Do Neuraxial Techniques Affect Perioperative Outcomes? The Story of Vantage Points and Number Games

Stavros G. Memtsoudis, MD, PhD, FCCP, and Spencer S. Liu, MD

A debate continues and has recently intensified among perioperative physicians on the question whether the technique used for anesthesia and/or analgesia can affect outcomes. Over the past decades, many attempts have been made to provide at least incremental evidence to support or refute the hypothesis that regional anesthesia and analgesia influences perioperative outcomes with definitive results still lacking.

In a review of the literature published in this edition, Kooij et al.[1] provide a critical assessment of a number of studies on the topic and conclude that neither neuraxial nor regional techniques improve perioperative outcomes in general surgical patients. While this interpretation of reviewed studies seems soundly founded on the presented scientific evidence, the article also highlights the complexity of the issue at hand.

In this context, it is not surprising that in the presence of the same data sources, there are those who conclude that regional anesthetic and analgesic techniques can indeed improve outcomes after surgery. This phenomenon is intriguing because it suggests that the difference in opinion may be based more on the difference in vantage point rather than on an alternative scientific basis. What then may be the reasons for such a dichotomy in conclusion? In our opinion, a number of points need to be considered before drawing conclusions from the literature.

First, a major problem and source of confusion that burdens the interpretation of results is the blurry line drawn between the use of regional techniques for anesthesia and/or analgesia. Kooij et al.,[1] recognizing the significance of this issue, have attempted to focus on the analgesic use, but this distinction is at best difficult to make, as evident by the inclusion of landmark publications such as that by Rodgers et al.[2]

After all, a regional technique used for intraoperative anesthesia may have a profound impact on subsequent analgesic needs, as suggested by the concept of preventive analgesia. Furthermore, neuraxial and regional anesthetics may suppress the stress response during the time of maximal injury and have long-term effects.

Perhaps such a distinction is indeed artificial and not even possible. It is a fact that many of the most frequently quoted studies have difficulties differentiating between the two from a purely methodological perspective, that is, it is often not clear what the purpose of the neuraxial/regional technique was. In this context, the systematic review performed by Guay et al.,[3] which also appears in this month's *Anesthesia & Analgesia*, suggests that the use of neuraxial compared with that of general anesthesia can affect 30-day mortality and the risk of pneumonia while positively influencing the latter outcome when neuraxial is added to a general anesthetic. Similarly, recent population-based analyses, targeted to investigate the impact of neuraxial anesthesia on perioperative outcomes in joint arthroplasty patients, must be mentioned because they have found significant reductions in mortality, cardiopulmonary, and other complications.[4–7] It is interesting to note that none of these studies could identify whether perhaps the use of these neuraxial techniques was pursued for postoperative "analgesia" in addition to their "anesthetic" purposes.

Second, the number of patients included in most studies evaluating this subject is relatively small compared with the relatively low incidence of postoperative complications, thus limiting the power of even well-conducted meta-analyses, which are further burdened by inclusion of studies with high heterogeneity of populations and methodology. It is therefore not surprising that in the systematic review presented here by Guay et al.[3] the authors conclude that larger sample sizes are needed to more definitively answer important questions on the topic. It must be pointed out, however, that in this[3] as in most other studies on the topic, many effects that were found to not reach statistical significance did show a trend toward better outcome compared with that of control groups. The impact of the limited power of traditional studies and meta-analyses in this setting may have become more obvious in the era of large database research, which, despite many disadvantages, has the ability to employ much larger populations for analysis. However, the benefits associated with neuraxial techniques shown in these studies have

From the Department of Anesthesiology, Hospital for Special Surgery, Weill-Cornell Medical College, New York, New York.

Accepted for publication March 12, 2014.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Stavros G. Memtsoudis, MD, PhD, FCCP, Department of Anesthesiology, Hospital for Special Surgery, Weill-Cornell Medical College, 535 East 70th St., New York, NY 10021. Address e-mail to memtsoudiss@hss.edu.

DOI: 10.1213/ANE.0000000000000276

also been criticized as being a function of very large sample sizes. Therefore, their clinical relevance in individual practice has been questioned.[8] However, this viewpoint has to be countered by the fact that with tens of millions of surgeries performed in the United States alone every year, even small increments in outcome improvement or effect sizes may have substantial impact on a public health level. In the case of total joint arthroplasties, assuming some level of causality, the use of neuraxial instead of general anesthesia may relate to hundreds of lives saved and tens of thousands of complications averted, given the fact that over 1 million procedures are performed annually.[4] This view of our specialty as a part of a population-based health care system should not be difficult to follow, especially because when it comes to assessing complications associated with neuraxial techniques, we have become accustomed to considering events that occur in the range of 1:10,000 to 1:200,000 as significant to our practice.

One final point to consider is the fact that while the literature can be interpreted as not sufficiently supporting the broad superiority of neuraxial techniques, especially analgesic ones, with respect to perioperative outcomes, one would be hard-pressed to conclude that outcomes are worse with regional techniques compared with alternative approaches, that is, general anesthesia or systemic analgesia.

In conclusion, while the literature on anesthetic and analgesic techniques and their effect on outcome is far from definitive, it is clear that the interpretation of studies depends on factors as simple as definitions chosen and as complex as the discussion regarding our role as anesthesiologists in the wider health care system.

As perioperative care has become complex, integrated, and is constantly changing, thus making it difficult for a single effect from a single component to be detected and isolated from the overall noise, alternative approaches to answer related questions may be needed. As such, practical clinical trials collecting large amounts of detailed observational data and using advanced analytical methodologies may bring at least incremental evidence to the debate. At the same time, it will be necessary to pursue studies identifying and documenting potential mechanisms by which these techniques can confer their suggested benefit.

While many more investigations will without a doubt be published on the topic, clinical judgment, patient and procedure-related characteristics, local preferences, and a multitude of other factors will have to continue to guide physicians' choices of anesthetic and analgesic techniques in day-to-day practice. We agree, however, with Kooij et al.[1] that designations of individual techniques and approaches as "standard of care" are of little value in the era of individualized health care and dynamic changes in scientific knowledge.

RECUSE NOTE

Dr. Spencer Liu is the Section Editor for Pain Medicine for the Journal. This manuscript was handled by Dr. Terese T. Horlocker, Section Editor for Regional Anesthesia, and Dr. Liu was not involved in any way with the editorial process or decision.

DISCLOSURES

Name: Stavros G. Memtsoudis, MD, PhD, FCCP.
Contribution: This author helped conceptualize and prepare the manuscript.
Attestation: Stavros G. Memtsoudis approved the final manuscript.
Name: Spencer S. Liu, MD.
Contribution: This author helped conceptualize and prepare the manuscript.
Attestation: Spencer S. Liu approved the final manuscript.

REFERENCES

1. Kooij FO, Schlack WS, Preckel B, Hollmann MW. Does regional anesthesia for major surgery improve outcome? Focus on epidural analgesia. Anesth Analg 2014;119:740–4
2. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van ZA, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000;321:1493
3. Guay J, Choi PT, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial anesthesia for the prevention of postoperative mortality and major morbidity: an overview of Cochrane systematic reviews. Anesth Analg 2014;119:716–25
4. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S, Mazumdar M, Sharrock NE. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology 2013;118:1046–58
5. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012;117:72–92
6. Liu J, Ma C, Elkassabany N, Fleisher LA, Neuman MD. Neuraxial anesthesia decreases postoperative systemic infection risk compared with general anesthesia in knee arthroplasty. Anesth Analg 2013;117:1010–6
7. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S, Callaghan JJ. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. J Bone Joint Surg Am 2013;95:193–9
8. Raw RM, Todd MM, Hindman BJ, Mueller R. The overpowered mega-study is a new class of study needing a new way of being reviewed. Anesthesiology 2014;120:245–6

CME

Does Regional Analgesia for Major Surgery Improve Outcome? Focus on Epidural Analgesia

Fabian O. Kooij, MD, Wolfgang S. Schlack, MD, PhD, DEAA, Benedikt Preckel, MD, PhD, DEAA, and Markus W. Hollmann, MD, PhD, DEAA

Epidural analgesia is often considered the optimal technique for pain relief after major surgery and has been studied as a measure to improve outcome. Although conclusions from historical studies were promising, more recent studies show no relevant effect.

In the following discussion, we will assume regional analgesia does not make a difference in mortality and morbidity and will try to convince ourselves otherwise critically appraising the studies available.

HISTORICAL OVERVIEW

Rodgers et al.[1] published the first and most cited meta-analysis on this topic. They concluded that neuraxial blockade reduces postoperative mortality and other serious complications. However, many of the trials included were already outdated, had methodological flaws, and do not represent current standard of care. All studies were performed before 1997 and a substantial number before 1985.

Several studies reported an unusually high mortality rate of up to 27% in the control group.[2–6] This neither represented the rest of the population in the meta-analysis nor does it represent current clinical practice with vastly improved outcomes due to less invasive surgical techniques and the widespread introduction of low molecular weight heparins.[2]

Ballantyne et al.[7] demonstrated that the difference in mortality was related to the year in which a study was done, with newer studies finding smaller or no differences in mortality.

The study by Yeager et al.,[8] included in many reviews and meta-analyses, was flawed both by a 76% incidence of adverse events in the nonepidural group (19 of 25 patients) and by premature termination of inclusion.[8] When this study was excluded from the meta-analysis by Beattie et al. (both in 2001 and 2003) as well as the Cochrane review, the mortality difference between epidural and general anesthesia was no longer significantly different.[9–11]

In a large retrospective study, Wijeysundera et al.[12] compared 88,188 patients with and without epidural anesthesia and/or analgesia and found a very small difference in patient outcome (0.2% absolute risk reduction) of borderline significance ($P = 0.02$). The authors concluded that "this study should not be used to justify the use of epidural analgesia for mortality reduction."

CLINICAL OUTCOMES: CARDIOVASCULAR COMPLICATIONS

It has been suggested that epidural analgesia reduces postoperative cardiovascular complications. Three meta-analyses, mainly including studies in vascular surgery, showed a significant reduction in cardiac morbidity with epidural techniques.[9–11] Beattie et al.[10] included 1173 patients and found a nonsignificant risk reduction of 0.56 (confidence interval [CI], 0.30–1.03, $P = 0.06$) for myocardial infarction (MI). Only a post hoc subgroup analysis for thoracic epidurals achieved significance ($P = 0.04$) with an odds ratio of 0.43 (CI, 0.19–0.97).[10] In patients undergoing open abdominal aortic surgery, Nishimori et al.[9] reported a significant relative risk reduction of 0.52 (CI, 0.29–0.93) for MI in the presence of thoracic epidural analgesia.

The results of these 3 studies critically depended on inclusion of the previously discussed study by Yeager et al.[8] Without this study, no significant results remained.

A meta-analysis focusing on cardiac surgery demonstrated a reduction in supraventricular arrhythmias but not in MI.[13] Another meta-analysis, including 70 randomized controlled trials (RCTs) and nearly 5500 mixed surgical patients, did not find a difference in the incidence of MI.[14] Two more meta-analyses and 2 RCTs, also including cardiac surgery, also did not demonstrate an effect of epidural analgesia on cardiovascular complications.[14–17]

In their systematic review of all available evidence, Liu and Wu[18] concluded that epidural analgesia failed to significantly reduce cardiovascular complications in a general surgical population. From the evidence above, we can add that the effects on cardiac complications are minimal and limited to a subpopulation of high-risk patients and procedures.

CLINICAL OUTCOME: PULMONARY COMPLICATIONS

Based on the shortcomings mentioned before and the unknown incidence of pneumonia in the control group, the odds ratio of 0.61 demonstrated by Rodgers et al.[1] should

From the Department of Anesthesiology, Academic Medical Center, Amsterdam, the Netherlands.

Accepted for publication January 10, 2014.

Funding: Departmental funding only.

The authors declare no conflicts of interest.

This report was previously presented, in part, at the multiple presentations, amongst others at the European Society of Anaesthesiology annual meeting.

Reprints will not be available from the authors.

Address correspondence to Markus W. Hollmann, MD, PhD, DEAA, Department of Anesthesiology, Academic Medical Center, P.O. Box 226601100 DD Amsterdam, the Netherlands. Address e-mail to M.W.Hollmann@amc.nl.

DOI: 10.1213/ANE.0000000000000245

be treated with caution. When comparing thoracic epidural analgesia to IV analgesia after coronary artery bypass graft surgery, an odds ratio of 0.41 (CI, 0.27–0.60) for pulmonary complications was found.[15] In a multicenter RCT, including 888 patients with at least 1 risk factor, the risk of postoperative respiratory failure was significantly reduced by epidural techniques from 30.2% to 23.3% ($P = 0.02$), and in a meta-analysis in cardiac surgery, a significant risk reduction of 0.53 (CI, 0.40–0.69) was shown on the compound end point "respiratory complications."[13,16]

A large RCT and a meta-analysis could not reproduce these effects.[14,17] Similarly, the meta-analysis by Liu and Wu[18] did not find a significant difference in pulmonary outcome between systemic and epidural analgesia. Taken together, the influence of epidural analgesia on pulmonary complications, if present at all, is limited to high-risk intrathoracic procedures and high-risk patients.

In conclusion, adding epidural analgesia to general anesthesia does not reduce postoperative morbidity and mortality in a general surgical population. It is unlikely that such evidence will appear in the next years because of the decreased incidence of complications. For example, the incidence of pneumonia has decreased from 20% to 28% in the 1980s to 8% to 10% in more recent trials.[17,19–22] Moreover, the beneficial effects of epidural analgesia on deep venous thrombosis and pulmonary embolism have been diminished by routine antithrombotic prophylaxis. Finally, surgical techniques advancing toward less invasive procedures, such as endovascular aortic aneurysm repair or thoracoscopic and laparoscopic surgery, are associated with less short-term postoperative morbidity and mortality, thereby further diminishing any potential for a benefit caused by epidural analgesia.[23]

QUALITY OF ANALGESIA AND FAILURE RATE

Most studies comparing epidural analgesia with systemic analgesia reported a difference, which was often statistically significant and in favor of epidural analgesia.[24–27] However, the absolute difference ranged from 6 to 17 mm on a 100-mm visual analog scale. Since a commonly accepted minimum difference to detect clinical superiority is 20 to 30 mm difference on a 100-mm visual analog scale, the small statistical difference is not clinically relevant.[28,29]

Second, treatment of control groups in most studies consisted of parenteral opioids alone or combined with acetaminophen, which cannot be considered state of the art.[30,31] An optimal regimen should contain a cyclooxygenase inhibitor (nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor, or dipyrone), an *N*-methyl-D-aspartate receptor antagonist ((S) ketamine), a descending inhibitory pain pathway inhibitor (e.g., clonidine) and possibly an anticonvulsive drug (e.g., pregabalin) in addition to opioids. IV lidocaine has also been proven beneficial.[32–41]

Clinically most important, the statistical superiority of epidural analgesia was offset by a failure rate of 13% to 47% in experienced hands.[42] In the MASTER trial, 42.5% of the inserted epidural catheters were removed before the scheduled 72 hours.[16] This was in accordance with other reports.[43–47]

In conclusion, epidural analgesia provides statistically, but not clinically, superior analgesia to 53% to 87% of patients. The other 13% to 47% will likely experience a period of inadequate analgesia, often requiring rescue systemic analgesia. Therefore, the effect on a group level is not superior to systemic analgesia.

ALTERNATIVES TO EPIDURAL ANALGESIA

For extremity surgery, continuous peripheral nerve blocks are widely used. As for epidural analgesia, there was no evidence for any effect on long-term outcome.[18] Nevertheless, 2 meta-analyses suggested that peripheral nerve blocks facilitated a quicker rehabilitation with less opioid use and less sleep disturbance.[48,49]

Epidural analgesia and femoral nerve block resulted in comparable analgesia, opioid consumption, postoperative nausea and vomiting incidence and speed of rehabilitation for major knee surgery although femoral blocks caused fewer side effects (hypotension, pruritus, and urinary retention), and increased patient satisfaction.[50]

For truncal surgery, paravertebral, intercostal, and transversus abdominal plane blocks and wound infusion catheters are alternatives for epidural or systemic analgesia.[51] Currently, there is insufficient evidence to judge their value.

Local anesthetics work beyond the direct inhibition of local signal transmission in the nerve and modulate the inflammatory response by acting on G protein-coupled receptors.[52] Clinical studies demonstrated that a perioperative IV infusion of lidocaine yielded a reduction in duration of postoperative ileus and length of hospital stay accompanied by a reduced stress/inflammation response.[33–38,41,53,54]

ENHANCED RECOVERY PROGRAMS

Thoracic epidural analgesia is sometimes promoted as part of fast-track or enhanced recovery after surgery (ERAS) programs.[55] There was substantial heterogeneity in the studies regarding type of surgery, care in the control group as well as the type, and number of interventions that were implemented. Although ERAS reduced length of stay and sometimes postoperative complications, it remains unclear which elements are essential for success and actually contribute to an improved outcome.[56] A meta-analysis concluded that implementation of at least 4 interventions, not necessarily including epidural analgesia, resulted in reduction of hospital stay of 2 days and a nearly 50% reduction in complications.[47] Success of ERAS is primarily based on a structured and protocol-based approach and a modified attitude toward rehabilitation goals.

Although excellent analgesia and dampening of the surgical stress response are needed, epidural analgesia is not the only way to achieve this. The 2 ERAS trials comparing thoracic epidural analgesia with IV analgesia did not find any difference in length of stay, morbidity, or mortality.[57,58] The reduction in length of stay achieved within an ERAS program using systemic lidocaine was comparable with that of studies using epidural analgesia.[38,41,54]

We conclude that there is no evidence that thoracic epidural analgesia should be a compulsory part of an ERAS program.

CANCER RECURRENCE

A small retrospective study suggested that regional analgesia could improve cancer-free survival, but more recent trials could not reliably reproduce these results.[59–62] This leaves the effect itself as well as dependent variables, such

as tumor type, anesthesia technique, and molecular mechanisms as a matter of debate.[60–63]

COMPLICATIONS OF EPIDURAL ANALGESIA

Epidural analgesia was considered a safe technique with an incidence of serious complications (neuraxial hematoma and abscess) of <1 in 100,000 patients. However, several studies demonstrated that the setting in which a neuraxial block was performed, as well as the technique used, made a difference in the risk of complications.[64–69] The incidence of permanent harm (including paraplegia and death) ranged from <1 in 200,000 spinal punctures performed in an obstetric setting to 1 in 5700 to 12,000 cases for thoracic epidurals in surgical patients.[66] These numbers were confirmed by several large studies, some of which report an incidence of up to 1 in every 1000 cases.[64–68] Considering the evidence from the last decade, it should now be accepted that a thoracic epidural catheter in surgical patients carries a 10- to 100-fold higher risk, that is, 1 in 1000 to 10,000 for serious complications.[64–68] It is unclear whether better reporting of complications is responsible for the higher figures or whether the incidence of neuraxial hematoma has actually increased over the years. Thromboprophylaxis with low molecular weight heparins and other agents might have caused both the decrease in thrombotic surgical complications as well as an increased risk of epidural hemorrhage.[70] Anesthesia societies have proposed guidelines for management of anticoagulated patients undergoing neuraxial block.[71] Most recommendations in these guidelines are based on case series, pharmacology, and expert opinion, but it is clear that anticoagulant therapy should prevail over the indication for neuraxial anesthesia/analgesia since the evidence for thromboprophylaxis (or other anticoagulants) is much stronger than the evidence for an epidural catheter.

In conclusion, there is strong evidence that epidural analgesia or peripheral regional analgesic techniques improve neither perioperative mortality nor postoperative pulmonary and cardiovascular complications to a clinically significant extent for the general surgical population. If any, the advantages of epidural analgesia are limited to high-risk morbid patients undergoing high-risk procedures.[51,70] Analgesia is statistically, but not clinically, superior using epidural techniques. The marginal superiority is further offset by failure rates and analgesic alternatives such as (S)-ketamine, clonidine, and IV lidocaine. Epidural analgesia is associated with a small but relevant number of serious complications, especially in the presence of anticoagulant therapy. The risk/benefit balance should be discussed with the patient in the preoperative consultation.

In our opinion, epidural analgesia remains a valid option for postoperative analgesia, and all authors regularly use it for patients undergoing major surgery after careful individual risk assessment. However, given the arguments discussed above, epidural analgesia can no longer be considered the standard of care for a general surgical population. ■

DISCLOSURES

Name: Fabian O. Kooij, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Fabian O. Kooij approved the final manuscript.
Name: Wolfgang S. Schlack, MD, PhD, DEAA.
Contribution: This author helped write the manuscript.
Attestation: Wolfgang S. Schlack approved the final manuscript.
Name: Benedikt Preckel, MD, PhD, DEAA.
Contribution: This author helped write the manuscript.
Attestation: Benedikt Preckel approved the final manuscript.
Name: Markus W. Hollmann, MD, PhD, DEAA.
Contribution: This author helped write the manuscript.
Attestation: Markus W. Hollmann approved the final manuscript.
This manuscript was handled by: Terese T. Horlocker, MD.

REFERENCES

1. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anesthesia: results from overview of randomised trials. BMJ 2000;321:1493
2. Borovskikh NA, Lebedev LV, Strashkov VI, Vinogradov AT. [Comparative evaluation of the effectiveness of epidural anesthesia with spontaneous respiration and general anesthesia in aorto-femoral bifurcation shunt]. Vestn Khir Im I I Grek 1990;145:95–8
3. McLaren AD, Stockwell MC, Reid VT. Anesthetic techniques for surgical correction of fractured neck of femur. A comparative study of spinal and general anesthesia in the elderly. Anaesthesia 1978;33:10–4
4. Valentin N, Lomholt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. Br J Anesth 1986;58:284–91
5. McKenzie PJ, Wishart HY, Smith G. Long-term outcome after repair of fractured neck of femur. Comparison of subarachnoid and general anesthesia. Br J Anesth 1984;56:581–5
6. Davis FM, Laurenson VG. Spinal anesthesia or general anesthesia for emergency hip surgery in elderly patients. Anesth Intensive Care 1981;9:352–8
7. Ballantyne JC, Kupelnick B, McPeek B, Lau J. Does the evidence support the use of spinal and epidural anesthesia for surgery? J Clin Anesth 2005;17:382–91
8. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729–36
9. Nishimori M, Ballantyne JC, Low JH. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 2006;3:CD005059
10. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001;93:853–8
11. Beattie WS, Badner NH, Choi PT. Meta-analysis demonstrates statistically significant reduction in postoperative myocardial infarction with the use of thoracic epidural analgesia. Anesth Analg 2003;97:919–20
12. Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Epidural anesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. Lancet 2008;372:562–9
13. Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJ, Bax L. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. Anesthesiology 2011;114:271–82
14. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. J Anesth 2006;20:335–40
15. Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 2004;101:153–61
16. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, Collins KS; MASTER Anethesia Trial Study Group. Epidural anesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002;359:1276–82
17. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized,

controlled Veterans Affairs cooperative study. Ann Surg 2001;234:560–9
18. Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesth Analg 2007;104:689–702
19. Addison NV, Brear FA, Budd K, Whittaker M. Epidural analgesia following cholecystectomy. Br J Surg 1974;61:850–2
20. Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. Br J Surg 1985;72:495–8
21. Hjortsø NC, Neumann P, Frøsig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled study on the effect of epidural analgesia with local anesthetics and morphine on morbidity after abdominal surgery. Acta Anesthesiol Scand 1985;29:790–6
22. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, Parsons R. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. Anesth Analg 2003;96:548
23. Schanzer A, Messina L. Two decades of endovascular abdominal aortic aneurysm repair: enormous progress with serious lessons learned. J Am Heart Assoc 2012;1:e000075
24. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005;1:CD004088
25. Marret E, Remy C, Bonnet F; Postoperative Pain Forum Group. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg 2007;94:665–73
26. Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. Anesth Analg 2007;105:789–808
27. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290:2455–63
28. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407–14
29. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–94
30. Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103:1296–304
31. Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anesth 2011;107 Suppl 1:i27–40
32. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;1:CD004603
33. De Oliveira GS Jr, Fitzgerald P, Streicher LF, Marcus RJ, McCarthy RJ. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. Anesth Analg 2012;115:262–7
34. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs 2010;70:1149–63
35. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, McIntyre LA, Nicole PC, Fergusson DA. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anesth 2011;58:22–37
36. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain 2012;28:567–72
37. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2012;55:1183–94
38. Herroeder S, Pecher S, Schönherr ME, Kaulitz G, Hahnenkamp K, Friess H, Böttiger BW, Bauer H, Dijkgraaf MG, Dijkgraaf OG, Durieux ME, Hollmann MW. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg 2007;246:192–200
39. Hollmann MW, Strümper D, Durieux ME. The poor man's epidural: systemic local anesthetics for improving postoperative outcomes. Med Hypotheses 2004;63:386–9
40. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. Health Technol Assess 2010;14:1–153, iii–iv
41. Swenson BR, Gottschalk A, Wells LT, Rowlingson JC, Thompson PW, Barclay M, Sawyer RG, Friel CM, Foley E, Durieux ME. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. Reg Anesth Pain Med 2010;35:370–6
42. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anesth 2012;109:144–54
43. Van Aken H, Gogarten W, Brüssel T, Brodner G. Epidural anesthesia and analgesia in mayor surgery. Lancet 2002;360:568
44. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ. Epidural anesthesia and analgesia in mayor surgery (author reply). Lancet 2002;360:569
45. Ready LB. Acute pain: lessons learned from 25,000 patients. Reg Anesth Pain Med 1999;24:499–505
46. Low J, Johnston N, Morris C. Epidural analgesia: first do no harm. Anaesthesia 2008;63:1–3
47. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 2010;29:434–40
48. Ilfeld BM. Continuous peripheral nerve blocks: a review of the published evidence. Anesth Analg 2011;113:904–25
49. Richman JM, Liu SS, Courpas G, Wong R, Rowlingson AJ, McGready J, Cohen SR, Wu CL. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg 2006;102:248–57
50. Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. Br J Anesth 2008;100:154–64
51. Rawal N. Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med 2012;37:310–7
52. Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. Anesthesiology 2001;95:113–22
53. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 2008;95:1331–8
54. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. Reg Anesth Pain Med 2011;36:241–8
55. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002;183:630–41
56. Vlug MS, Bartels SA, Wind J, Ubbink DT, Hollmann MW, Bemelman WA; Collaborative LAFA Study Group. Which fast track elements predict early recovery after colon cancer surgery? Colorectal Dis 2012;14:1001–8
57. Zutshi M, Delaney CP, Senagore AJ, Mekhail N, Lewis B, Connor JT, Fazio VW. Randomized controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with preemptive epidural anesthesia/analgesia after laparotomy and intestinal resection. Am J Surg 2005;189:268–72
58. Hemmerling TM, Prieto I, Choinière JL, Basile F, Fortier JD. Ultra-fast-track anesthesia in off-pump coronary artery bypass grafting: a prospective audit comparing opioid-based anesthesia vs thoracic epidural-based anesthesia. Can J Anesth 2004;51:163–8

59. 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
60. Forget P, Tombal B, Scholtès JL, Nzimbala J, Meulders C, Legrand C, Van Cangh P, Cosyns JP, De Kock M. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anesthesiol 2011;28:830–5
61. Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. Anesthesiology 2012;116:797–806
62. Capmas P, Billard V, Gouy S, Lhommé C, Pautier P, Morice P, Uzan C. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. Anticancer Res 2012;32:1537–42
63. Doornebal CW, Klarenbeek S, Braumuller TM, Klijn CN, Ciampricotti M, Hau CS, Hollmann MW, Jonkers J, de Visser KE. A preclinical mouse model of invasive lobular breast cancer metastasis. Cancer Res 2013;73:353–63
64. Cameron CM, Scott DA, McDonald WM, Davies MJ. A review of neuraxial epidural morbidity: experience of more than 8000 cases at a single teaching hospital. Anesthesiology 2007;106:997–1002
65. Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. Anaesthesia 2007;62:335–41
66. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 2004;101:950–9
67. Pöpping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anesth 2008;101:832–40
68. Cook TM, Counsell D, Wildsmith JA; Royal College of Anesthetists Third National Audit Project. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anesthetists. Br J Anesth 2009;102:179–90
69. Bateman BT, Mhyre JM, Ehrenfeld J, Kheterpal S, Abbey KR, Argalious M, Berman MF, Jacques PS, Levy W, Loeb RG, Paganelli W, Smith KW, Wethington KL, Wax D, Pace NL, Tremper K, Sandberg WS. The risk and outcomes of epidural hematomas after perioperative and obstetric epidural catheterization: a report from the Multicenter Perioperative Outcomes Group Research Consortium. Anesth Analg 2013;116:1380–5
70. Horlocker T, Kopp S. Epidural hematoma after epidural blockade in the United States: it's not just low molecular heparin following orthopedic surgery anymore. Anesth Analg 2013;116:1195–7
71. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010;35:64–101

Section Editor: **Terese T. Horlocker**

Neuraxial Anesthesia for the Prevention of Postoperative Mortality and Major Morbidity: An Overview of Cochrane Systematic Reviews

Joanne Guay, MD,* Peter T. Choi, MD,† Santhanam Suresh, MD,‡ Natalie Albert, MD,§ Sandra Kopp, MD,‖ and Nathan Leon Pace, MD¶

BACKGROUND: This analysis summarized Cochrane reviews that assess the effects of neuraxial anesthesia on perioperative rates of death, chest infections, and myocardial infarction.
METHODS: A search was performed in the Cochrane Database of Systematic Reviews on July 13, 2012. We have included all Cochrane systematic reviews that examined subjects of any age undergoing any type of surgical (open or endoscopic) procedure, compared neuraxial anesthesia to general anesthesia alone for the surgical anesthesia, or neuraxial anesthesia plus general anesthesia to general anesthesia alone for the surgical anesthesia, and included death, chest infections, myocardial infarction, and/or serious adverse events as outcomes. Studies included in these reviews were selected on the same criteria.
RESULTS: Nine Cochrane reviews were selected for this overview. Their scores on the Overview Quality Assessment Questionnaire varied from 4 to 6 of a maximal possible score of 7. Compared with general anesthesia, neuraxial anesthesia reduced the 0- to-30-day mortality (risk ratio [RR] 0.71; 95% confidence interval [CI], 0.53–0.94; I^2 = 0%) based on 20 studies that included 3006 participants. Neuraxial anesthesia also decreased the risk of pneumonia (RR 0.45; 95% CI, 0.26–0.79; I^2 = 0%) based on 5 studies that included 400 participants. No difference was detected in the risk of myocardial infarction between the 2 techniques (RR 1.17; 95% CI, 0.57–2.37; I^2 = 0%) based on 6 studies with 849 participants. Compared with general anesthesia alone, adding neuraxial anesthesia to general anesthesia did not affect the 0- to-30-day mortality (RR 1.07; 95% CI, 0.76–1.51; I^2 = 0%) based on 18 studies with 3228 participants. No difference was detected in the risk of myocardial infarction between combined neuraxial anesthesia–general anesthesia and general anesthesia alone (RR 0.69; 95% CI, 0.44–1.09; I^2 = 0%) based on 8 studies that included 1580 participants. Adding a neuraxial anesthesia to general anesthesia reduced the risk of pneumonia (RR 0.69; 95% CI, 0.49–0.98; I^2 = 9%) after adjustment for publication bias and based on 9 studies that included 2433 participants. The quality of the evidence was judged as moderate for all 6 comparisons. The quality of the reporting score of complications related to neuraxial blocks was 9 (4 to 12 [median {range}]) for a possible maximum score of 14.
CONCLUSIONS: Compared with general anesthesia, neuraxial anesthesia may reduce the 0-to-30-day mortality for patients undergoing a surgery with an intermediate-to-high cardiac risk (level of evidence moderate). Large randomized controlled trials on the difference in death and major outcomes between regional and general anesthesia are required. (Anesth Analg 2014;119:716–25)

From the *Department of Anesthesiology, CSSS Rouyn-Noranda, Rouyn-Noranda, Quebec, Canada; †Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia, Vancouver, Canada; ‡Department of Pediatric Anesthesiology and Pediatrics, Northwestern University's Feinberg School of Medicine, Chicago, Illinois; §Department of Anesthesiology, University Laval, Quebec, Canada; ‖Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota; and ¶Department of Anesthesiology, University of Utah, Salt Lake City, Utah.

Accepted for publication May 4, 2014.

Funding: The Cochrane Anaesthesia Review Group, Denmark: The search strategy was designed by Mr. Karen Hovhannisyan, Trials Search Coordinator for the Cochrane Anaesthesia Review Group, Rigshospitalet, Dept. 3342, Blegdamsvej 9, 2100 Copenhagen, Denmark. University of Montreal, Canada: Access to electronic databases and to major medical journals was provided by the University of Montreal, Montreal, Quebec, Canada.

Conflicts of Interests: See Disclosures at the end of the article.

The protocol of this study has been published: Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD010108. DOI: 10.1002/14651858.

Reprints will not be available from the authors.

Address correspondence to Joanne Guay, MD, Department of Anesthesiology, CSSS Rouyn-Noranda 4, 9e Rue, Rouyn-Noranda, Québec J9X 2B2, Canada. Address e-mail to joanneguay@bell.net.

DOI: 10.1213/ANE.0000000000000339

Postoperative death may occur after major infectious (superficial, deep, urinary tract, and organ infections or sepsis), hematological (postoperative bleeding requiring transfusion, deep-vein thrombosis, pulmonary embolus), cardiovascular (myocardial infarction, stroke), respiratory (pneumonia, unplanned intubation, prolonged mechanical ventilation), renal (acute kidney injury), and surgical (wound dehiscence, vascular graft loss) complications.

Neuraxial anesthesia with or without general anesthesia may reduce the incidence of some major complications that can lead to death such as pulmonary complications, time to tracheal extubation, cardiac dysrhythmias, venous thromboembolism, blood transfusion, surgical site infection, and acute kidney injury.[1–6] Maximal blood concentrations of stress response markers, such as epinephrine, norepinephrine, cortisol, and glucose, are lower in patients to whom epidural anesthesia is added to general anesthesia.[2] Several Cochrane reviews have evaluated the effect of neuraxial anesthesia for various types of surgical populations. There is currently no synthesis of those reviews reported in an overview.

Our primary objective was to summarize Cochrane systematic reviews that assess the effects of neuraxial anesthesia on perioperative rates of death, chest infections, and myocardial infarction by integrating the evidence from all Cochrane systematic reviews that have compared neuraxial anesthesia with or without general anesthesia versus general anesthesia alone for different types of surgery on various populations. Our secondary objective was to summarize the evidence about adverse effects (an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility) of neuraxial anesthesia.

METHODS

We considered all Cochrane systematic reviews that included randomized controlled trials (RCTs); examined participants of any age undergoing any type of surgical (open or endoscopic) procedure; compared neuraxial anesthesia to general anesthesia alone for the surgical anesthesia or compared neuraxial anesthesia plus general anesthesia to general anesthesia alone for the surgical anesthesia; and included death, chest infections, myocardial infarction, or serious adverse events as outcomes. Neuraxial anesthesia consisted of epidural, caudal, spinal, or combined spinal–epidural techniques administered as a bolus or continuous infusion intraoperatively. We searched the Cochrane Database of Systematic Reviews on July 13, 2012, using the following terms: #1 MeSH descriptor Anesthesia, Epidural explode all trees; #2 MeSH descriptor Nerve Block explode all trees; #3 MeSH descriptor Anesthetics, Local explode all trees; #4 MeSH descriptor Anesthesia, Intravenous explode all trees; #5 MeSH descriptor Analgesia, Epidural explode all trees; #6 MeSH descriptor Anesthesia, Caudal explode all trees; #7 ([epidural or caudal or spinal or spinal?epidural) near (techniq* or administ* or bolus* or infusion*]) or an?esthesia; #8 (an?esthesia or block* or analgesia) near (regional or local or neuraxial or nerve or caudal or spinal or epidural or lumbar or general); #9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8). We analyzed the data with RevMan 5.1 (Review Manager version 5.1) and Comprehensive Meta Analysis version 2.2.044 (http://www.Meta-Analysis.com). One author screened all the abstracts of reviews identified by the search. The full reports of the potential reviews were obtained. Two authors independently reviewed each report for inclusion.

From the included studies of selected reviews, studies were selected independently by 2 authors with the same criteria used for the selection of the reviews without any language restriction. Data of selected studies were reextracted by 1 author and compared with the data included in the corresponding review. Any discrepancy was checked by a second author.

Two of the authors independently assessed the methodological quality of included reviews using a 10-item index, the Overview Quality Assessment Questionnaire.[7] Because the latest version of the risk of bias tool was unavailable when some of the Cochrane reviews were performed, the methodological quality of included RCTs was reassessed using the current Cochrane tool for risk of bias. Studies were classified in to 2 groups: (1) neuraxial anesthesia versus general anesthesia for the surgery; and (2) neuraxial anesthesia added to general anesthesia versus general anesthesia alone for the surgery. Random-effects models were used and the effects were expressed as risk ratio (RR) and its 95% confidence interval (CI). Heterogeneity was quantified by the I^2 statistic, with the data entered in the direction (benefit or harm) yielding the lowest value. Although we planned to use a value of >25% as cutoff for exploration, this was not necessary. The I^2 value was 0% for 5 of the 6 comparisons and 9% for the outcome pneumonia, comparison neuraxial anesthesia added to general anesthesia versus general anesthesia alone. A priori factors chosen were as follows: ASA physical status (1 or 2 vs 3 or higher); age (<18 years versus 18 to <70 years versus 70 years or higher); type of surgery (high versus intermediate versus low cardiac risk);[8] type of neuraxial blockade (spinal versus epidural or caudal; lumbar versus thoracic epidural); type of neuraxial drug (long-acting opioid alone versus local anesthetic alone versus local anesthetic plus long-acting opioid versus other adjuvants [e.g., clonidine, neostigmine, or ketamine]); duration of neuraxial blockade (intraoperative only versus infusion continued for at least 48 hours after surgery); use of thromboprophylaxis (appropriate or not according to current standards); type of thromboprophylaxis (low-molecular weight heparin, ximelagatran, fondaparinux, or rivaroxaban versus regional blockade, pneumatic compression, and aspirin versus warfarin); pregnancy; and mode of analgesia in the control group (IV analgesia versus other routes).

For results where the intervention produced an effect, a number-needed-to-treat (NNT) or number-needed-to-harm was calculated based on the odds ratio (http://www.nntonline.net/visualrx/). Publication bias was assessed with a funnel plot followed by Duval and Tweedie's trim and fill technique for each outcome or classical fail-safe number (number of studies with no effect required to bring the P value to 0.05; $\alpha = 0.05$, 2-tails). The quality of the body of evidence for each outcome was judged as high, moderate, or low according to the system developed by the GRADE Working Group.[9,10] With a high quality of evidence, further research is unlikely to change our confidence in the estimated effect. When the quality is moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Three authors independently applied these criteria. Discrepancies were resolved by discussion.

For adverse effects of neuraxial blockade, all selected studies were assessed according to the 7 criteria proposed by Stojadinovic et al.[11] method of accrual, duration of data collection, definition of complication, morbidity and mortality rates, grade of complication severity, exclusion criteria, and study follow-up. The following complications related to neuraxial blockade were sought specifically: mortality (anytime up to 5 years), seizure or cardiac arrest related to local anesthetic toxicity (any significant prolonged neurological sequelae related to these events were to be described), prolonged central or peripheral neurological injury lasting >1 month, and infection secondary to neuraxial blockade.

Table 1. Overview Quality Assessment Questionnaire

Item	Afolabi et al.[12]	Barbosa et al.[13]	Choi et al.[14]	Craven et al.[15]	Cyna and Middleton [16]	Jørgensen et al. [17]	Nishimori et al.[1]	Parker et al.[3]	Werawatganon and Charuluxanun[18]
1. Were the search methods reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the search comprehensive?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Partially
3. Were the inclusion criteria reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was selection bias avoided?	Yes	Yes	Yes	Partially	Yes	Partially	Yes	Partially	Yes
5. Were the validity criteria reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was validity of the included studies assessed appropriately?	Partially	Yes	Partially	Partially	Partially	Partially	Yes	Partially	Yes
7. Were the methods used to combine studies reported?	Yes	Yes	Partially	Partially	Partially	Partially	Yes	Yes	Partially
8. Were the findings combined appropriately?	Partially	Yes	Partially	Partially	Partially	Partially	Partially	Partially	Yes
9. Were the conclusions supported by the reported data?	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes
10. What was the overall scientific quality of the overview? (Likert scale from 1 to 7)	5	6	5	4	4	5	6	5	5

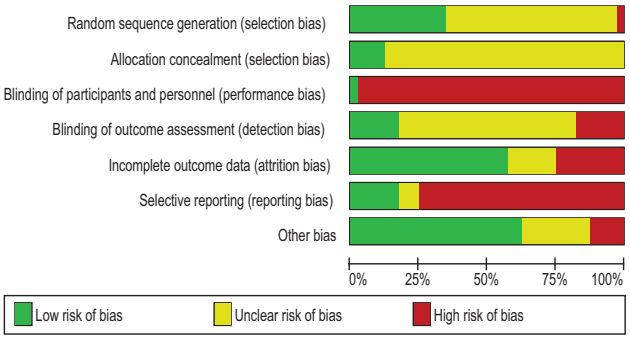

Figure 1. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. Green is the percentages of studies for which each item was judged as appropriate and red the percentages of studies for which each specific item was judged as inappropriate. Yellow means that there was not enough information in the report to make a judgment.

RESULTS

A total of 1158 titles/abstracts were screened. Of these, 304 were protocols, 844 were not relevant to neuraxial blockade used during surgery, and 1 did not contain a control group with general anesthesia. Therefore, we retrieved and kept 9 systematic reviews.[1,4,12–18] The overall quality of included reviews was average (Table 1). These 9 reviews included 117 trials but only 40 studies met our inclusion criteria and were retained (Afolabi, 3; Barbosa, 4; Choi, 1; Craven, 0; Cyna, 0; Jorgensen, 4; Nishimori, 12; Parker, 13; and Werawatganon, 3).[1,3,12–58] Altogether we retained 40 studies for the new analysis.[19–58] All the retained trials studied adults patients undergoing surgeries with an intermediate, or high cardiac risk, or a mixture of both. These surgeries were performed on the lower limb, in the intra-abdominal cavity or at various parts of the body. Three trials studied pregnant women undergoing cesarean deliveries.[19–21] The quality of the 40 studies retained for reanalysis can be found in Figure 1.

Compared with general anesthesia, neuraxial anesthesia reduced the 0- to 30-day mortality (classical fail safe number = 7; Fig. 2 and Table 2). The NNT calculated on the odds ratio was 44 (95% CI, 27–228) for an incidence of 7.9% for general anesthesia versus 5.2% for neuraxial anesthesia (Fig. 2). Cardiac risk was classified as intermediate for 76.5% (2300/3006) (intraperitoneal or orthopedic surgery) and high for 23.5% (706/3006) (aortic or peripheral vascular surgery) of the participants. With Duval and Tweedie's trim and fill analysis, the adjusted RR was 0.72 (95% CI, 0.54–0.95) looking for missing studies to the right, and unchanged while looking for missing studies to the left. Egger's regression intercept did not indicate a small-study effect. Mortality data were available for 896 participants for the 1- to-6-month follow-up (RR 1.52; 95% CI, 0.89–2.62) and for 726 participants at 6- to-12-month follow-up (RR 1.27; 95% CI, 0.74–2.17). Neuraxial anesthesia also decreased the risk of pneumonia (classical fail safe number = 3; Table 2 and Fig. 3). The NNT was 11 (95% CI, 8–27) for incidences of 7.6% and 16.8% for neuraxial anesthesia and general anesthesia, respectively. Egger's regression intercept did not indicate a small-study effect. The RR adjusted for a possible publication bias was 0.44 (95% CI, 0.26–0.73). There was no difference in the risk of myocardial infarction between neuraxial anesthesia and general anesthesia (Table 2 and Fig. 4). There was no evidence of publication bias for this comparison.

For the studies where neuraxial anesthesia was added to general anesthesia, a spinal block was used in 1 study and an epidural block was used for 19 studies. The epidural block was used intra and postoperatively for all studies: time unspecified for 2 studies and mean time 59 hours (95% CI, 46–98 hours) for the other studies. Adding neuraxial anesthesia to general anesthesia did not affect the mortality risk (Table 2 and Fig. 2). With Duval and Tweedie's trim and fill analysis, the effect was almost unchanged (RR 1.13; 95% CI, 0.80–1.59). The risk of myocardial infarction was not different between the 2 anesthetic techniques (Table 2 and Fig. 4). The power to detect a 25% reduction in incidence from 5.7% was only 0.25 (α = 0.05, 2-sided test). With an adjustment for a possible publication bias, the RR would be 0.72 (95% CI, 0.46–1.13). Likewise, the addition of neuraxial anesthesia did not change the risk of a pneumonia when a random model effects was used (Table 2 and Fig. 3) and was marginally suggestive of an effect when a fixed effect model was used (RR 0.74; 95% CI, 0.56–0.98). For the

random effects model, the power to detect a 25% reduction is 0.58 ($\alpha = 0.05$, 2-sided test) from an incidence of 9.5%. For the fixed effect model, the NNT was 40 (95% CI, 24–387). Egger's regression intercept did not indicate a small-study effect. The funnel plot revealed that 2 studies might be missing on the left side. With Duval and Tweedie's trim and fill analysis, the adjusted RR was 0.69 (95% CI, 0.49–0.98) with a random effects model. If only studies with an a priori definition for the diagnosis of pneumonia were included, then adding neuraxial anesthesia to general anesthesia reduced the risk of pneumonia (RR 0.70 [95% CI, 0.49–1.00] versus RR 1.28 [95% CI, 0.31–5.19] for the studies where it was not).

For the effect of neuraxial anesthesia on the risk of pneumonia by the type of neuraxial block, the RR was 0.90 (95% CI, 0.31–2.62) for spinal anesthesia, RR was 5.5 (95% CI, 0.28–107.78) for lumbar epidural anesthesia, RR was 0.64 (95% CI, 0.17–2.47) for thoracic epidural anesthesia, and RR was 0.69 (95% CI, 0.45–1.06) when either lumbar or thoracic epidural anesthesia could be used. All studies for this comparison included a local anesthetic in the neuraxial block. There was no correlation between the effect size (RR) and the mean age of the patients included in the studies.

No serious adverse events were reported. The quality score of the reporting of complications related to neuraxial

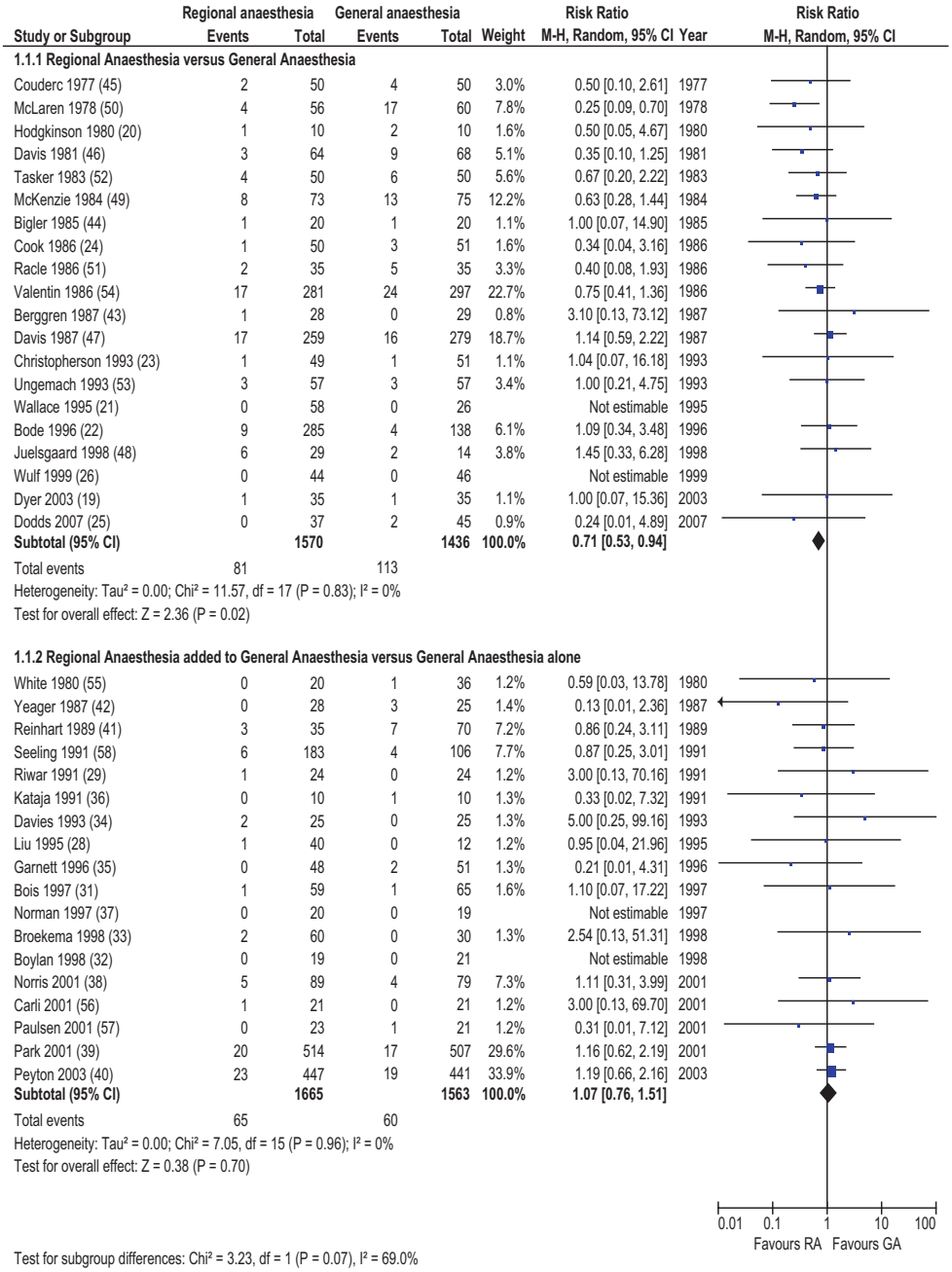

Figure 2. Forest plots for mortality 0 to 30 days. The upper part of the figure illustrates the comparison neuraxial anesthesia versus general anesthesia. The lower part of the figure illustrates the comparison neuraxial anesthesia added to general anesthesia versus general anesthesia alone.

Table 2. Summary of New Findings

Neuraxial blockade (GA) compared with general anesthesia (GA) for perioperative mortality, myocardial infarction or chest infection

Patient or population: Patients with perioperative mortality
Settings: In hospital or ambulatory surgery
Intervention: Neuraxial blockade (GA)
Comparison: General anesthesia (GA)

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk General anesthesia (GA)	Corresponding risk Neuraxial blockade (GA)				
RA versus GA: mortality—Follow-up: 30 days	Study population 79 per 1000	56 per 1000 (42 –74)	RR 0.71 (0.53–0.94)	3006 (20 studies)	⊕⊕⊕⊖ moderate[b]	
	Low-risk population 20 per 1000	14 per 1000 (11–19)				
	High-risk population 100 per 1000	71 per 1000 (53–94)				
RA versus GA: myocardial infarction—Follow-up: 30 days	Study population 34 per 1000	40 per 1000 (19–81)	RR 1.17 (0.57–2.37)	849 (6 studies)	⊕⊕⊕⊖ moderate[b]	
	Low-risk population 20 per 1000	23 per 1000 (11–47)				
	High-risk population 60 per 1000	70 per 1000 (34–142)				
RA versus GA: pneumonia—Follow-up: 30 days	Study population 167 per 1000	75 per 1000 (43–132)	RR 0.45 (0.26–0.79)	400 (5 studies[c])	⊕⊕⊕⊖ moderate[b,d,e]	
	Low-risk population 40 per 1000	18 per 1000 (10–32)				
	High-risk population 200 per 1000	90 per 1000 (52–158)				
RA added to GA versus GA: mortality—Follow-up: 30 days	Study population 38 per 1000	41 per 1000 (29–57)	RR 1.07 (0.76–1.51)	3228 (18 studies)	⊕⊕⊕⊖ moderate[b]	
	Low-risk population 20 per 1000	21 per 1000 (15–30)				
	High-risk population 60 per 1000	64 per 1000 (46–91)				
RA added to GA versus GA: myocardial infarction—Follow-up: 30 days	Study population 57 per 1000	39 per 1000 (25–62)	RR 0.69 (0.44–1.09)	1580 (8 studies)	⊕⊕⊕⊖ moderate[b]	
	Low-risk population 20 per 1000	14 per 1000 (9–22)				
	High-risk population 80 per 1000	55 per 1000 (35–87)				
RA added to GA versus GA: pneumonia—Follow-up: 30 days	Study population 95 per 1000	71 per 1000 (50–98)	RR 0.74 (0.53–1.03)	2433 (10 studies)	⊕⊕⊕⊖ moderate[b]	
	Low-risk population 40 per 1000	30 per 1000 (21–41)				
	High-risk population 120 per 1000	89 per 1000 (64–124)				

[a]The assumed risk is based on the mean control risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence. High quality = Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality = We are very uncertain about the estimate.

CI = confidence interval; RR = risk ratio; RA = regional anesthesia; GA = general anesthesia.

[b]Blinding.

[c]For the comparison RA versus GA, outcome pneumonia, studies were published between 1981 and 1987.

[d]Classical fail safe number = 3.

[e]RR < 0.5.

blockade was: 9 (4–12) (median [range]) from a possible maximal score of 14. The quality of the evidence was rated as moderate for all 6 comparisons (Table 2). Risk of bias introduced by study design was the reason for downgrading the quality from high to moderate with the absence of blinding of outcome assessors being the most serious potentially avoidable concern (Fig. 1). For the effect on pneumonia of the comparison of neuraxial anesthesia versus general anesthesia, the small fail-safe number (possibility of publication bias) was compensated by the large (<0.5) effect size.

DISCUSSION

Compared with general anesthesia, neuraxial anesthesia reduced the mortality rate by approximately 2.5% (Fig. 2) and the risk of perioperative pneumonia (Fig. 3). Adding neuraxial anesthesia to general anesthesia may reduce the incidence of pneumonia; however, this is less conclusive because the results varied depending on whether the effect size was adjusted or not for a possible publication bias. We decided to use only random effects models regardless of the amount of heterogeneity because we wanted to reduce the

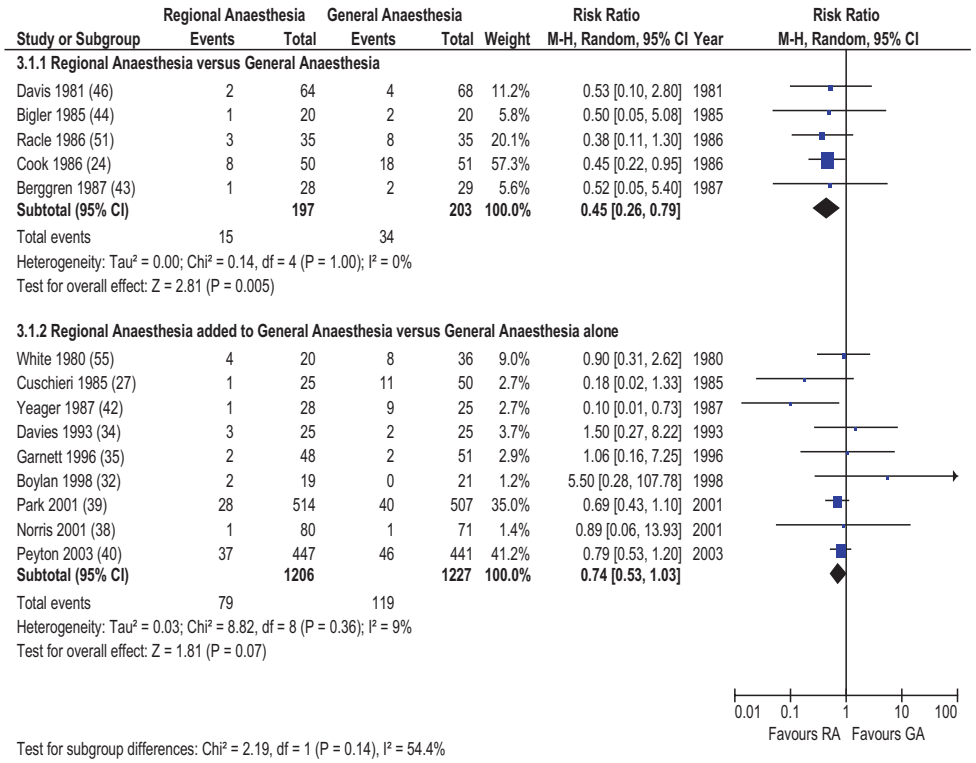

Figure 3. Forest plots for pneumonia 0 to 30 days. The upper part of the figure illustrates the comparison neuraxial anesthesia versus general anesthesia. The lower part of the figure illustrates the comparison neuraxial anesthesia added to general anesthesia versus general anesthesia alone.

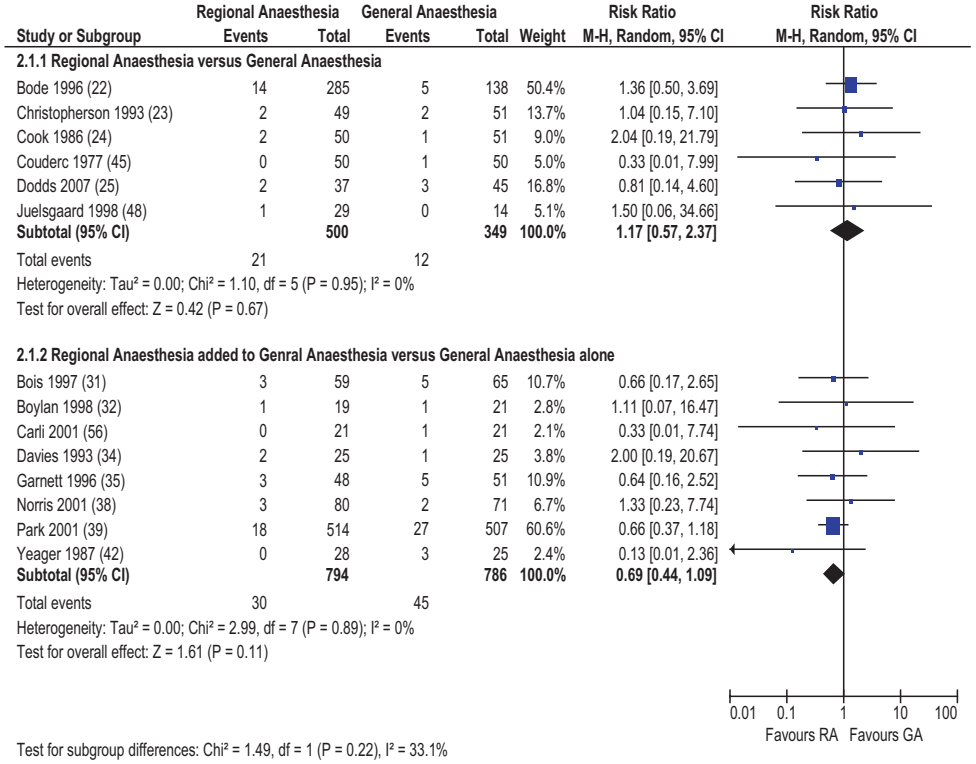

Figure 4. Forest plots for myocardial infarction 0 to 30 days. The upper part of the figure illustrates the comparison neuraxial anesthesia versus general anesthesia. The lower part of the figure illustrates the comparison neuraxial anesthesia added to general anesthesia versus general anesthesia alone.

possibility of finding an effect where there was none. When heterogeneity is present, a random effects model will usually widen the confidence interval. The only comparison where we saw statistical heterogeneity was the effect on the risk of pneumonia when neuraxial anesthesia was added to general anesthesia compared with general anesthesia alone (I^2 = 9%). If data were pooled with a fixed effect model, then adding neuraxial anesthesia to general anesthesia reduced the incidence of pneumonia, whereas no effect was detected if data were pooled with a random effects model. However, when we included only the studies where an a priori definition for the diagnosis of pneumonia was reported, addition of neuraxial anesthesia to general anesthesia reduced the risk of pneumonia regardless of the model used. None of the interventions (neuraxial anesthesia compared with general anesthesia or neuraxial anesthesia added to general anesthesia versus general anesthesia alone) reduced the risk of myocardial infarction (Fig. 4), but the power to detect a 25% risk reduction from the addition of neuraxial anesthesia to general anesthesia was only 0.25 (α = 0.05, 2-sided test).

When deciding which intervention to choose for a patient, one has to balance the benefits versus the risks. Although many studies gave an appropriate description of the techniques used, a clear mention of the presence or absence of complications related to the techniques, with an adequate duration of follow-up, was lacking in many of the reports.[20,22,23,25,29,31,32,34–36,41–43,45,48,49,51–54,57,58] There is no doubt for the authors of this overview that complications will need to be evaluated in future trials. Currently, we have to rely on the data provided by the most recent large prospective studies to estimate the incidence of complications related to neuraxial blockade.

The 40 studies retained for analysis are of good quality except for 2 criteria. First, blinding was usually not used in these studies. Considering the potentially serious (although rare) side effects that can be associated with the insertion of an epidural catheter, many clinicians would consider insertion of an epidural catheter to be unethical if it is not used to provide neuraxial blockade. Second, many of our studies suffered from the absence of reporting of side effects of neuraxial blocks, which resulted in lower scores of quality.[20,22,23,25,29,31,32,34–36,41–43,45,48,49,51–54,57,58]

Using systematic reviews to find relevant studies to answer a question could be considered an unusual technique, but we do not think that this led us to "biased" results. First, all the included systematic reviews used very comprehensive search strategies. Second, by using Duval and Tweedie's trim and fill analysis, we were able to quantify the effects sizes while considering any potential publication bias. Publication bias occurs when medical journals publish more studies favoring one intervention than studies favoring another one or a placebo. No matter the search technique used, it is never possible to be certain that all studies will be included. One simple reason for this is that authors themselves may simply not submit a study with absence of effect. When performing a study, we do not measure all the population to whom the treatment may apply, instead we choose a fair sample of participants and then assume that the treatment will be equally effective or ineffective to other patients with characteristics similar to those included in our study. Likewise, we chose a sample of studies while clearly defining in advance our criteria for inclusion. As in the example above, results of our overview apply to patients with characteristics similar to those included in our overview.

In a metaanalysis published in 2000, Rodgers et al.[6] concluded that neuraxial blockade reduced the overall 30-day mortality by approximately one-third and that this would apply to trials in which neuraxial blockade was combined with general anesthesia as well as to trials in which neuraxial blockade was used alone. The metaanalysis of Rodgers et al.[6] included studies published up to 1996, while we were able to include 13 studies published after 1996. We demonstrated that these 2 interventions (neuraxial anesthesia compared with general anesthesia versus adding neuraxial anesthesia to general anesthesia) are not equivalent (I^2 for heterogeneity between the 2 interventions is 69%) (Fig. 2). Using neuraxial anesthesia as the sole anesthetic technique reduced the 30-day mortality rate, while adding neuraxial anesthesia to general anesthesia did not. Our overview does not allow us to determine whether this difference between the 2 interventions is due to a diminishing of the beneficial effects of neuraxial anesthesia by general anesthesia, to adverse effects of general anesthesia itself, or a combination of both. Our results apply to patients undergoing an intermediate-to-high cardiac risk procedure (peripheral vascular, intraperitoneal, orthopedic, and prostate surgery). The magnitude of this effect requires further exploration because the overall quality of the included trials was moderate. Large high-quality trials will be required to confirm or refute our results on the effects of using neuraxial anesthesia as opposed to general anesthesia on the mortality rate. A larger sample size is required before drawing any conclusions on the effects of adding neuraxial anesthesia to general anesthesia on the risk of myocardial infarction. These trials should include appropriate follow-up and description of side effects of each technique to allow the reader to balance the risks and benefits of each technique.

Although neuraxial analgesia was used for the vast majority of the studies in the group neuraxial anesthesia added to general anesthesia (19 of 20), the effects of postoperative neuraxial analgesia cannot be determined from our overview because we retained studies where neuraxial anesthesia was used for the intraoperative period regardless of their use or not for the postoperative period.

In conclusion, compared with general anesthesia, neuraxial anesthesia may reduce the 0- to-30-day mortality for patients undergoing a surgery with an intermediate-to-high cardiac risk (level of evidence moderate). Large RCTs on the difference in death and major outcomes between regional and general anesthesia are required. ■

DISCLOSURES

Name: Joanne Guay, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Joanne Guay has seen the original study data (data contained in the published reports), reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: The author has no conflicts of interest to declare.

Name: Peter T. Choi, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Peter T. Choi has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Peter T. Choi has published a prior systematic review included in this Cochrane overview. He had no participation in judging the quality of his own review or in selecting studies or extracting data from studies pertaining to his review. The author has no other conflicts of interest.
Name: Santhanam Suresh, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Santhanam Suresh has seen the original study data (data contained in the published reports), reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Natalie Albert, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Natalie Albert has seen the original study data (data contained in the published reports), reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Sandra Kopp, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Sandra Kopp has seen the original study data (data contained in the published reports), reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Nathan Leon Pace, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Nathan Leon Pace has seen the original study data (data contained in the published reports), reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
This manuscript was handled by: Terese T. Horlocker, MD.

ACKNOWLEDGMENTS

The authors thank Karen Hovhannisyan, Trials Search Coordinator for the Cochrane Anesthesia Review Group (CARG) for designing the search and the University of Montreal for access to electronic databases and major medical journals. We also thank Dr. Stephan Schwarz for the translation of the 2 German articles in our systematic overview, Dr. Helen Handoll for providing translations of some Japanese and Italian articles, and Dr. Mina Nishimori for granting us access to her data extraction sheets. Finally, we are also indebted to Drs. Mark Neuman (content editor), Marialena Trivella (statistical editor), Lorne Becker, Denise Thompson, Jørn Wetterselv, and Mina Nishimori (peer reviewers) for their help and editorial advice during the preparation of this for overview.

REFERENCES

1. Nishimori M, Low JH, Zheng H, Ballantyne JC. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 2012;7:CD005059
2. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. J Anesth 2006;20:335–40
3. Parker MJ, Handoll HH, Griffiths R. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev 2004;4:CD000521
4. Guay J. The effect of neuraxial blocks on surgical blood loss and blood transfusion requirements: a meta-analysis. J Clin Anesth 2006;18:124–8
5. Chang CC, Lin HC, Lin HW, Lin HC. Anesthetic management and surgical site infections in total hip or knee replacement: a population-based study. Anesthesiology 2010;113:279–84
6. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000;321:1493
7. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991;44:1271–8
8. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery); American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society for Vascular Surgery. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:e418–99
9. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, Liberati A, O'Connell D, Oxman AD, Phillips B, Schünemann H, Edejer TT, Vist GE, Williams JW Jr; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004;4:38
10. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94
11. Stojadinovic A, Shockey SM, Croll SM, Buckenmaier CC 3rd. Quality of reporting of regional anesthesia outcomes in the literature. Pain Med 2009;10:1123–31
12. Afolabi BB, Lesi FE, Merah NA. Regional versus general anaesthesia for caesarean section. Cochrane Database Syst Rev 2006;4:CD004350
13. Barbosa FT, Cavalcante JC, Jucá MJ, Castro AA. Neuraxial anaesthesia for lower-limb revascularization. Cochrane Database Syst Rev 2010;1:CD007083
14. Choi PT, Bhandari M, Scott J, Douketis J. Epidural analgesia for pain relief following hip or knee replacement. Cochrane Database Syst Rev 2003;3:CD003071
15. Craven PD, Badawi N, Henderson-Smart DJ, O'Brien M. Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy. Cochrane Database Syst Rev 2003;3:CD003669
16. Cyna AM, Middleton P. Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. Cochrane Database Syst Rev 2008;4:CD003005

17. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000;4:CD001893
18. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005;1:CD004088
19. Dyer RA, Els I, Farbas J, Torr GJ, Schoeman LK, James MF. Prospective, randomized trial comparing general with spinal anesthesia for cesarean delivery in preeclamptic patients with a nonreassuring fetal heart trace. Anesthesiology 2003;99:561–9
20. Hodgkinson R, Husain FJ, Hayashi RH. Systemic and pulmonary blood pressure during caesarean section in parturients with gestational hypertension. Can Anaesth Soc J 1980;27:389–94
21. Wallace DH, Leveno KJ, Cunningham FG, Giesecke AH, Shearer VE, Sidawi JE. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. Obstet Gynecol 1995;86:193–9
22. Bode RH Jr, Lewis KP, Zarich SW, Pierce ET, Roberts M, Kowalchuk GJ, Satwicz PR, Gibbons GW, Hunter JA, Espanola CC. Cardiac outcome after peripheral vascular surgery. Comparison of general and regional anesthesia. Anesthesiology 1996;84:3–13
23. Christopherson R, Beattie C, Frank SM, Norris EJ, Meinert CL, Gottlieb SO, Yates H, Rock P, Parker SD, Perler BA. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993;79:422–34
24. Cook PT, Davies MJ, Cronin KD, Moran P. A prospective randomised trial comparing spinal anaesthesia using hyperbaric cinchocaine with general anaesthesia for lower limb vascular surgery. Anaesth Intensive Care 1986;14:373–80
25. Dodds TM, Fillinger MP, Walsh DB, Surgenor SD, Mandel D, Yeager MP. Clinical outcomes after lower extremity revascularization: a comparison of epidural and general anaesthesia. J Appl Res 2007;7: 238–49
26. Wulf H, Biscoping J, Beland B, Bachmann-Mennenga B, Motsch J. Ropivacaine epidural anesthesia and analgesia versus general anesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. Ropivacaine Hip Replacement Multicenter Study Group. Anesth Analg 1999;89:111–6
27. Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. Br J Surg 1985;72:495–8
28. Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TS, Feinglass NG, Metzger PP, Fulmer JT, Smith SL. Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology 1995;83:757–65
29. Riwar A, Schär B, Grötzinger U. [Effect of continuous postoperative analgesia with peridural bupivacaine on intestinal motility following colorectal resection]. Helv Chir Acta 1992;58:729–33
30. Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. Acta Anaesthesiol Scand 1987;31:161–4
31. Bois S, Couture P, Boudreault D, Lacombe P, Fugère F, Girard D, Nadeau N. Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. Anesth Analg 1997;85:1233–9
32. Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DC, DeMajo WC, Walker PM, Johnston KW, Sandler AN. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. Anesthesiology 1998;89:585–93
33. Broekema AA, Veen A, Fidler V, Gielen MJ, Hennis PJ. Postoperative analgesia with intramuscular morphine at fixed rate versus epidural morphine or sufentanil and bupivacaine in patients undergoing major abdominal surgery. Anesth Analg 1998;87:1346–53
34. Davies MJ, Silbert BS, Mooney PJ, Dysart RH, Meads AC. Combined epidural and general anaesthesia versus general anaesthesia for abdominal aortic surgery: a prospective randomised trial. Anaesth Intensive Care 1993;21:790–4
35. Garnett RL, MacIntyre A, Lindsay P, Barber GG, Cole CW, Hajjar G, McPhail NV, Ruddy TD, Stark R, Boisvert D. Perioperative ischaemia in aortic surgery: combined epidural/general anaesthesia and epidural analgesia vs general anaesthesia and i.v. analgesia. Can J Anaesth 1996;43:769–77
36. Kataja J. Thoracolumbar epidural anaesthesia and isoflurane to prevent hypertension and tachycardia in patients undergoing abdominal aortic surgery. Eur J Anaesthesiol 1991;8:427–36
37. Norman JG, Fink GW. The effects of epidural anesthesia on the neuroendocrine response to major surgical stress: a randomized prospective trial. Am Surg 1997;63:75–80
38. Norris EJ, Beattie C, Perler BA, Martinez EA, Meinert CL, Anderson GF, Grass JA, Sakima NT, Gorman R, Achuff SC, Martin BK, Minken SL, Williams GM, Traystman RJ. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. Anesthesiology 2001;95:1054–67
39. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. Ann Surg 2001;234:560–9
40. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, Parsons R. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. Anesth Analg 2003;96:548–54
41. Reinhart K, Foehring U, Kersting T, Schaefer M, Bredle D, Hirner A, Eyrich K. Effects of thoracic epidural anesthesia on systemic hemodynamic function and systemic oxygen supply-demand relationship. Anesth Analg 1989;69:360–9
42. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729–36
43. Berggren D, Gustafson Y, Eriksson B, Bucht G, Hansson LI, Reiz S, Winblad B. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg 1987;66:497–504
44. Bigler D, Adelhøj B, Petring OU, Pederson NO, Busch P, Kalhke P. Mental function and morbidity after acute hip surgery during spinal and general anaesthesia. Anaesthesia 1985;40:672–6
45. Couderc E, Mauge F, Duvaldestin P, Desmonts JM. [Comparative results of general and peridural anesthesia for hip surgery in the very old patient]. [Article in French] Anesth Analg (Paris) 1977;34:987–97
46. Davis FM, Laurenson VG. Spinal anaesthesia or general anaesthesia for emergency hip surgery in elderly patients. Anaesth Intensive Care 1981;9:352–8
47. Davis FM, Woolner DF, Frampton C, Wilkinson A, Grant A, Harrison RT, Roberts MT, Thadaka R. Prospective, multicentre trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. Br J Anaesth 1987;59:1080–8
48. Juelsgaard P, Sand NP, Felsby S, Dalsgaard J, Jakobsen KB, Brink O, Carlsson PS, Thygesen K. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. Eur J Anaesthesiol 1998;15:656–63
49. McKenzie PJ, Wishart HY, Smith G. Long-term outcome after repair of fractured neck of femur. Comparison of subarachnoid and general anaesthesia. Br J Anaesth 1984;56:581–5
50. McLaren AD, Stockwell MC, Reid VT. Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of spinal and general anaesthesia in the elderly. Anaesthesia 1978;33:10–4
51. Racle JP, Benkhadra A, Poy JY, Gleizal B, Gaudray A. [Comparative study of general and spinal anesthesia in elderly women in hip surgery]. Ann Fr Anesth Reanim 1986; 5:24–30
52. Tasker TPB, Raitt DG, Kohn RLJ, Vater M, Crashaw C. Subarachnoid block or general anaesthesia?: a study of the stress response during and after surgery for prosthetic replacement of fractured neck of femur. J Bone Joint Surg Br 1993;65:660–

53. Ungemach JW, Andres FJ, Eggert E, Schoder K. The role of anaesthesia in geriatric patients with hip fractures: A prospective study. Eur J Anaesthesiol 1993;10:380
54. Valentin N, Lomholt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anaesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. Br J Anaesth 1986;58:284–91
55. White IW, Chappell WA. Anaesthesia for surgical correction of fractured femoral neck. A comparison of three techniques. Anaesthesia 1980;35:1107–10
56. Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. Dis Colon Rectum 2001;44:1083–9
57. Paulsen EK, Porter MG, Helmer SD, Linhardt PW, Kliewer ML. Thoracic epidural versus patient-controlled analgesia in elective bowel resections. Am J Surg 2001;182:570–7
58. Seeling W, Bothner U, Eifert B, Rockemann M, Schreiber M, Schürmann W, Steffen P, Zeininger A. [Patient-controlled analgesia versus epidural analgesia using bupivacaine or morphine following major abdominal surgery. No difference in postoperative morbidity]. [Article in German] Anaesthesist 1991;40:614–23