Does regional anaesthesia really improve outcome?

S. C. Kettner, H. Willschke and P. Marhofer*

Department of Anaesthesia, Intensive Care Medicine and Pain Therapy, Medical University of Vienna, A-1090 Vienna, Austria

* Corresponding author. E-mail: peter.marhofer@meduniwien.ac.at

Editor’s key points

- Outcome studies showing differences in mortality between regional and general anaesthetic techniques are probably impossible.
- Meta-analyses have shown improved outcomes for specific endpoints associated with specific regional anaesthesia techniques.

Summary. In recent decades, a number of studies have attempted to determine whether regional anaesthesia offers convincing benefits over general anaesthesia. However, today we interpret meta-analyses more carefully, and it remains unclear whether regional anaesthesia reduces mortality. However, regional anaesthesia offers superior analgesia over opioid-based analgesia, and a significant reduction in postoperative pain is still a worthwhile outcome. Recent developments in technical aspects of regional anaesthesia have the potential to provide significant advantages for many patients in all age groups. Moreover, studies focusing on specific outcomes have shown benefits for regional anaesthesia used for surgery and postoperative analgesia.

Keywords: economy; outcome; regional anaesthesia

In 1987, Yeager and colleagues showed a dramatically reduced mortality by epidural analgesia in high-risk surgical patients. In 2000, Rodgers and colleagues published an extensive meta-analysis showing a reduction in postoperative mortality and morbidity with neuraxial anaesthesia with the subsequent recommendation of more widespread use of neuraxial anaesthesia. As in all fields of medicine, evidence in regional anaesthesia is rapidly growing. It is hard to review all relevant studies, and therefore meta-analyses are very helpful to categorize the available evidence. Although the popularity of meta-analyses has increased dramatically over the last two decades, many are poorly conducted, the results are sometimes questionable, and interpretation can lead to deceptive results. Evidence-based medicine has limitations, and some medical questions can simply not be answered by randomized controlled trials. Perhaps, it is an unrealistic expectation that regional anaesthesia influences perioperative mortality. With estimated anaesthesia-related mortality as low as 8.2 per million hospital surgical discharges, it might be impossible to detect differences in mortality in randomized controlled trials that would have to include millions of patients. The Cochrane collaboration has published strict rules for meta-analyses, often resulting in differing conclusions of Cochrane meta-analyses compared with meta-analyses published in other journals. The following review discusses the influence of various regional anaesthetic techniques on outcome parameters. Given the high quality of the Cochrane collaboration, we will consider Cochrane analyses as the best available evidence in this review.

Peripheral nerve blocks

Consideration of the various techniques of peripheral nerve blocks and potential advances in comparison with general anaesthesia requires a short discussion of the safe and effective performance of peripheral nerve block. Peripheral nerve blocks and local anaesthesia have very few cardiovascular or pulmonary side-effects. There are still potential complications, and peripheral nerve block must be done with adequate safety precautions by anaesthetists with appropriate experience. In rare cases, such as accidental block of the phrenic nerve during interscalene brachial plexus block, nerve blocks can compromise pulmonary function, usually without clinical consequences. A potentially significant side-effect is systemic toxicity of local anaesthetics. With ultrasound guidance, the volumes of injected local anaesthetics can be decreased dramatically, limiting the risk of toxic side-effects.

In experienced hands, it seems likely that peripheral nerve block would be safer than general anaesthesia due primarily to the avoidance of airway management. However, evidence to prove this assumption will never be available due to the low numbers of severe anaesthesia-related complications. Nevertheless, perioperative opioid consumption can be reduced or even avoided, in particular with peripheral perineural catheter techniques. Subsequently, opioid-related side-effects can be reduced when perineural block is performed. Optimal performance of single-shot or continuous perineural block is the major prerequisite for implementation of these techniques in daily clinical practice.

Epidural anaesthesia

Postoperative epidural analgesia after major abdominal and thoracic surgery has been extensively investigated. However, most of the studies did not include enough patients for definitive conclusions. Accordingly, a number of meta-analyses have addressed the question whether and which outcome
variables are improved by epidural analgesia in comparison with conventional opioid-based analgesia concepts. The largest available meta-analysis was published in 2000 by Rodgers and colleagues and included data available before January 1997. Although the analysis is impressive, there are some weaknesses based on current standards. First, the analysis included patients undergoing various neuraxial techniques, including spinal, epidural, or epidural anaesthesia, combined with general anaesthesia in comparison with general anaesthesia alone. Such significant clinical heterogeneity limits meta-analysis. Thus, the data by Rodgers and colleagues are appropriate for a systematic review but not for meta-analysis. Secondly, many of the included studies were rather small, with <100 patients. Thirdly, the oldest studies were published in 1971 and many in the 1980s. The progress in anaesthesiology and surgery since that time has been enormous. Therefore, these data simply do not reflect today's practice. Fourthly, many of the included studies have methodological weaknesses, such as not using allocation concealment or incomplete reporting of outcome data. In the light of these issues, the main conclusion of Rodgers' analysis that neuraxial anaesthesia reduces mortality compared with general anaesthesia is questionable.

Newer, more conservative meta-analyses have drawn less optimistic conclusions. Two Cochrane analyses showed benefits of epidural analgesia for major abdominal surgery and abdominal aortic surgery. The clearest finding in that light is that epidural analgesia provides superior analgesia compared with opioid-based analgesia. The use of epidural analgesia resulted in reduced need for postoperative mechanical ventilation, reduced rate of postoperative myocardial infarction, and reduced gastric and renal complications. However, these benefits did not result in a reduction in mortality.

Owing to the need for anticoagulation and the consecutive risk of epidural haematoma, thoracic epidural analgesia for open heart surgery is even more controversial than epidural analgesia for major abdominal surgery. A recent meta-analysis tried to answer the question of potential risks and benefits of thoracic epidural anaesthesia for heart surgery. Once again, the authors showed some benefits, such as a reduction of respiratory complications and supraventricular arrhythmias. There was no evidence for a reduction in myocardial infarction, stroke, or mortality.

**Spinal anaesthesia**

Spinal anaesthesia is the preferred anaesthetic method for sub-umbilical surgery, particularly in elderly patients and parturients. While insufficient data are available for obstetric anaesthesia, a large number of studies have attempted to establish the best evidence for neuraxial anaesthesia for various surgical procedures, mainly in elderly patients. Parker and colleagues investigated in a Cochrane meta-analysis 22 clinical trials involving 2567 patients where neuraxial (mainly spinal) anaesthesia was compared with general anaesthesia. Despite the fact that all included trials had methodical problems, the authors found a reduced risk for postoperative deep venous thrombosis (30% compared with 47%) and acute postoperative confusion (9.4% compared with 19.2%) in patients treated with neuraxial (mainly spinal) anaesthesia compared with general anaesthesia. There was no evidence for reduced perioperative mortality or other outcome parameters (myocardial infarction, pulmonary embolism, etc.).

Luger and colleagues investigated 18 715 patients from 34 randomized controlled trials in which spinal anaesthesia was compared with general anaesthesia for hip surgery in elderly patients. Their conclusions are much more optimistic compared with the Cochrane meta-analysis above with a clear statement to use regional (spinal) anaesthesia for hip surgery in elderly patients. Contrary to other publications, Luger and colleagues highlight the individual decision process and the multi-disciplinary approach for optimal treatment of these patients.

**Regional anaesthesia and specific outcome parameters**

The following chapter describes possible positive influences of regional anaesthesia on various particular outcome parameters, which is summarized in Table 1.

**Anti-inflammatory effects**

Possible mechanisms of anti-inflammatory effects after regional anaesthesia include C-fibre block, reduced cytokine production, and block of sympathetic nerve activity. Since postoperative pain is mainly caused by tissue inflammation and C-fibre activation, reduced cytokine production might limit the inflammatory response after surgery and the severity of postoperative pain. Cytokines can also influence the development of postoperative hyperalgesia.

Martin and colleagues recently investigated the possible anti-inflammatory effects of peripheral nerve block after major knee surgery. They showed that combined sciatic and femoral nerve block reduced clinical inflammation (evaluated by local skin temperature and circumference of the knee) after major knee surgery compared with morphine analgesia, while capsule and synovial membrane cytokines (IL6, TNF, IL1, IL10) and plasma cytokine concentrations (IL6, IL1β, TNF, IL10, sTNF-R1) did not differ between the study groups.

Freise and colleagues showed that liver perfusion and hepatic inflammatory response might be influenced by thoracic epidural anaesthesia independently from cardiac output. These animal studies demonstrate that thoracic epidural anaesthesia can cause effective sympathetic block with subsequent reductions in inflammation. The effects of thoracic epidural anaesthesia on C-reactive protein levels in patients undergoing cardiac bypass surgery have been investigated by Palomero and colleagues. Despite an attenuated inflammatory response in those cases with epidural anaesthesia, this effect was not reflected by improved outcome variables.
Functional recovery
A study by Martin and colleagues\textsuperscript{25} investigating pain at rest and upon movement after major knee surgery observed improved knee flexion in the immediate postoperative period and 1 month after surgery with regional anaesthesia compared with systemic opioid pain control. These results are supported by a study from Capdevila and colleagues,\textsuperscript{28} where immediate and long-term postoperative knee movement was significantly better with epidural and peripheral nerve block compared with systemic pain therapy. Whether bolus or continuous administration via perineural or epidural catheters provide better results during the postoperative period remains unanswered.

Cardiopulmonary effects
The cardiac and pulmonary effects of neuraxial regional anaesthesia are well known. Whereas direct cardiac and pulmonary effects of peripheral nerve block are negligible, neuraxial anaesthesia causes profound sympathetic block with subsequent consequences on cardiac output and peripheral perfusion. Cardiopulmonary effects of neuraxial block are well investigated, and thoracic epidural anaesthesia can be used even during cardiac failure as a bridge to surgery.\textsuperscript{29} According to a meta-analysis by Svircevic and colleagues,\textsuperscript{15} epidural anaesthesia during cardiac surgery reduces postoperative supraventricular arrhythmias and respiratory complications, but definitive conclusions regarding mortality, myocardial infarction, and stroke were precluded due to the diversity of data, although a reduced risk of cardiopulmonary complications was estimated.

van Lier and colleagues\textsuperscript{30} investigated the impact of epidural anaesthesia in patients with chronic obstructive pulmonary disease on outcome after major abdominal surgery in 324 patients. Postoperative pulmonary complications were reduced mainly in patients with severe chronic obstructive pulmonary disease. Powell and colleagues\textsuperscript{31} compared the influence of paravertebral block with thoracic epidural block on major post-pneumonectomy complications in 312 patients. Although some data favour paravertebral block regarding the incidence of postoperative complications in this patient population, further data are required for definitive statements regarding the optimal regional anaesthetic method during lung surgery.

<table>
<thead>
<tr>
<th>Study topic</th>
<th>Regional anaesthetic technique</th>
<th>Study</th>
<th>Study topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory effects</td>
<td>Combined sciatic and femoral nerve blockade</td>
<td>Martin and colleagues\textsuperscript{25}</td>
<td>Knee surgery and inflammation</td>
</tr>
<tr>
<td></td>
<td>Thoracic epidural anaesthesia</td>
<td>Freise and colleagues\textsuperscript{26}</td>
<td>Liver perfusion and hepatic inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Thoracic epidural anaesthesia</td>
<td>Palomero and colleagues\textsuperscript{27}</td>
<td>Cardiac bypass surgery and C-reactive protein levels</td>
</tr>
<tr>
<td>Functional recovery</td>
<td>Combined sciatic and femoral nerve blockade</td>
<td>Martin and colleagues\textsuperscript{25}</td>
<td>Improved function after major knee surgery</td>
</tr>
<tr>
<td></td>
<td>Epidural anaesthesia, peripheral nerve blockade</td>
<td>Capdevila and colleagues\textsuperscript{28}</td>
<td>Improved function after major knee surgery</td>
</tr>
<tr>
<td>Cardiopulmonary effects</td>
<td>Thoracic epidural anaesthesia</td>
<td>Shuang and colleagues\textsuperscript{29}</td>
<td>Bridging for surgery during cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Thoracic epidural anaesthesia</td>
<td>van Lier and colleagues\textsuperscript{30}</td>
<td>Chronic obstructive disease and major abdominal surgery</td>
</tr>
<tr>
<td></td>
<td>Thoracic paravertebral blockade</td>
<td>Powell and colleagues\textsuperscript{31}</td>
<td>Less post-pneumonectomy complications as compared with thoracic epidural anaesthesia</td>
</tr>
<tr>
<td>Gastrointestinal effects</td>
<td>Thoracic epidural anaesthesia</td>
<td>Taqi and colleagues\textsuperscript{34}</td>
<td>Improved bowel function</td>
</tr>
<tr>
<td>Effects on blood coagulation</td>
<td>Lumbar epidural anaesthesia</td>
<td>Naesh and colleagues\textsuperscript{37 38}</td>
<td>Positive influence on platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Epidural anaesthesia</td>
<td>Delis and colleagues\textsuperscript{39}</td>
<td>Prevention of perioperative venous stasis</td>
</tr>
<tr>
<td></td>
<td>Systemic administration of local anaesthetic</td>
<td>Davies and colleagues\textsuperscript{40}</td>
<td>Direct effect on platelet function</td>
</tr>
<tr>
<td>Cancer recurrence</td>
<td>Thoracic paravertebral blockade</td>
<td>Exadaktylos and colleagues\textsuperscript{44}</td>
<td>Positive effect on breast cancer outcome (retrospective analysis)</td>
</tr>
<tr>
<td></td>
<td>Epidural anaesthesia</td>
<td>Biki and colleagues\textsuperscript{46}</td>
<td>Positive effect on prostate cancer outcome (retrospective analysis)</td>
</tr>
<tr>
<td></td>
<td>Epidural anaesthesia</td>
<td>Myles and colleagues\textsuperscript{47}</td>
<td>No improved outcome after major abdominal cancer surgery</td>
</tr>
</tbody>
</table>
Regional anaesthesia and outcome

It is likely that reduction or even avoidance of opioids and optimized postoperative pain therapy via neuraxial regional analgesia is superior regarding pulmonary postoperative function. However, the use of neuraxial regional anaesthesia for major surgery should be carefully balanced. Individual risk assessment and physician skills are important to attain optimal regional anaesthesia effects during abdominal and thoracic surgery.

Gastrointestinal effects

Postoperative ileus is an important morbidity and mortality factor. Thoracic epidural anaesthesia causes sympatholysis and improved microcirculation with subsequent improved bowel function.\(^\text{32–34}\) The prevention and treatment of postoperative ileus are multifactorial and should include the avoidance of opioids, use of epidural block, use of a nasogastric tube, and correction of electrolyte imbalance.\(^\text{32}\)

Effects on blood coagulation

The effects of neuraxial regional anaesthesia on platelet function are well known.\(^\text{35–38}\) Recent publications show that epidural anaesthesia also prevents perioperative venous stasis.\(^\text{39}\) The incidence of perioperative venous thrombosis can be significantly reduced, as shown by a Cochrane meta-analysis from Parker and colleagues.\(^\text{16}\)

With regard to the influence of various regional anaesthetic techniques on blood coagulation, local anaesthetics do have a direct effect on platelet function.\(^\text{40–42}\) Thus, a combination of indirect and direct mechanisms for regional anaesthesia effects on blood coagulation seems to be responsible for the antithrombotic effects of regional block.

Cancer recurrence

Studies both in vivo and in vitro suggest several mechanisms by which cancer surgery might affect cellular immunity: stress response to tissue injury, general anaesthesia, and the use of perioperative opioids. A hypothesis currently under investigation is that regional anaesthesia can influence cancer recurrence by several mechanisms: decreased neuroendocrine stress response to surgical tissue injury, reduced need for general anaesthesia, and reduced opioid consumption.\(^\text{43}\) In addition, pain is an important stress factor and perioperative pain therapy is superior when successful regional anaesthesia is performed.

The relationship between regional anaesthesia and cancer recurrence is one of the most fascinating topics in anaesthesia today. The concept that anaesthesia can influence the outcome of cancer would raise our speciality to a new level. An initial retrospective analysis of survival rates after breast cancer surgery showed impressively improved results for patients treated with paravertebral block (94% metastasis-free and survival) compared with those receiving general anaesthesia (77% metastasis-free and survival).\(^\text{44}\) A prospective multicentre trial will determine whether these retrospective data can be confirmed.\(^\text{45}\)

A positive influence of regional anaesthesia on cancer outcome after surgery is also suggested for prostate cancer.\(^\text{46}\) On the other hand, Myles and colleagues\(^\text{47}\) did not find a positive correlation between the use of epidural anaesthesia and abdominal cancer surgery. Therefore, the entire topic of regional anaesthesia and cancer is evolving and potentially complex. Further experimental and prospective clinical studies have to investigate possible beneficial effects of regional anaesthesia on cancer recurrence.

Regional anaesthesia and outcome: what we know and what we wish

Whether regional anaesthesia influences outcome after surgery is a controversial topic. Several meta-analyses have investigated this important topic with controversial results. Cochrane analyses probably represent the highest standards of meta-analyses. Accordingly, conclusions are very carefully expressed by authors of Cochrane reviews. On the other hand, large outcome studies and meta-analyses are only one side of the coin. Expert opinions represent lower levels of evidence that are still useful in informing current practice, but must be considered even more cautiously. In skilled hands, various regional anaesthetic techniques are powerful tools providing almost perfect perioperative pain therapy. Using an optimal balance between appropriate techniques, application of advanced equipment, and optimal doses of drugs, regional anaesthesia plays an important role in perioperative medicine. No outcome study or meta-analysis considers the individual skills and the directly associated success rates. In the author’s opinion, failed blocks are probably the most important factors for negative outcome. Improvement in outcome can probably be achieved when the skills of individual practitioners are improved and regional anaesthesia is used wisely and appropriately leading to reduced failure rates.

Whether specific regional anaesthetic techniques or local anaesthetics influence the course of illness is an important topic in the future. The theoretical approach is fascinating, and retrospective data in specific fields are promising. Either way, performing a successful regional block during cancer surgery is rarely harmful and should therefore be performed whenever applicable. Whether it influences cancer outcome—let’s find out!

Conflict of interest

None declared.

Funding

Supported solely by departmental funds.

References


Regional anaesthesia and outcome

40 Davies J, Fernando R. Effect of ropivacaine on platelet function. *Anaesthesia* 2001; **56**: 709–10

41 Porter J, Crowe B, Cahill M, Shorten G. The effects of ropivacaine hydrochloride on platelet function: an assessment using the platelet function analyser (PFA-100). *Anaesthesia* 2001; **56**: 15–8

42 Porter JM, McGinley J, O’Hare B, Shorten GD. The effects of ropivacaine hydrochloride on coagulation and fibrinolysis. An assessment using thromboelastography. *Anaesthesia* 1999; **54**: 902–6


44 Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; **105**: 660–4

