioration in neuropsychological test results is not significantly different between healthy volunteers and patients, with approximately 6% showing POCD. Thus, only a few have tried to estimate the incidence of POCD in patients less than 60 years of age. It seems fair to conclude, however, that POCD does occur in middle-aged patients, but the incidence is lower than in elderly patients, and after 3 months it is not detectable.

INCIDENCE OF POCD AFTER MINOR SURGERY WITH GENERAL ANAESTHESIA IN THE ELDERLY

Studies investigating POCD after minor surgery have mainly involved outpatient surgery. The objective has been to detect differences between the situations just prior to and a few days after anaesthesia and surgery^{21,22}, or to compare the incidence of POCD after different anaesthetic techniques.²³ In the latter study, 60 patients aged 18–60 years were randomised to thiopentone or propofol anaesthesia. In addition, 30 age-matched control subjects were included. It was possible to find a significant difference between patients and controls only at testing 1 and 2 hours after anaesthesia. At 24 hours, no difference was found. In a smaller study of outpatient surgery, it was not possible to detect any significant differences in neuropsychological test results between 20 patients (aged 21–45 years) and 10 control subjects from the waiting list. Both groups underwent testing on two occasions with an interval of approximately 4 hours.²⁴

In a study using the ISPOCD test battery and the associated analyses and definition of POCD, 372 patients were recruited.²⁵ They underwent minor surgery, defined as a surgical procedure performed with a maximum hospital stay of 1 night (inpatient surgery), or as an ambulatory procedure where the patient left hospital on the day of surgery (outpatient surgery). At 7 days, POCD was found in 22/323 (6.8%). After excluding 18 outpatients who stayed for 1 unplanned night it was found that out of 164 inpatients, 16 (9.8%) had POCD and five out of 141 (3.5%) outpatients had POCD ($P=0.033$). There were 34 patients over 75 years of age in the inpatient group and 32 in the outpatient group. POCD was found in six inpatients (18%) versus 0 outpatients ($P=0.01$). After 3 months no significant difference was found in the incidence of POCD between the two groups (8.8% for inpatients and 4.5% for outpatients).

In a recent study including 30 patients with a mean age of 73 years, POCD was found in 47% at 24 hours after minor surgery.²⁶ The patients were randomised to propofol or sevoflurane anaesthesia, but there was no difference between the two agents. All patients spent 1 night postoperatively at the hospital.

Neuropsychological testing may be difficult to interpret as soon as 24 hours after surgery, as many factors may complicate the evaluation. POCD after 1 week appeared to be much less common than after major surgery, and outpatient procedures seem preferable, but a number of limitations must be considered. Patients undergoing minor surgery on an outpatient basis were more fit (based on preoperative evaluation of activities of daily living) and the surgical procedures were not entirely similar. Also, another very important limitation is that the patients were not randomised to inpatient and outpatient management in this study. Accordingly, we are not able to conclude that outpatient management can reduce POCD as compared to inpatient management. It seems fair to conclude, however, that elderly patients should not be excluded from outpatient surgery exclusively on the basis of age since they may benefit from outpatient management.

PREVENTION OF POCD

In the risk factor analysis of the ISPOCD I study, age was found to be a significant and independent risk factor. The incidence of POCD after 3 months was 7% in those aged 60–69 and 14% in those over 69 years of age.¹⁴ Risk factors other than age after 1 week

were: duration of anaesthesia, respiratory complications, infectious complications, and second operation. Level of education was also important because well-educated patients experienced less POCD after 1 week. Surprisingly, no statistically significant correlation was found with hypoxaemia or hypotensive episodes.¹⁴

Ancelin et al also performed some analyses of risk factors.¹⁷ A connection was found between POCD and increasing age, low level of education, poor preoperative test performance, depression, and type of anaesthesia (general versus epidural). In middle-aged patients, those who avoided alcohol were at a higher risk of developing POCD, and this could perhaps be explained by a particular sensitivity to CNS-acting substances.²⁰ Supplementary epidural analgesia was related to a higher risk of POCD at 1 week in that study and we have no explanation for this as yet.²⁰ To summarize, no correctable factor has been identified.

REGIONAL VERSUS GENERAL ANAESTHESIA

If general anaesthesia was an important factor in the development of POCD, then we would expect regional anaesthesia to reduce the incidence. Previous studies using neuropsychological testing have not been able to demonstrate this, but methodological limitations could be an important explanation (Table 1). If POCD is not detected then it will be impossible to detect a difference in the incidence.

Only one study has reported a statistically significant difference between general and regional anaesthesia beyond the first postoperative day. Hole et al included 60 patients (mean age 70 years) undergoing hip replacement and randomised to general versus epidural anaesthesia. Neuropsychological testing was not performed, but 'mental changes' (such as lack of orientation and amnesia for personal data) occurred in 0/29 in the epidural group and in 7/31 in the general anaesthesia group ($P=0.01$).⁴¹

In the largest study so far (including 438 patients) the incidence of POCD at 1 week after general anaesthesia was 19.7%, and after regional anaesthesia it was 12.5% ($P=0.06$).²⁹ Regional anaesthesia was unsuccessful in 24 patients allocated to regional anaesthesia in whom general anaesthesia was therefore necessary. Also, 35 patients allocated to general anaesthesia actually received spinal or epidural anaesthesia. Not all of these 59 patients completed the study, but when excluded in a per protocol analysis, the incidence of POCD after general versus regional anaesthesia was 33/156 (21.2%) versus 20/158 (12.7%) ($P=0.04$) after 1 week, but after 3 months no difference was found at all.

The composition of the test battery and the statistical analysis are some factors that may affect the possibility of detecting a difference, if it exists. A true difference may be overlooked if tests with low sensitivity are used or if group mean values are analysed instead of the incidence of individual deterioration. On the other hand, when so many small studies have been performed, it is hard to tell whether a few of them could have detected a significant difference if regional anaesthesia was an important protective factor. A meta-analysis does not seem to be relevant because of the enormous differences between the research designs. Thus, there is no firm evidence that cognitive function is less affected after regional anaesthesia. Today, such randomised studies are difficult to conduct since many patients, surgeons, and anaesthetists have firm opinions regarding which type of anaesthesia should be used. The underlying reasons vary greatly, but include reduced incidence of deep venous thrombosis or bleeding with regional anaesthesia.

Table 1. Randomised studies comparing general and regional anaesthesia using neuropsychological testing.

Author	n/age/tests	Type of surgery	Results
O'Dwyer et al, 2003 ²⁷	279 randomised, 255 complete, test at 3 days, some also at 6 and 24 hours, mean age 55 years	Hernia repair	No significant difference
Casati et al, 2003 ²⁸	30 patients all complete, MMSE pre, 1, 7 days, median age 84 years	Hip fracture repair	No significant difference, decrease of at least two points seen in 8 versus 9
Rasmussen et al, 2003 ²⁹	428 randomised, 340 complete at 3 months, median age 71 years	Mixed	No difference at 3 months, POCD in 14% Per protocol difference at 1 week 21 versus 13% in favour of regional
Somprakit et al, 2002 ³⁰	120, two age groups (mean 37 versus mean 67 years) all complete, MMSE at 1 and 3 days	Mixed	No significant difference, but difference between age groups
Williams-Russo et al, 1995 ¹⁰	262 recruited, 231 complete, 1 week and 6 months, median age 69 years	Knee replacement	Decline at 1 week and return to baseline or improvement at 6 months Overall 5% had cognitive deficit at 6 months No difference between groups
Campbell et al, 1993 ³¹	169, 157 complete, mean 77 years, testing 24 hours, 2 weeks, 3 months	Cataract surgery	Decrease after surgery but recovery at 2 weeks in six test variables and one questionnaire and one activity index No differences between groups
Haan et al, 1991 ³²	40 randomised, 37 complete. MMSE and four other tests pre, 4 days and 3 months, mean age 72 years	Urology	No significant difference
Nielson et al, 1990 ⁹	98 recruited, 64 complete at 3 months, mean age 69 years	Knee replacement	Improvement in both groups with no difference in seven comparisons of test results
Jones et al, 1990 ³³	146 age > 60 years, complete in 129, 50 controls on waiting list with no change over 3 months	Knee or hip replacement	At 3 months significant improvement in 2/5 variables in general anaesthesia group, no change in regional ($P=0.03$ and 0.04 between groups)

Chung et al, 1989 ³⁴	44, test at 6 hours, 1, 3, 5 days and 1 month using MMSE, mean age 72 years	Urology	No difference, both deteriorated at 6 hours
Asbjørn et al, 1989 ³⁵	71, mean age 69 years, only 40 complete with test on day 4 and after 3 weeks	Prostatectomy	Overall deterioration at day 4 and improvement after 3 weeks No difference between groups (only in one of nine variables)
Ghoneim et al, 1988 ⁸	119 recruited and 105 complete with data, mean age 61 years	Mixed	After 1–7 days and at 3 months No difference in five tests Improvement after 3 months
Hughes et al, 1988 ³⁶	30, mean age 68 years	Hip arthroplasty	Two tests 24, 48 hours and 1 week after surgery One test significantly worse in spinal, one significantly worse in general, no difference after 1 week
Chung et al, 1987 ³⁷	44, test at 6 hours, 1, 3, 5 days and 1 month using MMSE, mean age 72 years	Prostate resection	MMSE overall significantly higher in regional due to difference at 6 hours
Bigler et al, 1985 ³⁸	40, mean age 79 years, 38 complete	Repair of hip fracture	1 week and 3 months, 10 questions: improvement in both with no difference between the two regimens
Riis et al, 1983 ³⁹	30 over 60 years 13 test variables	Hip replacement: general, epidural or combined	Attention tests 2, 4, 7 days, 3 months: initial decline at baseline at 4 days and then improvement, with no group differences
Karhunen and Jöhn, 1982 ⁴⁰	60 randomised, data complete in 47, mean age 73 years	Cataract surgery	A 3-months improvement with no group differences After 1 week significantly more deterioration in local anaesthesia group in one of two combined scores

CHOICE OF GENERAL ANAESTHETICS

Cognitive function may be adversely affected by drug administration, and perioperatively numerous drugs are given, including not only anaesthetics but also analgesics, anti-emetics, hypnotics, antibiotics, fluids, etc. POCD could be related to the effects of such medication on the brain. Many studies have compared cognitive function in the first few hours after anaesthesia, focusing on recovery, but very few have involved neuropsychological testing that allows a comparison of the incidence of POCD after different types of general anaesthetic. No significant advantage of any particular technique or drug has yet been documented in relation to non-cardiac surgery.¹⁴ Benzodiazepines are well known for their effect on cognitive function, and they are characterized by a slow and variable metabolism, especially in the case of diazepam. In addition to slow metabolism, diazepam has several active metabolites. This was specifically studied in a group of elderly patients, but there was no statistically significant relationship between POCD and blood concentrations of diazepam and desmethyldiazepam.⁴² In young patients and healthy volunteers, a statistically significant correlation has been found between plasma concentration of diazepam and slowing of reaction time, but only very briefly (i.e. 1 hour) after intravenous administration.^{43,44} In a study of 18 patients aged 18–60 years receiving midazolam sedation for dental treatment on two occasions, flumazenil reversal was given on one of the occasions.⁴⁵ It was found that the neuropsychological test results at 1–2 hours were significantly better when flumazenil was given. However, it is noteworthy that after 7 hours several tests had still not returned to the pre-midazolam level. Fredman et al studied 90 patients aged 65 years or over who underwent minor urological procedures.⁴⁶ Midazolam premedication did not affect the results of neuropsychological testing, not even on arrival in the recovery room, but interestingly discharge from the recovery room was delayed after midazolam.⁴⁶ On the basis of these findings, benzodiazepines do not seem to play a major role in cognitive dysfunction after anaesthesia.

CAROTID SURGERY

Carotid endarterectomy is a surgical procedure in which a stenosis of the internal carotid artery is repaired and a source of embolism is removed. During endarterectomy, it is necessary to clamp the artery. Cerebral ischaemia may therefore occur as a result of hypoperfusion, and emboli may also reach the brain during manipulation of the vessel. After surgery, cerebral perfusion may be improved, but undesirable hyperperfusion has been described.

Carotid endarterectomy (CEA) is performed in patients with a tight (>70%) stenosis of the internal carotid artery. Postoperatively, neurological complications may arise as a result of brain ischaemia, embolism or brain hyperperfusion. On the other hand, some authors have suggested that an improvement in brain function could be found if brain perfusion was corrected or perhaps because the carotid plaque is a source of brain emboli. Cognitive function has been the primary outcome measure of quite a lot of studies of carotid surgery (Table 2).

The studies are difficult to compare due to differences in timing of postoperative tests (from 1 day to 1 year), different definitions of improvement and deterioration, and

Table 2. Studies on changes in cognitive function after carotid endarterectomy (CEA).

Author	n, timing of testing	Anaesthesia	Results
Bossema et al, 2005 ⁴⁷	60, 56 complete and 23 surgical controls, testing at 3 months and 1 year	Not reported	Postoperative improvement in cognitive function with no significant difference between groups
Sahlein et al, 2003 ⁴⁸	43, same method as Heyer et al, 2002 ⁵¹	GA	1 day after CEA total deficit score was worse in 13 (30%)
Kishikawa et al, 2003 ⁴⁹	23, and 17 controls, testing with 6-week interval	GA	Significant improvement in 4/8 variables in patients at 4 weeks, no significant change in controls
Conolly et al, 2001 ⁵⁰	55, 53 complete, same method as Heyer, 2002. No controls (deleted in proof)	GA	1 day after CEA total deficit score was worse in 12 (23%)
Heyer et al, 2002 ⁵¹	83 and 25 lumbar spine surgery Test at day 1 and day 30 (complete in 48) Deficits defined on the basis of Z-scores from four variables, converted to scores, POCD corresponding to deterioration of 2 SD	GA	Day 1: POCD in 22/80=28%; controls 1/25=4% Day 30: 11/48=23%; controls: 0/17
Rasmussen et al, 2000 ⁵²	22 (16 complete), 176 controls not operated 1 week, 3 months, ISPOCD definition	GA	POCD in 10 and 19%
Heyer et al, 1998 ⁵³	112, 33 complete at 5 months, also tests at 1–6 days and 1 month POCD defined as 25% deterioration in 1/8 variables	GA	Decline in 86% at first test, 68% at second, 55% at third Corresponding improvement in 57, 76, and 94%
Ucles et al, 1997 ⁵⁴	28, two tests at 4 weeks	GA	Significant improvement in two tests
Iddon et al, 1997 ⁵⁵	30, nine test variables, <72 hours	Not reported	No significant change
Gaunt et al, 1994 ⁵⁶	94 included, test at 5–7 days	GA	Deterioration of 1 SD in 26/94, in two tests in 6/94
Mononen et al, 1990 ⁵⁷	In total, seven variables 46 (30 TIA, 16 previous stroke), test at 2 weeks and 2 months Seven variables	GA	At 2 weeks, significant improvement in four tests for TIA group and in one for stroke group (different sample sizes) Problems with interpretation of stroop test (Continued on next page)

Table 2 (continued)

Author	n, timing of testing	Anaesthesia	Results
Casey et al, 1989 ⁵⁸	24, 12 non-operated controls with cerebrovascular disease 15 variables at 8 weeks	GA	No significant differences between groups, but general improvement
Hemmingsen et al, 1986 ⁵⁹	31, 11 controls (other vascular surgery patients) 11 variables at 3 months	GA	Significant improvement in three tests right-sided operations, five tests left, one test controls, but sample sizes different
Bennion et al, 1985 ⁶⁰	55 recruited, 53 complete Test at 3–7 days, 3 months Nine variables, composite Z-score calculated	GA	No significant change at 3–7 days but composite Z-score improved significantly at that time Deterioration at 3 months
Jacobs et al, 1983 ⁶¹	12 with significant stenosis (only nine endarterectomies), and 12 with insignificant stenosis Test at 1 week, 1 month, 3 months, 6 months Approximately 10 variables	Not reported	Significant improvement in 5/10 variables (at different time points), more improvement than in controls for 3/10 variables
Hemmingsen et al, 1982 ⁶²	25 Test at 2 weeks and 8 months 13 variables	GA	At 2 weeks three tests deteriorated significantly At 8 months, two improved significantly
Boeke, 1981 ⁶³	15, 14 controls for cholecystectomy Test at 4 weeks 10 variables	Not reported	Significant improvement in three variables in both groups
Bornstein et al, 1981 ⁶⁴	55 (43 complete), 13 controls for other operations, 14 controls with cerebrovascular disease and no surgery Test at 6 months 65 variables	GA	Significant improvement in 41.5% of tests in carotid group (n=32) and in 13.8% of controls (n=25)
Kelly et al, 1980 ⁶⁵	35 and 17 peripheral vascular Test at 4–8 weeks	GA	Significant improvement in 2/15 variables in both groups but in an additional two in carotid

Owens et al, 1980 ⁶⁶	28 (25 complete) Test at 3–10 days and 3 months Eight variables	GA	Significant improvement in 4/8 variables at 3 months
Haynes et al, 1976 ⁶⁷	17, nine major surgery controls Test at 4–8 weeks Four variables	GA	Significant improvement in all four variables in carotid patients in comparison with controls
Perry et al, 1975 ⁶⁸	20	GA	Significant improvement in 4/8 variables and in composite score
Duke et al, 1968 ⁶⁹	Test at 3 months 47, 16 operated Test at approx. 1 year Six variables	Not reported	Significant improvement in one variable in operated No significant change in unoperated No unpaired comparison and sample sizes different
Williams and McGee, 1964 ⁷⁰	11, nine endarterectomies, six examined at 1 month, 11 variables	Not reported	No statistical analysis, improvement reported

GA, general anaesthesia; ISPOCD, International Study of Postoperative Cognitive Dysfunction; TIA, transient ischaemic attack.

different use of control groups. A paired group analysis considering a continuous measure may document a significant deterioration or improvement, but it is difficult to interpret because:

- patients do not change performance uniformly;
- a high number of test variables increases the risk of type I error (up to 65 variables analysed);
- an improvement may represent practice effects.

An analysis including a control group is preferable as practice effects may then be acknowledged. Controls may be patients with cerebrovascular disease in whom surgery was not indicated⁵⁸, patients undergoing other types of surgery^{47,51,63,65,67}, or several control groups.⁶⁴ However, if the control group is smaller than the groups of carotid surgery patients, then there will be less probability of detecting a true change in that smaller group.^{59,64,65}

Early postoperatively (within the first week), a deterioration may be found using the group analysis approach⁶⁴, but after several months improvement is often reported. This improvement may or may not be larger than the corresponding results found in a control group. The use of a control group undergoing other types of surgery should be avoided (unless the aim is to compare the effect of surgery itself) because POCD may also occur in such patients.

It seems that carotid endarterectomy is associated with POCD early after surgery, and there is no convincing evidence that cognitive function improves after weeks to months, because the studies including appropriate controls have not documented any significant difference. Kishikawa et al assessed only changes within the groups, and they did not compare the changes between the two groups.⁴⁹ The conclusion is, however, based on a number of rather small studies, which implies the risk of overlooking a true improvement. This is in accordance with a systematic review which was published in 1999.⁷¹

VARIABILITY IN RELATION TO INTERPRETATION OF POCD

The impact of the variability is probably a very important factor in the assessment of POCD. Several analyses can be valuable in evaluating this problem. Data from a control group give some information because we would not expect true deterioration to occur in any of these healthy volunteers over a short period of time. The detection of an improvement in postoperative cognitive function is also expected to represent variability, and the incidence of this phenomenon should be significantly less in the patient groups where POCD is found. Finally, few authors have analysed and reported on the consistency between sessions. Failure to consider the consistency may lead to the erroneous conclusion that cognitive dysfunction is persisting from the first to subsequent session(s), while in fact different subjects fulfil the criteria at the different sessions. It seems that most patients with POCD at late follow-up deteriorate after surgery (between the two postoperative test sessions).⁷² Thus, the literature on POCD is difficult to interpret, and the research findings should be carefully assessed before changes in clinical practice are suggested.

CONCLUSION

A large number of methodological limitations must be considered in the evaluation of scientific studies of cognitive dysfunction after surgery and anaesthesia. Nevertheless, POCD must now be regarded as a verified and important complication after both cardiac and non-cardiac surgery. Risk factors for POCD are first of all increasing age and type of surgery.

Practice points

- elderly patients undergoing major surgery should be taken seriously if they complain about a deterioration in cognitive function postoperatively
- increasing age is the most important factor for POCD
- elderly patients should not be excluded from outpatient surgery exclusively on the basis of age

Research agenda

- we need to elucidate underlying pathophysiological mechanisms behind POCD by brain imaging and the assessment of possible long-term effects of anaesthetics on central neurotransmission
- perhaps genetic or acquired variability in drug metabolism could explain the differences in drug sensitivity and maybe also the disruption of receptor function
- surgery-induced inflammatory and metabolic endocrine stress response is of major interest; both cytokines and cortisol are known to have effects on brain function

SUMMARY

Postoperative cognitive dysfunction (POCD) is a subtle decline in cognitive function where neuropsychological testing is necessary for its detection. The interpretation of literature on POCD is difficult because of numerous methodological limitations, above all the definition of POCD and the lack of data from control groups. POCD is common after cardiac surgery, and recent studies have now verified that POCD also exists after major non-cardiac surgery, although at a lower incidence. The risk of POCD increases with age, and the type of surgery also seems to be important because there is a very small risk associated with minor surgery, especially if performed on an outpatient basis. Regional anaesthesia does not seem to reduce the incidence of POCD, and cognitive function does not seem to improve after carotid surgery as has been suggested previously. Future research should focus on

patients who have not been studied previously, and on possible clarification of underlying pathophysiological mechanisms.

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Patient satisfaction with anaesthesia care: What is patient satisfaction, how should it be measured, and what is the evidence for assuring high patient satisfaction?

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Patient satisfaction is a part of outcome quality. Many theories of satisfaction include patients' expectation. One definition of satisfaction is therefore the degree of congruence between expectation and accomplishment. The involvement of patients as well as experts is therefore an important step in the development of an instrument to measure patient satisfaction. Results of single-item ratings or overall satisfaction surveys are over-optimistic and do not represent the true indication of care. The construction of highly standardized (psychometric) questionnaires should include elements of content validity, criterion and construct validity, reliability and practicability. Based on the few available studies in anaesthesia, patient satisfaction is primarily determined by information and communication. There is great potential for improvement in this area. However, we do not know the best way to continuously improve patient satisfaction with anaesthesia care, or to what extent decisions should be shared between the anaesthetist and the patient.

Key words: patient satisfaction; outcome; psychometric development; measurement technique; questionnaire.

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It does not matter whether the degree of patients' satisfaction reflects the competence of the physician or the quality of care. The important thing is that if patients are dissatisfied, health care has not achieved its goal.¹

Outcome as an indicator of quality of care has become increasingly important in the past decade. Assessment of patient satisfaction—which forms a part of outcome—reflects care from the patient's point of view. The development of valid and reliable instruments to measure patient satisfaction with (anaesthesia) care is the first step in continuously improving the care of our patients.

WHAT IS PATIENT SATISFACTION?

Satisfaction is a part of outcome quality, in addition to clinically orientated 'traditional' outcomes (e.g. mortality and major morbidity), economic measurements (costs), and health-related quality of life, and has become an important endpoint in outcomes research and benchmarking of services.²⁻⁴ Sometimes the quality of recovery⁵ is also integrated into outcome quality, and is combined with patient satisfaction and health-related quality of life to form a 'patient-orientated' outcome. The concept of satisfaction is very complicated and far from clear. It is influenced by cultural, socio-demographic, cognitive and affective components.⁶ A major problem is to subdivide the term 'satisfaction' into areas which are easy to understand and measure, and which provide useful results so that practical conclusions can be drawn by administrators and health service providers to improve the quality of care. Many theories include patients' expectations as the basic concept of satisfaction.⁷⁻¹⁰ A traditional definition of satisfaction is therefore the degree of congruence between expectation and accomplishment.^{11,12} Logically, we have to know what patients expect before we ask them about their satisfaction with the care they received. Consequently, the involvement of patients in the development of an instrument to measure satisfaction is very important and must be an integral part of development (see below).^{13,14}

Unfortunately, most instruments have not considered this aspect and are therefore of questionable value.^{9,15} This is true not only for questionnaires regarding anaesthesia but also for instruments used in social sciences. Sitzia, for instance, assessed the psychometric properties of instruments to measure satisfaction and demonstrated that only 6% of 181 quantitative studies fulfilled the requirements of psychometric construction.¹³ This has contributed to the poor reputation of patient satisfaction as an indicator of the quality of health-care services.¹⁶

From a survey of the 'Picker-Commonwealth Program' in the United States of America that consciously adopted the patient's perspective and included thousands of patients, we know that patient satisfaction is primarily determined by aspects such as respect for patients' values, information, coordination and continuity of care, physical comfort, emotional support, and involvement of family.^{17,18} Hospital services and medical care are also evaluated, but these are difficult to judge, and furthermore patients expect that the care they receive will be technically sophisticated and up-to-date.¹⁷

Also, little has been published on patient satisfaction with anaesthesia care based on validated and reliable questionnaires.^{9,14} Two large surveys, both performed with psychometrically developed instruments, demonstrated very similar areas behind the term 'satisfaction' (Table 1).^{19,20}

Table 1. Areas (dimensions) behind the term 'patient satisfaction' and number of underlying questions in each dimension.

Study from Switzerland and Austria ¹⁹	Study from France ²⁰
Information and involvement in decision-making (9)	Information (5)
Continuity of care by anaesthetist (4)	Attention (5)
Respect and confidence (6)	Privacy (4)
Delay management (4)	Waiting (2)
Nursing care in the recovery room (2)	Discomfort (5)
Pain management (4)	Pain (5)

Because involvement of patients in the development of an instrument to measure patient satisfaction is a crucial aspect, all the dimensions and their underlying items are important. If this is not the case, such surveys reflect the bias of the experts who constructed them. Nevertheless, the different dimensions do have different levels of importance and should therefore be (re)assessed to determine the primary area for improvement measures (together with dimensions with high dissatisfaction). Surveys on anaesthesia care from Switzerland showed that the dimension 'Information and involvement in decision-making' had by far the greatest influence on patient satisfaction with anaesthesia care.^{19,21} The underlying questions in this dimension are shown in [Table 2](#).

SURROGATE ENDPOINTS

Some clinical outcome events of interest—mortality, for example—occur with such a low frequency that analysis requires large sample sizes, and it is very difficult to draw conclusions. Investigators therefore try to find incidents that occur more frequently and are easy to measure. The main problem with surrogate endpoints is the assumption—and most of the time lack of validation—of a positive relationship between the surrogate endpoint and the true outcome.²² Commonly used surrogates

Table 2. Questions underlying of the dimension 'information and involvement in decision-making'.

Information and involvement in decision-making
Were you able to talk to the anaesthetist about the anxiety/doubts you felt concerning your forthcoming anaesthetic?
If you asked the anaesthetist questions during this discussion, did you fully understand the replies you got?
Did you feel you had a choice in the method of anaesthesia?
Did the anaesthetist tell you how you would feel after the anaesthesia?
Did you feel that the anaesthetist gave you enough of their time?
Did you have enough privacy during your meeting with your anaesthetist?
At the start of anaesthesia, did the anaesthesia team keep you fully informed about what was happening to you?
For regional anaesthesia: did the anaesthesia team (anaesthetist and anaesthetic nurse) keep you fully informed about what was happening during the operation?

in anaesthesia are myocardial ischaemia and postoperative mortality, postoperative pain or nausea/vomiting, and patient satisfaction.

Lauritsen and Møller²³, for instance, reviewed major journals and found that more than one third of the outcomes they studied in randomised studies, systematic reviews and meta-analyses were actually surrogate endpoints. They strongly advise against the use of surrogate outcomes for making clinical decisions unless a definite correlation has been scientifically established. These types of study have also been criticized by others. For example, concerning studies on postoperative nausea and vomiting²⁴, Fisher said that one cannot extrapolate that a greater incidence of patients free of vomiting with medication implies that this treatment increases patient satisfaction²⁵; he pointed out that new drugs should be judged not only by their purported success but also by their reported adverse events. Relating to postoperative pain, Svensson et al²⁶ studied the influence of expectations and pain experiences on satisfaction with pain management in a random sample of 191 surgical patients. Even though 91% of patients expected moderate to severe pain and 76% reported such pain, only 8% were dissatisfied. He concluded that having postoperative pain is not the same as being dissatisfied with pain management.

HOW SHOULD PATIENT SATISFACTION BE MEASURED?

As with empirical research in general, measuring patient satisfaction with anaesthesia care requires the application of a valid and reliable method of measurement. Only a high-quality psychometric instrument will be able to generate high-quality data. In the following section, we will focus on the main points of measurement concerning patient satisfaction surveys. For detailed information on measurement methods in patient satisfaction surveys in general, and on measurement methods in anaesthesia in particular, we refer to literature from the social sciences.²⁷⁻³⁹

Quantitative and qualitative research

For economic reasons, most instruments used are questionnaires that are completed by the patients themselves. This technique allows surveys with relatively higher numbers and a lower budget than face-to-face or other personal interview methods. Another advantage is that all patients coming to a specific unit over a specific period can be included, minimizing the risk of selection bias. This type of research is termed quantitative, and usually highly standardized instruments are applied (check boxes, not text).

Qualitative interviews are of great importance in the phase of generating instruments in order to dig deeper into the context and evaluate all relevant aspects. This approach is, however, (usually) too expensive for broad-based data collection.

Cross-sectional and longitudinal studies

When a study is done only once (or for the first time) it is called cross-sectional, and when it is repeated in the same setting several times it is called longitudinal. The latter has the advantage that dynamic aspects can be analysed. This is very important for the evaluation of quality management processes: following concrete improvement

measures in the hospital in a particular dimension based on a first survey, do subsequent surveys show better scores for that dimension?

In the following, we will be focusing on self-administered, highly standardized questionnaires as measurement instruments. The construction of such a questionnaire has to consider several points of measurement quality. The most important are:

- content validity;
- criterion validity;
- construct validity;
- reliability;
- practicability.

Content validity

Have all important aspects of the construct or domain to be measured been included? Is item selection adequate?

It is difficult to assure—and indeed impossible to demonstrate—that all relevant aspects of a certain construct, such as satisfaction with anaesthesia care, have been included in a questionnaire. It is always possible to imagine a new aspect of patient satisfaction with anaesthesia that has not been included. However, we have to try to come as close as possible to a complete list of relevant aspects. The development of a questionnaire should therefore include the following.

- The patient's view. Patients must be included in the collection of items to assure content validity. If they are not, the questionnaire may omit relevant parts of patient perception of anaesthesia care. One possibility is to conduct focus groups with patients who have already undergone anaesthesia.
- The evaluation of the 'state of the art'. Important aspects from other studies measuring the same or neighbouring constructs have to be considered and incorporated, if appropriate.
- The expert's view. Experts in the field (in our case, the hospital setting) should contribute what they feel are relevant factors in the construct under measurement.

A last point is the dynamic aspect. Since the way in which anaesthesia is performed in hospital—and therefore the factors potentially influencing patient satisfaction—change over time, content validity should be reassessed dynamically. This means that studying literature, consulting experts, and asking patients is an ongoing process. The easiest way to achieve the latter is to include an open question in the standard questionnaire asking for suggestions for further relevant aspects.

Criterion-related validity

Which factors are related to the outcome factors and how strong are these relationships?

Aspects related statistically to the criterion variable (the outcome) show criterion-related validity. Sometimes this is also called 'predictive validity' or 'concurrent validity', depending on how the relationship is interpreted in a causal or temporal manner. Basically, however, the concept of criterion validity is an empirical rather than a theoretical one; factors empirically related to the outcome show criterion validity even

if there is no theory or hypothesis to explain it. Factors believed to be related to the outcomes must also, of course, show this criterion validity.

Construct validity

Are the questions constructed in a way that assures valid measurement? Do the relationships between the variables 'behave' in the way the construct purports³⁶?

A main point in this context is whether the aspects collected are 'translated' (operationalized) in a comprehensive way into questions. With good operationalization, the indicators measured in the questionnaire should show the relations postulated for the theoretical constructs. (Is it measuring what we think it should?)

Another method to check for construct validity is the inclusion of already validated scales in the test questionnaire. The relationship between analogous constructs in the new questionnaire with gold standard scales then becomes a measure of the external or concurrent validity.

Besides these general techniques, two special issues, which are important in patient satisfaction surveys must be mentioned.

Multi-item technique

In the case of patient satisfaction, most studies^{14,40} have shown that questions simply relating to overall satisfaction are not adequate: first, because they lead to highly skewed distributions with over-estimation of satisfaction; patients are 'notoriously satisfied' (strong ceiling effects) when asked in a general way only, but we know that they will report deficits beyond this when we ask in a more concrete manner. And second, such 'overall satisfaction questions' do not help in formulating improvement strategies; one only knows that 97% of the patients are satisfied and 3% are dissatisfied, but not what should be improved.

Patient satisfaction—or rather patient perceptions—should therefore be measured multi-dimensionally using a multi-item technique for each domain (or at least for the most important domains). A scale has to be constructed for each domain that not only reflects a multi-item-based overall assessment of the domain but also provides more in-depth information on what should be incorporated in improvement strategies for each aspect of the domain in question.

Level of importance of quality aspects or dimensions

A questionnaire with high content validity will, by its very nature, include only relevant items for the perception of patient satisfaction. But of course some items can and will be more important than others, and for the quality management process it is very important to establish the relative importance of the different aspects or deficits in overall patient satisfaction. What is needed is a measure of the importance of the different domains included in overall satisfaction.³⁸ This can be done by asking the patients to assess the relevance of all aspects and not just respond to questions on performance (direct assessment). One disadvantage of this is that it doubles the number of questions, and finding appropriate wording for such questions is sometimes very difficult.

Another possibility is indirect assessment achieved by calculating the influence of each of the subdimensions on parameters of overall satisfaction in multivariate

statistical models. In this case, some questions on overall satisfaction have to be included in the questionnaire.

Reliability

Are the measurement process and the instrument itself reliable?

Test–retest reliability

To test the test–retest reliability, the questionnaire is completed by the same persons in the same situation at least twice, and the results are compared (stability of answers over time). In the real hospital setting, it is simply not possible to fulfil this requirement, since at least the time since discharge will not be identical in the two surveys. If test–retest reliability is assessed, this is usually done with non-patient respondents.

Scale reliability

Scales have the great advantage that they distil responses to many single items into information that can be assessed quickly. The construction of such ‘supervariables’ is indispensable when a multi-item approach with a large number of individual aspects is used. The most important question when collapsing the information of many single items down to one scale value is: to what extent do the items incorporated into one scale really measure the same underlying construct? ‘Scales are reliable to the extent that they are comprised of reliable items that share a common latent variable’.³⁶

The classic approach is to generate such scales following an exploratory or confirmatory approach (i.e. factor analysis), and then to determine the Cronbach α reliability coefficient as a measure of internal consistency of a (presumed) scale. In general, values > 0.70 are considered acceptable.^{36,39}

There are many other techniques for assessing reliability in special situations.³⁶ The most important aspect, however, is that researchers demonstrate an adequate procedure for developing and testing their constructs before presenting them as scales.

Practicability

Are the instrument and the measurement setting practicable? This point often receives too little consideration. One important point is that the instrument should be as economical as possible: It should include everything that is necessary for the measurement of patient satisfaction (content validity) and nothing more (brevity)!

Practicability should be included as a question in the pre-test questionnaire. A further main factor in estimating practicability and acceptance is the response rate (total and item response). To achieve high response rates ($> 60\%$), questionnaires should be concise and short; one reminder should be sent, if possible.

Bias

There are many ways that bias can be introduced into a study. Researchers must consider bias and minimize it. The most important types of bias in patient surveys are the following.

- *Selection bias*: systematic inclusion or exclusion of patients with certain criteria. This is less of a problem if all patients in a certain setting (hospital and period) can be asked to participate.
- *Interviewer bias*: bias introduced by different behaviours of interviewers. This is a very important factor in face-to-face interviews, but is not relevant in self-administered postal surveys.
- *Non-responder bias*: systematic differences between persons participating in the study and those not participating.⁴¹ For example, will highly satisfied patients participate to the same extent as poorly satisfied patients? If not, the study results will be biased towards artificially low or high satisfaction levels. A direct assessment of this effect is usually not possible, since the level of satisfaction of the non-responders is not known. Indirect assessment is, however, sometimes possible when structural data on the non-responders are available. If so, the patient mix of responders can be compared to the patient mix of non-responders, and the non-responder bias can be estimated based on knowledge of the satisfaction levels according to patient mix parameters in the responders.
- *Social desirability bias*: social desirability describes a tendency to answer questions as expected or in a way society regards as positive. This is a more relevant factor if the survey is conducted while the patient is still an inpatient than if it is conducted after discharge.^{33,36}
- *Confounder bias*: an existing relationship between two variables—e.g. information given and patient satisfaction—can be confounded by other variables. Confounding means that the relationship found does not reflect the reality but is disturbed by the effect of one or more other variables (confounders or covariates). In the context of patient satisfaction studies and the comparison of different units (benchmarking of wards or hospitals) the influence of the 'patient mix' as a confounder is one of the main points discussed. For example, do the differences in patient satisfaction between hospitals found in a survey reflect the reality of different levels of quality in care, or are they due to different characteristics of the patients ('patient mix') in these units? The solution is to check whether the selected⁴² parameters have an effect on the outcomes and, in a second step, to adjust the raw outcome values for these confounding parameters if necessary.

The main steps (quality criteria) which should be included in the process of creating a psychometrically developed questionnaire and the content of the questionnaire (item characteristics) are shown below.⁴³

Questionnaire construction

- Literature review, state of the art.
- Expert interviews.
- Patient interviews/focus groups.
- First broad collection of aspects; content validity.
- Translate aspects into questions.
- Build pre-test questionnaire.
- Conduct pre-test survey, minimize bias factors.
- Analysis of pre-test data.
- Assess:
 - content validity;
 - construct validity;

- reliability;
- practicability.
- Omit redundant and unimportant questions, modification of questions.
- Build final questionnaire.
- Conduct main survey, minimize bias.
- Analysis of main study data.
- Reassess:
 - content validity;
 - construct validity;
 - reliability;
 - practicability.
- Publication of methods and instrument.

Questionnaire content (item characteristics)

- Multiple items for each construct/scale.
- Open question for supplementary aspects.
- Overall satisfaction questions (not for the report but for assessment of construct validity and importance of constructs).
- Socio-demographic data.
- Disease- and treatment-related data.

WHAT IS THE EVIDENCE FOR ASSURING HIGH PATIENT SATISFACTION?

Satisfaction as part of outcome quality, evidence of measuring true satisfaction

Outcomes as indicators of quality have the important advantage of being integrative. They reflect the contributions of all those who provide care, including the contribution of patients to their own care. Outcomes do not directly assess the quality of performance. They permit only inference of the quality of the process and structure of care. The availability of information, its completeness, its accuracy, its susceptibility to manipulation, and the cost of its acquisition are important considerations. In selecting any item as an indicator of quality, the two key questions are: (1) does this indicator tell me what I want to know about this aspect of quality, and (2) can I easily get complete, accurate information about the indicator? The secret of success in quality assessment is the proper choice of the relevant indicators.⁴⁴ Clinical outcomes and care have a relevant relationship to patient satisfaction.⁴⁵⁻⁴⁷ It is therefore essential to have the proper tools to assess patient satisfaction, in our case with anaesthesia care. To uncover problems in the different processes of care, the question design must be able to distinguish between different dimensions of satisfaction and establish this with different gradations. Simple yes/no questions yield falsely high satisfaction rates when compared with sophisticated questionnaires.^{14,46,48}

Despite this, it must be emphasized that any assessment of patient satisfaction is not necessarily an assessment of the true quality of medical care; as mentioned above,

Table 3. Valid instruments for measuring patient satisfaction perioperatively (pre-, intra- and postoperatively).

Author/year	Psychometric testing	Number of patients/ response rate/type of instrument	Anaesthesia	Problem area/ satisfaction
Whitty et al, 1996 (UK) ⁴⁶	Content validity (focus group)	172/73%/mailed-back questionnaire	General	Information, fasting, reassur- ance pre-op/ very satisfied: 67%
	Pilot study for validation Internal consist- ency Importance	Consecutive sample, one hospital		
Pernoud et al, 1999 (France) ⁵¹	Content validity (expert group)	742/99%/in-hospital questionnaire 24-h postop	General, regional	Information/glo- bal score: 76%
	Pilot study for validation Internal consist- ency	Consecutive sample, three hospitals No day or emergency surgery		
Fung and Cohen, 2001 (Canada) ⁵⁵	Content validity (focus group)	45/71%/mailed-back questionnaire	General	Information, communication/ no satisfaction score
	Pilot study for validation Importance	Consecutive sample, two hospitals Only day surgery		
Heidegger et al, 2002 (Switzer- land and Aus- tria) ¹⁹	Content validity (focus group)	2348/62%/mailed- back questionnaire	General, regional	Information, continuity of care/global sat- isfaction score: 81.4%
	Pilot study for validation Importance, internal consistency Confounders	Consecutive sample, six hospitals No day or emergency surgery		
Auquier et al, 2005 (France) ²⁰	Content validity (focus group)	977/89,5%/in-hospital questionnaire	General	Information/glo- bal satisfaction score: 75%
	Pilot study for validation Internal consist- ency Confounders	4–48 hours postop Consecutive sample, eight hospitals		
Capuzzo et al, 2005 (Italy) ⁵²	Content validity (expert group)	219/100%/interview 48 hours postop	General, regional	Information, emotional sup- port/satisfac- tion: 90.5%

Table 3 (continued)

Author/year	Psychometric testing	Number of patients/ response rate/type of instrument	Anaesthesia	Problem area/ satisfaction
	Pilot study for validation Re-test reliability after 24 hours	Consecutive sample, one hospital Hospital stay > 48 hours		

patients may be satisfied with low-quality care and can be dissatisfied with high-quality care, depending on their expectations. Thus, patient satisfaction reflects the qualitative part of the outcome of care. The collection of standardized data therefore remains a complementary, quantitative and equally important part of outcome quality.⁴⁹

As mentioned earlier, only validated and reliable instruments offer an accurate assessment of patient satisfaction.^{9,14,15,46,48,49} Proper validation implies that the patient's view is included in the development of the instrument. Concerning this, focus groups comprising patients ('consumers') are an essential part of any attempt to learn about how consumers define quality and describe experiences with a health-care system.⁴⁹

Different instruments have been used to assess patient satisfaction. Questionnaires provide standardized and anonymous assessment, but response rates are lower compared to those of interviews. Conversely, interviews may be biased, as the patient is under pressure from social desirability (see above), and the interviewer introduces a higher 'error' variability that may reduce the reliability of an instrument.^{33,36} One study on two surveys, however, did show an even more critical appraisal from interviews as compared to questionnaires, but both surveys were conducted in hospital and were not based on mailed questionnaires after discharge.⁵⁰

Quality instruments for measuring patient satisfaction with anaesthesia care

A recent search in PubMed with the keywords 'Patient satisfaction' AND 'Questionnaire' AND 'Anesthesia' led to 303 citations.¹³ Out of these, we chose the following studies because the instruments had undergone thorough psychometric testing (questionnaire/structured interview) (Tables 3–5).^{9,13,14} The instruments were developed as part of the study and were then used to assess patient satisfaction with anaesthesia care. We considered these instruments to be valid tools for measuring true patient satisfaction. This reflects the best evidence for evaluating the complex concept of patient satisfaction so far. The cited studies covered different problem areas within anaesthesia care depending on the aspect of anaesthesia that was under study: either the whole process of anaesthesia care from the pre-anaesthetic visit until discharge from hospital, or parts, e.g. monitored anaesthesia care (MAC) and postoperative outcome (after general anaesthesia).

As yet, no valid instruments for the assessment of satisfaction with regional versus general anaesthesia are available,⁹ although three studies included patients who had undergone both regional and general anaesthesia. These were not compared in the studies, however.^{19,51,52}

Table 4. Valid instruments for measuring patient satisfaction with monitored anaesthesia care (MAC) intraoperatively.

Author/year	Psychometric testing	Number of patients/ response rate/type of instrument	Anaesthesia	Problem area/ satisfaction
Dexter et al, 1997 (USA) ⁵⁶	Content validity (expert group) Pilot study for validation	94/92%/in-hospital questionnaire Consecutive sample, one hospital	MAC	Pain/no satisfaction score
Fung et al, 2005 (Canada) ⁵⁷	Internal consistency Content validity (expert) Pilot study for validation Internal consistency	Mainly day surgery 328/93%/in-hospital questionnaire immediately after surgery, one hospital Ophthalmic (cataract) day surgery	MAC	Pain, surgeon preoperative anxiety/ISAS score 5,6 (of 6)

Table 5. Valid instruments for measuring patient satisfaction with postoperative outcome.

Author/year	Psychometric testing	Number of patients/ response rate/type of instrument	Anaesthesia	Problem area/ satisfaction
Myles et al, 1999 (Australia) ⁵	Content validity (focus group) Pilot study for validation Internal consistency Importance	389/99%/in-hospital questionnaire 1-4 days postop Consecutive sample; day, minor, major surgery, one hospital	General	Communication, support, comfort/QoR-score (maximum 18), depending on time of recovery
Bauer et al, 2001 (Germany) ⁵⁰	Content validity (expert group) Pilot study for validation Internal consistency	700/84%/in-hospital questionnaire or interview (50:50) 48 hours postop Consecutive sample; one hospital, no day surgery	General	Drowsiness, pain, thirst Question: 74% satisfied Interview: 43% satisfied
Hueppe et al, 2003 (Germany) ⁵⁸	Content validity (expert group) Re-test reliability	1490/74.6%/in-hospital questionnaire 1-3 days postop Consecutive sample; elective surgery	General	Memory, thirst, pain/no satisfaction score

What is the evidence?

Based on the few published studies available, information and communication are the most important dimensions to assure patient satisfaction throughout the entire perioperative period.^{19,20} This is followed by continuity of care by the anaesthetist. Good pain management, comfort and support are the most important predictors for patient satisfaction in the postoperative period. Satisfaction with anaesthesia care during MAC is inversely correlated to the amount of pain experienced during surgery.

How to improve communication and presentation of information?

There has been extensive research on the topics of postoperative pain management, nausea and well-being. Little is known, however, on how to improve communication with the patient to improve patient satisfaction with the information provided about anaesthesia and its associated risks.

Heidegger et al²¹ showed that an attempt to improve the provision of information about anaesthesia by distributing information leaflets did not alter patient satisfaction with anaesthesia care. Snyder-Ramos et al⁵³ compared video-assisted information at the pre-anaesthetic visit with the average pre-anaesthetic interview and handing out an information brochure. Although their results showed that video-assisted information increased patient satisfaction, the measuring instrument was not validated. Harms et al⁵⁴ tried to improve patient satisfaction by communication training for anaesthetists. This yielded better self-esteem amongst the trainees, but the effects on patient satisfaction have not yet been evaluated.

Practice points

- the development of a valid instrument is an expensive and time-consuming process; it would therefore make sense to use established instruments in other hospital settings and refine them by introducing or cancelling items to adapt the instrument to other patient collectives
- the involvement of patients in the development of an instrument to measure patient satisfaction is fundamental
- by applying the same instrument to different (large) populations, knowledge about patient satisfaction in anaesthesia care may increase worldwide because of comparability
- patient satisfaction with anaesthesia care is primarily determined by information and communication
- results of single-item ratings or overall satisfaction surveys are over-optimistic and do not represent the true indication of care
- generally speaking, satisfaction is hard to grasp, so the less bias introduced during surveys the more powerful the results will be
- conclusions should be drawn only from results of well-designed, psychometric-developed instruments

Research agenda

- to what extent should decision-making in anaesthesia be shared between the anaesthetist and patient?
- what are really good results in patient satisfaction surveys? Is maximum satisfaction possible and economically useful?
- what is the best way to continuously improve patient satisfaction with anaesthesia care?
- continuity of personal care (by the anaesthetist) versus continuity of quality of care: does it matter?
- establish effective communication/information techniques in anaesthesia
- comparison of regional with general anaesthesia
- further (more extensive) studies may reveal subgroups of patients or type of surgery deserving special treatment

SUMMARY

Patient satisfaction as part of outcome quality has gained great importance in the past decade. The development of highly standardized, valid and reliable instruments is a time-consuming process. The patient's view should be an integral part of this process. Results of single-item ratings are over-optimistic and do not represent the true indication of care. Based on the few published studies available, information and communication are the most important dimensions to assure patient satisfaction throughout the entire perioperative period. However, the best way in which to continuously improve patient satisfaction is still unclear.

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Evidence-based anaesthesia and health economics

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The aim of this chapter is to focus on evidence-based health economics in anaesthesia. More and more, requests for additional facilities will have to be based on detailed arguments supported by 'hard evidence' as to the gain to be expected from the patient's angle and the cost. Evidence-based clinical practice in anaesthesia isolated from economic issues is not an optimal goal. As clinicians we have to demonstrate not only the need for the use of evidence-based principles in economic evaluation, but also that such principles should themselves be based on health economics. This chapter shows how to bring economic evaluation and systematic review together, and how to use such evaluations in the clinical setting. It shows how economics can be used to broaden the evidence base for a more efficient and equitable health policy, and sets a future research agenda for this challenging area of work in Cochrane reviews dealing with anaesthesia topics.

Key words: health economics; cost-effectiveness; costs; anaesthesia; evidence-based medicine.

The aim of evidence-based medicine has been to inform clinical practice and to change practice where patient and public health can be improved. However, evidence-based practice isolated from economic issues is not optimal, and may ultimately harm patients and the public. Evidence-based health economics recognizes not only the need for the use of evidence-based principles in economic decision-making but also that such principles should themselves be based on economic concepts.

EVIDENCE-BASED MEDICINE AND HEALTH ECONOMICS

Sackett et al¹ stressed that evidence-based medicine is the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of

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optimum clinical care to patients. But in modern health care there is a greater demand for quality health-care interventions. Evidence-based medicine provides the best basis on which to decide which interventions should be abandoned and which are beneficial and cost-effective. So, evidence-based medicine is important in relation to decision-making in anaesthesia, namely, in its impact on health economics. The father of evidence-based medicine, Archie Cochrane, said in his most famous work *Effectiveness and Efficiency*.² 'Allocations of funds and facilities are nearly always based on the opinions of senior consultants, but, more and more, requests for additional facilities will have to be based on detailed arguments with hard evidence as to the gain to be expected from the patients' angle and the cost'. That is, considering cost-effectiveness (or efficiency) is more important than considering clinical excellence (or effectiveness) alone. To consider efficiency, we have to link data on costs and benefits of care, and we have to accept that decisions made on the basis of such information will involve valuation of human life, pain and suffering, as stressed by Donaldson et al³

Economic evaluations of interventions are central to informing us as clinicians, the National Health Organizations, and the policy makers. The types of questions that can be addressed are: 'For this group of patients, is drug A more effective and less costly than current treatment?' Or 'because drug A is more costly than current treatment, if we are considering implementing drug A, where would the resources come from?' So, the intention of this chapter is to discuss economic evaluation in health care and anaesthesia in relation to evidence-based medicine, and to provide studies to demonstrate how decision-making can be used in economics evaluation in randomized controlled trials and systematic reviews.

WHAT IS HEALTH ECONOMICS?

Economics is the science of scarcity. It analyses how choices are structured and prioritized to maximize welfare within constrained resources. We all use economics on a daily basis ('do I buy the cheaper chocolate bar or pay a bit more for the nicer one?') as we work within our own resource constraints (our taste says, 'buy the nicer one'; our bank manager says, 'buy the cheaper one'). By comparing the costs and benefits arising from each option, we are able to optimize our decision-making. If we routinely use such economic principles in our private lives, then surely we should also apply them in our professional lives. This is the basis of health economics.

Given this notion of *scarcity*, it follows that use of resources for a given form of health care inevitably involves a sacrifice. That is, the health-care system forgoes the opportunity to use the same resources in other beneficial activities. Consequently the economist measures cost in terms of the benefit that would be derived from using resources in their best alternative use. The application of health economics reflects a universal desire to obtain maximum value for money by ensuring not just the clinical effectiveness but also the cost-effectiveness of health-care provision.

Once health-care decision-makers have accepted the need for choice, they must inform that choice by examining the costs and benefits of different options. However, it is important to recognize that, in terms of economics, the field of health-care exhibits a range of special characteristics. Essentially, the application of health economics reflects

a universal desire to obtain maximum value for money by ensuring not just the clinical effectiveness but also the cost-effectiveness of health-care provision.

The economic problem is a major issue for virtually all health-care systems, confronted as they are by an exponential increase in demand for health-care services against limited resources with which to meet these levels of demand. The economic problem arises because there will never be enough resources to completely satisfy human desires. Because resources are scarce, choices have to be made about different ways of using them. In addition, despite the growth in evidence relating effectiveness and ineffectiveness, there remain many areas in which there is a dearth of such evidence. Occasionally it is instructive to see how evidence is used in making decisions in scientific areas outside medicine.

Suppose there were data, which showed a highly significant inverse correlation between central bank independence and inflation: low inflation occurred in countries with highly independent central banks. The obvious decision, if the aim is low inflation, would be to create an independent central bank, and that has been a major tenet of economic thinking for a decade or so. James Forder's trashing of this theory⁴ originates in the fact that measures of central bank independence were so poor and inconsistent as to deny any relationship. We cannot measure independence, so we can't pontificate as to causation. Health-care decisions likewise require outcomes which make sense, and in whose measurements we can trust.

TECHNIQUES OF ECONOMIC EVALUATION

Economic evaluation provides a systematic and objective framework for drawing up a balance sheet of costs and benefits, which can assist decision-makers to make more informed choices. All economic evaluations have a common structure which involves explicit measurement of inputs ('costs') and outcomes ('benefits').

What is cost-effectiveness analysis?

Cost-effectiveness analysis (CEA) is one of the techniques of economic evaluation designed to compare the costs and benefits of a health-care intervention to assess whether it is worth implementing.^{5,6} The choice of technique depends on the nature of the benefits specified. In CEA the benefits are expressed in non-monetary terms related to health effects, such as life-years gained or symptom-free days, whereas in cost-utility analysis they are expressed as quality-adjusted life-years (QALYs) (see later) and in cost-benefit analysis in monetary terms. As with all economic evaluation techniques, the aim of CEA is to maximize the level of benefits—health effects—relative to the resources available. The *cost-effectiveness* of a particular form of health care can be defined as the ratio of the net change in health-care costs to the net change in health outcomes. Following these definitions of cost and cost-effectiveness, it is possible to state what information economists require in order to perform cost-effectiveness analyses or other types of economic evaluations:

- identification of all main event pathways that have distinct resource implications or outcome values associated with them;
- estimation of the probabilities associated with the main event pathways;

- descriptive data to enable the resource consequences associated with each pathway to be measured;
- descriptive data to enable the outcomes associated with each pathway to be valued.

What identifies costs and benefits?

The identification of costs and benefits involves placing them in certain categories. Costs are seen differently from different points of view. In economics the notion of cost is based on the value that would be gained from using resources elsewhere—referred to as the opportunity cost. In other words, resources used in one programme are not available for use in other programmes, and, as a result, the benefits that would have been derived have been sacrificed. It is usual, in practice, to assume that the price paid reflects the opportunity cost, and to adopt a pragmatic approach to costing and use market prices wherever possible. In CEA it is conventional to distinguish between the direct costs and the indirect costs associated with the intervention, together with what are termed intangibles which, although they may be difficult to quantify, are often consequences of the intervention and should be included in the cost profile:

- direct costs: *medical* (anaesthesia drugs, staff time, equipment) and *patient* (transport, out-of-pocket expenses);
- indirect costs: production losses, other uses of time;
- intangibles: pain, suffering, adverse effects.

It is essential to specify which costs are included in a CEA and which are not, to ensure that the findings are not subject to misinterpretation.

CATEGORIES OF EFFECTS/BENEFIT

Effects in relation to benefit can be categorized in:

- *disease-specific effects*: specific outcomes resulting from anaesthesia, such as recovery time, improvements in pain scores, and return to normal functioning;
- *utility effects*: measures that can be used to compare health status across all health-care interventions, such as healthy days, quality-adjusted life year (QALY);
- *economic effects*: resources released, and expressed in monetary terms, by improvement in recovery and discharge times and the treatment of emesis rather than prophylaxis.

Valuation of costs and benefits

There are two main techniques that can be used here: *conjoint analysis* and *willingness-to-pay*. Conjoint analysis assumes that the attributes of a service determine the satisfaction (utility) that individuals receive from that service, whereas willingness-to-pay is based on the premise that the maximum amount of money an individual is willing to pay for

Excluded	+ Costs Cost-effective
- Effective treatment Questionable	+ Effective treatment Dominant - Costs

Fig. 1. The cost-effectiveness plane for new and existing therapies.

a commodity is an indicator of the value to them of that commodity. For example, in one study the median willingness-to-pay for a reduction in the risk of post-operative nausea and vomiting (PONV) from a 1-in-3 chance to a 1-in-10 chance was €50.

The process of calculating the cost-effectiveness ratio should take into account the context of the decision. If a new treatment is being considered, it is unlikely that it will replace all existing therapies. Instead, some patients are switched to the new treatment, whereas others will remain on existing treatments. In comparing new therapies with placebo or existing alternatives, the question is whether the additional costs of the new therapy justify the additional benefits to gain. The *incremental cost-effectiveness ratio* (ICER)—the difference in costs divided by the difference in benefits - is used to address this issue. The ICER can be placed on a cost-effectiveness plane, as shown in Fig. 1.

Interventions with ICERs in the north-east quadrant require some consideration. They improve health but cost more than the alternative. The decision whether or not to choose them should be based on the level of additional resources available, or by viewing the ICER in the light of a specific acceptable threshold. For example, a request could be that interventions with cost/QALY ratios of between €3000 and €20,000 are adjusted to be cost-effective when there is evidence of their effectiveness.

How to use cost-effectiveness analysis in anaesthesia

The specialty of anaesthesia has seen major advances thanks to the development of safer anaesthetic agents, improved knowledge of pain physiology and pain management, and incorporation of a better understanding of perioperative pathophysiology into perioperative care.⁷ Concomitantly, development of minimally invasive surgery has further reduced stress responses and pain, thereby providing potential for enhanced recovery. However, an increasing proportion of elderly patients with organ dysfunction has led to demands for further reductions in post-operative complications and the costs of treating them. Kehlet and Dahl⁷ based their review on work published mostly within the past 5 years from the major anaesthesiological, surgical, and pain journals and systematic and Cochrane reviews. However, a distinction must be made between those interventions that are completely independent (i.e. where the costs and effects of one intervention are not affected by the introduction or otherwise of other interventions) and those that are mutually exclusive (i.e. where implementing one intervention means that another cannot be implemented, or where the implementation of one intervention results in changes to the costs and effects of another).

Table 1. Examples of cost-effectiveness of three independent perioperative programmes.

Perioperative programmes	Cost in € (C)	Health effect (life-years gained ^a) (E)	Cost-effectiveness ratio (C/E)
A: Minimally invasive surgery	150,000	1850	81.08
B: Pharmacological intervention ^b	100,000	1200	83.33
C: Afferent neural blockade ^c	120,000	1350	88.89

^a Reduce morbidity (cardiac, pulmonary, infective, thromboembolic).

^b β -Blockade, glucocorticoids, anabolic agents, nutrition.

^c Infiltration anaesthesia, peripheral nerve blocks, spinal/epidural anaesthesia and multidisciplinary post-operative treatment.

INDEPENDENT PROGRAMMES

Using CEA with independent programmes requires that cost-effectiveness ratios (CERs) are calculated for each programme and placed in rank order:

$CER = \text{costs of intervention/health effects produced (e.g. life – years gained)}$

Let us focus on perioperative pathophysiology and on the challenges for the anaesthetist in improving post-operative recovery, as described by Kehlet and Dahl⁷, and to integrate these advances with developments in surgical care, achieved by a multidisciplinary collaboration within the context of fast-track surgery.⁸ For example, in Table 1 there are three interventions for different patient groups (minimally invasive surgery, pharmacological intervention with β -blockade, glucocorticoids, anabolic agents, nutrition and afferent neural blockade with infiltration anaesthesia, peripheral nerve blocks, spinal/epidural anaesthesia), with the alternative for each of them of 'doing nothing'. According to CEA, programme A should be given priority over B since it has a lower CER, but, in order to decide which programme to implement, the extent of resources available must be considered (Table 2). Resources for the new programme should be considered in the same manner as above.

Mutually exclusive interventions

In reality, the likelihood is that choices will have to be made between different treatment regimens for the same condition, or different dosages or treatment versus

Table 2. The extent of resources available for the programmes in Table 1.

Budget available (€)	Programme to be implemented
< 150,000	As much of programme A as budget allows
150,000	All of programme A
150,000–250,000	All of programme A and as much of B as budget allows
250,000	All of programmes A and B
250,000–370,000	All of programmes A and B and as much of C as budget allows
370,000	All three programmes

Table 3. Incremental cost-effectiveness ratios in hypothetical cases.

Programmes	Cost in € (C)	Effects (life-years gained (E))	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER ($\Delta C/\Delta E$)
P1: Preoperative optimisation	125,000	1300	125,000	1300	96
P2: Oral (enteral) nutritional support	100,000	1500	-25,000	200	-125
P3: Accelerated post- operative recovery programmes	160,000	2000	60,000	500	120
P4: Optimized dynamic pain relief	140,000	2200	-20,000	200	-100
P5: Minimally invasive fast-track surgery	170,000	2600	30,000	400	75

prophylaxis, i.e. mutually exclusive interventions in perioperative medicine. In these situations, incremental cost-effectiveness ratios (ICERs) are used:

$$\text{ICER} = \frac{\text{difference in costs between programmes P1 and P2}}{\text{difference in health effects between programmes P1 and P2}}$$

The alternative interventions are ranked according to their effectiveness—on the basis of securing maximum effect rather than considering cost—and ICERs are calculated as shown in Table 3 with hypothetical cases (P1, preoperative optimization, P2, oral (enteral) nutritional support, P3, accelerated post-operative recovery programmes, P4, optimized dynamic pain relief, and P5, minimally invasive fast-track surgery). The least effective intervention (P1) has the same average CER as its ICER, because it is compared with the alternative of ‘doing nothing’.

The negative ICER for P2 means that by adopting P2 rather than P1 there is an improvement in life-years gained *and* a reduction in costs. The ICER for P3 works out to be 120, which means that it costs €120 to generate each additional life-year gained compared with P2. Alternatives that are more expensive and less effective are excluded. In Table 3 both P1 and P3 are followed by programmes that have increased effectiveness and reduced cost. In other words, P2 and P4 are associated with a negative ICER. P1 and P3 are, therefore, excluded. Having excluded P1 and P3, ICERs are recalculated for P2, P4 and P5 and are shown in Table 4. P2 is ‘dominated’ by P4 since the latter is more effective and costs less to produce an additional unit of effect (€57.14 compared with €66.67). The dominated alternative is then excluded and the ICERs are recalculated again (Table 5). The process can be illustrated as shown in Fig. 1. In our example, programmes P4 and P5 would be in the *cost-effective* quadrant. In deciding between them, the size of the available budget must be brought to bear. If the available budget is €140 000, all patients should receive intervention P4, while if the available budget is €170 000, all patients should receive the more effective P5. However, if the budget is, say, €150 000, then, since the cost difference between P4 and P5 is €30 000 and the budget surplus is €10 000, it is possible to switch one third of patients to P5 and still remain within budget.

Table 4. Exclusion of more costly and less effective alternatives.

Programme	Costs in € (C)	Effects (life-years gained) (E)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER ($\Delta C/\Delta E$)
P2	100,000	1500	100,000	1500	66.67
P4	140,000	2200	40,000	700	57.14
P5	170,000	2600	30,000	400	75.00

APPLICATIONS OF COST-EFFECTIVENESS IN ANAESTHESIA

A multicentre randomized controlled trial by Elliott et al⁹ compared the cost-effectiveness of general anaesthetic agents in adult and paediatric day surgery populations. They randomly assigned 1063 adult and 322 paediatric elective patients to one of four (adult) or two (paediatric) anaesthesia groups. Total costs were calculated from individual patient resource use to 7 days post-discharge. Incremental cost-effectiveness ratios were expressed as cost per episode of PONV avoided. In adults, variable secondary care costs were higher for propofol induction and propofol maintenance (propofol/propofol) than other groups, and lower in propofol induction and isoflurane maintenance (propofol/isoflurane). In both studies pre-discharge PONV was higher if sevoflurane was used compared with use of propofol for induction. In both studies there was no difference in post-discharge outcomes at day 7. Sevoflurane/sevoflurane was more costly with higher PONV rates in both studies. In adults, the cost per extra episode of PONV avoided was £296 (propofol/propofol versus propofol/sevoflurane) and £333 (propofol/sevoflurane versus propofol/isoflurane).

Important results from this study for decision-makers are that there are differences in variable costs between inhalational arms, indicating that choice of different anaesthetic agents will translate into secondary care budget differences. Claims that the newer anaesthetic agents cancel out their increased acquisition costs by a reduced incidence of side-effects are not supported by this study. Also, claims that shorter recovery times with different anaesthetic agents increase patient turnover are not supported, as this study shows no difference in length of stay between anaesthetic agents. Finally, at these two sites, discharge policies seem to be appropriate due to low post-discharge costs. Until now there have been uncertainty and conflicting opinions among anaesthetists about the impact of different anaesthetic regimens on PONV and the associated effect on costs.

The choice of anaesthetic will have an increasing impact upon hospital budgets around the country. This study shows considerable differences in the anaesthetic costs and short-term impact on pre-discharge PONV of different regimens, but no differences in post-discharge outcomes or costs. Furthermore, our study suggests

Table 5. Exclusion of dominated alternative.

Programme	Costs in € (C)	Effects (life-years gained) (E)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER ($\Delta C/\Delta E$)
P4	140,000	2200	140,000	2200	63.64
P5	170,000	2600	30,000	400	75.00

that the use of different anaesthetics does not affect length of stay and so cannot affect throughput of patients.

Another randomized controlled trial¹⁰ compared the cost-effectiveness of the two antiemetic agents ondansetron and prochlorperazine for the prevention of PONV in 78 patients undergoing total hip replacement or total knee replacement procedures. Patients were enrolled in a randomized, double-blind manner to receive either ondansetron 4 mg intravenously or prochlorperazine 10 mg intramuscularly immediately upon completion of surgery, and were monitored for occurrences of PONV during the subsequent 48 hours. In the analysis, the cost-effectiveness ratio—defined as the cost per successfully treated patient—was measured for each antiemetic agent using the clinical data obtained from the previous study. The incidence of PONV and use of rescue antiemetics was significantly greater in the ondansetron group compared with the prochlorperazine group. The mean total costs of PONV management per patient in the prochlorperazine and ondansetron groups were \$13.99 and 51.98, respectively. The cost of successfully treating one patient with prochlorperazine and ondansetron was \$31.87 and 275.01, respectively. One-way sensitivity analysis was performed adjusting the percentage efficacy rate of each antiemetic and the drug cost of ondansetron. Prochlorperazine remained the dominant strategy across each scenario. The results indicate that prochlorperazine is a more cost-effective antiemetic compared with ondansetron for the prevention of PONV in a mixed-gender adult inpatient population undergoing total joint arthroplasty.

Cost-effectiveness of anaesthetics in relation to the post-anaesthesia care unit

Cost containment and reduction have become major goals in post-anaesthesia care units (PACUs). To decrease costs, hospital managers need to know the principal determinants of cost. Poor understanding of the individual factors comprising the total cost of providing care for surgical patients may hamper efforts to decrease costs. The goal of a study by Dexter and Tinker¹¹ was to use a patient database and computer simulation to test putative ways to significantly decrease costs of caring for patients in an ambulatory PACU. They tested three hypotheses: (1) greater use of short-acting anaesthetics would decrease PACU costs; (2) elimination, by some hypothetical method, of nausea and vomiting would decrease PACU costs; (3) operating room scheduling practices can be adjusted to reduce PACU costs. Supplies and medications accounted for only 2% of PACU charges. Personnel costs, which depend on the peak number of patients in the PACU, accounted for almost all the PACU costs. If nausea and vomiting could have been eliminated in each patient who suffered this complication, without causing sedation, the total time to discharge for all patients would have been decreased by less than 4.8% (95% confidence interval <7.3%). Arrival rates to and times to discharge from the PACU followed triangular and log-normal distributions, respectively. Computer simulations, using published times to discharge for drugs with 'faster recovery' such as propofol, showed that the use of these drugs would decrease PACU costs only if operating rooms were consistently scheduled to run later each day. Such earlier discharge also might be beneficial if used at night, but only if the PACU could close after a single patient leaves. However, reasonably achievable decreases in the times to discharge for all patients undergoing general anaesthesia are unlikely to substantively decrease PACU costs. In contrast, arranging an operating room schedule to optimize admission rates would greatly affect the number of PACU nurses needed.

The authors examined interventions that anaesthesiologists and hospitals might make to decrease the costs of running a PACU. Decreasing use or costs of supplies or medications would not significantly decrease projected total costs. Surprisingly, using more or better antiemetics to prevent nausea and/or vomiting also would not significantly decrease costs. In fact, if they are expensive, they are likely to increase costs. Newer drugs, such as propofol or desflurane, decrease the time to discharge for ambulatory patients. Using these drugs would save money if used to permit operating rooms to run later while still permitting the patients to leave the hospital that day. Such agents might be beneficial when used after hours or at any time the PACU could close once no patients were in it. However, practically achievable decreases in time to discharge may not significantly decrease the peak number of patients in a PACU throughout the day. Expanding the use of drugs with rapidly dissipating effect for all patients having general anaesthesia is unlikely to significantly decrease PACU costs. Anaesthesiologists have little control over PACU economics via choice of anaesthetic drugs. It was concluded that the major determinant of PACU costs is, by far, the distribution of admissions.

Indeed, work carried out in this area suggests that the organization of day surgery services—such as optimizing operating theatre efficiency, reduction of late cancellations and non-attendance, and integration into the remainder of surgical services—are the main factors influencing patient turnover, rather than choice of anaesthetic.

Using systematic Cochrane reviews in economic evaluation

In health-care systems there are never enough resources to meet all potential uses. The need to make choices where there is scarcity leads us to consider the economic principle of opportunity cost. Randomized controlled trials and systematic reviews of effectiveness are methods for comparing alternative ways to treat similar groups of patients. The framework they provide is a useful vehicle for deriving estimates of relative costs and effectiveness of alternative procedures, thus making it possible to determine whether a new procedure is more costly, and more effective, than the comparator, in which case a judgement would have to be made about whether the extra cost of the new procedure is worth incurring given the gains in health achieved. The allocative efficiency question brings us back to the notion of opportunity cost. Given that a new procedure is more beneficial but is going to cost more than current practice, should we allocate more resources to that area of care given the alternative uses of the resources available? For example, given that perioperative monitoring with pulse oximetry is more effective than using clinical assessment of circulation¹², should we allocate more resources to it, given that the extra cost per QALY (quality-adjusted life year) gained is €20 000, and that the extra resources could be used to improve preoperative smoking intervention¹³ or to treat other needy patients?

No matter how much information we are in possession of, making a decision is often difficult. Derek Pooley, faced with decision-making on renewable energy sources, used the guide of cost per tonne as a way of sharpening the mind.¹⁴ This is a bit like a cost per QALY used in health care. Many people think it is a crude measure, but since adequate measures are unavailable (and may be impossible to get anyway), it has to serve. Several authors give a good explanation of QALYs and costs^{15–17}, and some examples illustrative of costs per QALY estimated in 2005 prices are shown in Table 6.

Table 6. Examples of cost per QALY for medical and perioperative interventions.

Intervention	€/QALY
Neurosurgical intervention for head injury	220
Preoperative advice to stop smoking	245
Neurosurgical intervention for subarachnoid haemorrhage	440
Pacemaker implant	990
Hip replacement	1060
Coronary arterial bypass graft (left main vessel disease, severe angina)	1880
Kidney transplant	4240
Heart transplant	7056
Hospital dialysis	19,770
Addition of interferon to conventional treatment in newly diagnosed multiple myeloma	49,554
Neurosurgical intervention for malignant intracranial tumours	97,000

What is a QALY?

A QALY takes into account both the quantity and the quality of life generated by health-care interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life years. A year of perfect health is worth 1; however, a year of less than perfect health life expectancy is worth less than 1. Death is considered to be equivalent to 0; however, some health states may be considered worse than death and have negative scores. QALY provides a common currency to assess the extent of the benefits gained from a variety of interventions in terms of health-related quality of life and survival for the patient. When combined with the costs of providing the interventions, *cost-utility ratios* result; these indicate the additional costs required to generate a year of perfect health (1 QALY). Comparisons can be made between interventions, and priorities can be established based on those interventions that are relatively inexpensive (low cost per QALY) and those that are relatively expensive (high cost per QALY). A cost-utility ratio is the difference between the costs of two interventions divided by the difference in the QALYs they produce.

Limitations of QALYs

While QALYs provide an indication of the benefits gained from a variety of medical procedures, in terms of quality of life and survival for patients they are far from perfect as a measure of outcome. For example, they suffer from a lack of sensitivity when comparing the efficacy of two competing but similar drugs and in the treatment of less severe health problems.

Quick and clean

Just how to use cost per QALY in health-care decision-making is shown in a superb paper from Andrew Stevens and his colleagues from Wessex in 1995.¹⁸ This paper, which draws together all the themes in making decisions about new interventions,

Decision-making on evidence and cost
Cost per QALY (EUR 1,000)

Evidence	<3	3-20	>20	Negative
I	Strongly support	Strongly support	Limited support	Not supported
II	Strongly support	Supported	Limited support	Not supported
III	Supported	Limited support	Limited support	Not supported
IV	Not proven	Not proven	Not proven	Not proven

Fig. 2. Decision-making on evidence and cost.

should be required reading for everyone involved in decision-making in health-care sectors. It provides guidance for ordering one's thoughts. The paper also introduces Buxton's Law: 'it is always too early to evaluate a new technology until unfortunately suddenly it's too late'. It sets out seven stages needed for assessing technology (loaded towards the new, but highly applicable to existing technologies), and emphasizes the importance both of analysis—drawing together information from a wide range of sources to bolster evidence from systematic review and meta-analysis—and costs, which have to be dealt with pragmatically. They give us a simple guide to making decisions based on levels of evidence and cost per QALY. Pragmatism is the name of the game. If, for instance, costs are lower than €3000 per QALY, then the need for randomized trials may be relaxed (Fig. 2). It is worth having a copy of this thoughtful and influential paper on your desk for re-reading at quiet moments.

The values of evidence are ranked according to the following classification in descending order of credibility:¹⁹

- I. strong evidence from at least one systematic review of multiple well-designed randomized controlled trials;
- II. strong evidence from at least one properly designed randomized controlled trial of appropriate size;
- III. evidence from well-designed trials such as non-randomized trials, cohort studies, time series or matched case-controlled studies;
- IV. evidence from well-designed non-experimental studies from more than one centre or research group, opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees.

INCORPORATION OF ECONOMICS INTO THE SYSTEMATIC COCHRANE REVIEW

There are many alternative methods of incorporating economic evaluation into the process of systematic review. These approaches, though having the same objective,

differ in their complexity and in the quality and completeness of information they require and produce. A review of trials included in the Cochrane systematic reviews showed that few had reported full economic evaluations, although more had included measures of resource use.²⁰ Currently, many Cochrane reviews do report economic outcomes that were measured within one or more trials. However, these are not usually set within a discussion of the economic issues around the technology, nor are they included in a model of the current estimated cost-effectiveness. The Cochrane reviews are seen as a vital first step in compiling these rapid reviews, but the challenge for the Cochrane reviews is in the future at least to provide data in a more useful form for the economic analysis.

Practice points

- evidence-based anaesthesia from systematic Cochrane reviews of effectiveness should be used in economic evaluation
- economic analysis adds composite measures of the value of interventions and their outcomes through measures such as quality-adjusted life years and willingness to pay
- for any economic evaluation, it is important to identify, measure and value costs and outcomes, and to be transparent on what you did and how you did it

Research agenda

- the quality of economic research and medical interventions combined in systematic review is often insufficient to address economic issues
- the incorporation of health economics into clinical studies has generally failed to utilize the broad conceptual basis and has instead been constrained by traditional clinical epidemiology
- current reporting of Cochrane reviews could be enhanced to make reviews more helpful for decision-makers by including economic questions in the protocol, and reporting data about resource use, costs and economic outcomes, where necessary reporting continuous data rather than—or in addition to—categorized outcomes

CONCLUSION

Cost-effectiveness analyses of anaesthesia regimens will become more and more important in the future because of increasing pressure to reduce the cost of health care. This chapter has aimed to show how the utilization of economic techniques alongside evidence-based practice can enhance the quality of decision-making in anaesthesia. The health-care dilemma means that choices will always have to be made regarding the level of resources allocated to health care and, within health care, which areas receive a greater share and which areas receive less. The development of evidence-based

practice and an awareness of the need for fairness in resource allocation and service provision are major steps along the road to answering the question of how much of the resources should be put into anaesthesia services and into health care in general.

The evidence-based anaesthesia is intended to provide busy clinicians with tools to aid in the care of patients. We say these tools need to be combined with clinical experience and patient preferences, but the message is that it also has to be combined with cost-effectiveness analysis. So in the future the goal is that when we evaluate health care we all integrate individual clinical expertise, the best external evidence, patient preferences, and cost-effectiveness.

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