Regional Anesthesia and Pain

Best evidence in anesthetic practice

Prevention: epidural anesthesia and analgesia does not reduce 30-day all-cause mortality and major morbidity after abdominal surgery

Article #1 appraised

Park WY, Thompson JS, Lee KK, and the Department of Veterans Affairs Cooperative Study #345 Study Group. Effect of epidural anesthesia and analgesia on perioperative outcomes. A randomized, controlled Veterans Affairs Cooperative Study. *Ann Surg* 2001; 234: 560–71.

Structured abstract

Question: For patients undergoing major abdominal operations, does epidural/general anesthesia and postoperative epidural analgesia reduce the 30-day frequency of postoperative death and major complications compared to general anesthesia and postoperative systemic opioid analgesia?

Design: Multicenter, randomized, unblinded trial.

Setting: Fifteen hospitals of the US Department of Veterans Affairs.

Patients: Two thousand seven hundred and thirty-one patients undergoing abdominal aortic, gastric, biliary, or colon surgery were screened. Exclusion criteria included age < 21 yr; female gender; American Society of Anesthesiologists physical status class I, II, or V; mental confusion; emergency surgery; myocardial infarction within the past six months; abdominal procedure within the past three months; previous aortic surgery; use of chemotherapeutic or immunosuppressive drugs (other than steroids); tracheostomy or endotracheal intubation; contraindications to any study drug or technique; insistence of surgeon or anesthesiologist on a particular anesthetic; or participation in another study. Of the 1,371 eligible patients, 1,021 consented to participate. After randomization, 37 patients (25 in the epidural group; 12 in the systemic group) were excluded due to surgical cancellation or patient withdrawal. Eleven patients did not complete the 30-day follow-up.

Intervention: Five hundred and fourteen patients were allocated to receive lumbar or thoracic epidural anesthesia using 0.5% bupivacaine with epinephrine plus balanced general anesthesia (nitrous oxide, isoflurane, fentanyl, vecuronium) and postoperative epidural morphine 3 to 6 mg every 12 to 24 hr. Five hundred and seven patients were allocated to receive a thiopental or midazolam/fentanyl induction plus balanced general anesthesia (as described above) and postoperative intramuscular or intravenous morphine or meperidine.

Main outcomes: The primary outcome was the combined endpoint of 30-day all-cause mortality, myocardial infarction, congestive heart failure, ventricular tachyarrhythmia, complete atrioventricular block, severe hypotension, cardiac arrest, pulmonary embolism, respiratory failure, stroke, and renal failure. The secondary outcomes were angina, respiratory depression, pneumonia, sepsis, gastrointestinal bleeding, epidural hematoma, and reoperation. Postoperative pain at rest, physical mobilization, and lengths of intensive care unit (ICU) and hospital stay were evaluated also.

Main results: Analysis was intention-to-treat. Clinical characteristics, indicators of surgical severity, and surgical complexity were similar. Mean duration of epidural analgesia was 55.2 hr. The two groups did not have any significant differences in the frequencies of primary or secondary outcomes, the average postoperative physical performance scores, or lengths of ICU or hospital stay. Visual analogue pain scores were lower in the epidural group ($P \leq 0.03$) on postoperative days one, three, and seven. Subgroup analysis showed statistically significant reductions in the frequency of the primary outcome, respiratory failure, and stroke in patients undergoing abdominal aortic surgery in the epidural group (Table).

TABLE Selected results from two recent large randomized controlled trials of epidural anesthesia and analgesia in abdominal surgery

<i>Postoperative Outcome</i>	<i>Epidural Group</i>	<i>Systemic Group</i>	<i>Relative risk (95% Confidence Interval)</i>	<i>Number-needed-to-prevent</i>	<i>P-value</i>
Veterans Affairs Study – all patients					
Death/morbidity*	91/514	111/507	0.81 (0.63–1.04)	not applicable	0.11
Death	20/514	17/507	1.16 (0.61–2.19)	not applicable	0.74
Cardiac events†	44/514	57/507	0.76 (0.52–1.10)	not applicable	0.18
Respiratory failure	51/514	71/507	0.71 (0.51–1.00)	not applicable	0.06
Renal failure	9/514	7/507	1.27 (0.48–3.38)	not applicable	0.82
Stroke	8/514	9/507	0.88 (0.34–2.26)	not applicable	0.98
Veterans Affairs Study – aortic surgery					
Death/morbidity*	40/184	70/190	0.59 (0.42–0.82)	6.6	< 0.01
Death	4/184	5/190	0.83 (0.23–3.04)	not applicable	0.96
Cardiac events†	18/184	34/190	0.55 (0.32–0.94)	12.3	0.03
Respiratory failure	26/184	53/190	0.51 (0.33–0.78)	7.3	< 0.01
Renal failure	5/184	4/190	1.29 (0.35–4.73)	not applicable	0.96
Stroke	1/184	9/190	0.11 (0.01–0.86)	23.8	0.03
MASTER Anaesthesia Trial					
Death/morbidity*	255/447	268/441	0.94 (0.84–1.05)	not applicable	0.29
Death	23/447	19/441	1.19 (0.66–2.15)	not applicable	
Cardiac events‡	115 / 447	106 / 441	1.07 (0.85 – 1.35)	not applicable	0.61
Respiratory failure	104/447	133/441	0.77 (0.62–0.96)	14.5	0.02
Renal failure	33/447	36/441	0.90 (0.57–1.42)	not applicable	0.75

* Please see text for details on the primary outcome (death or major morbidity); † Cardiac events were myocardial infarction, congestive heart failure, ventricular tachyarrhythmia, atrioventricular block, severe hypotension, and cardiac arrest; ‡ Cardiac events were myocardial infarction, angina, congestive heart failure, cardiac shock, atrioventricular block, and ventricular or supraventricular tachyarrhythmias.

Conclusion: Overall, epidural/general anesthesia and epidural analgesia does not reduce 30-day mortality or major morbidity but does provide better pain control than general anesthesia and systemic analgesia.

Funding: US Department of Veterans Affairs Cooperative Studies Program, Veterans Health Administration.

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Article #2 appraised

Rigg JRA, Jamrozik K, Myles PS, et al., for the MASTER Anaesthesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; 359: 1276–82.

Structured abstract

Question: For patients undergoing major abdominal or esophageal operations, does epidural/general anesthesia and 72-hr postoperative epidural analgesia reduce the 30-day frequency of perioperative death and major complications compared to general anesthesia and postoperative systemic opioid analgesia?

Design: Multicenter, randomized trial. Outcome adjudicators were blinded.

Setting: Twenty-five hospitals in Australia, Hong Kong, Malaysia, Saudi Arabia, Singapore, and Thailand.

Patients: Patients were eligible if they were undergoing elective, non-laparoscopic abdominal or esophageal operations lasting more than one hour, and were ≥ 18 yr old with morbid obesity, diabetes mellitus, chronic renal failure, respiratory insufficiency, major hepatocellular disease, or cardiac disease within the past two years, or ≥ 75 yr old with two or more risk factors (significant respiratory disease, cardiac dysrhythmia, hypertension, moderate obesity, frailty, or myocardial infarction). Patients with contraindications to epidural use were excluded.

Intervention: Four hundred and sixty-one patients were allocated to receive lumbar or thoracic epidural anesthesia using local anesthetic with or without opioids plus balanced general anesthesia and postoperative 72-hr continuous epidural analgesia with bupivacaine or ropivacaine, with or without meperidine or fentanyl. Four hundred and fifty-four patients were allocated to receive balanced general anesthesia and postoperative intravenous opioids. After randomization, 27 patients

were excluded due to surgical cancellation or ineligible procedure, leaving 447 and 441 patients in the epidural and systemic groups respectively.

Main outcomes: The primary outcome was the combined endpoint of 30-day all-cause mortality and major postoperative complications (myocardial infarction, angina, congestive heart failure, cardiac shock, ventricular or supraventricular tachyarrhythmia, complete atrioventricular block, respiratory failure, gastrointestinal failure, hepatic failure, pancreatic failure, renal failure, hematological failure, and major inflammatory complications [infection, pneumonia, or sepsis]). Postoperative pain at rest and after coughing were also assessed.

Main results: Analysis was intention-to-treat. Frequencies of preoperative risk factors were similar in the two groups. Mean duration of epidural analgesia was 73.6 hr. There was no significant difference in the frequency of the primary outcome. Visual analogue pain scores were significantly lower in the epidural group at rest on postoperative day one ($P = 0.0002$) and after coughing on postoperative days one to three ($P \leq 0.0007$). Epidural/general anesthesia and epidural analgesia reduced the frequency of respiratory failure compared to general anesthesia and systemic analgesia (Table). Twenty-nine patients (6.5%) in the epidural group did not receive an epidural; nineteen patients (4.3%) in the systemic group received epidural analgesia. "As treated" analysis yielded similar results to the intention-to-treat analysis.

Conclusion: Overall, epidural/general anesthesia and epidural analgesia does not reduce 30-day mortality or major morbidity but does provide better pain control than general anesthesia and systemic analgesia.

Funding: The Australian and New Zealand College of Anaesthetists, the Health Department of Western Australia, and the National Health and Medical Research Council.

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Commentary by S. Ganapathy

As an avid regional anesthesiologist, I have been very disappointed by the lack of evidence of improved outcome with regional anesthesia other than the initial enthusiasm generated by Yeager's study and Rodgers's meta-analysis.^{1,2} By and large, outcome studies of regional anesthesia have inadequate sample sizes, group different regional anesthetic techniques (e.g., lumbar and thoracic epidurals and spinals), and/or terminate recruitment before reaching their proposed

sample sizes. The sample size is often based on an outcome that is impacted by many factors aside from the intervention. The studies appraised in this feature are no exception except the sample sizes are considerably larger; one hopes this reduces the effect of other contributing factors on the outcome.

The study by Park and colleagues used intraoperative lumbar or thoracic epidural local anesthetic without narcotics for abdominal surgery followed by postoperative analgesia with epidural narcotics. There are two fundamental problems with the intervention. First, the benefits of epidural analgesia following abdominal surgery are seen only with local anesthetics administered via the thoracic epidural route.³ Second, epidural opioids alone or lumbar epidural local anesthetics have not been efficacious in reducing postoperative complications.³ Thus, the intervention in Park's study may not have been optimal. In spite of this limitation, patients receiving an epidural in the aortic surgery subgroup were less likely to experience one or more primary endpoints ($P < 0.01$), or cardiovascular ($P = 0.03$), cerebrovascular ($P = 0.03$), or pulmonary ($P < 0.01$) complications. The discussants of this paper clearly bring out some of the pitfalls with this study.

The study by Rigg and colleagues is more robust with regards to its design, clinical applicability, sample size, and population. Other than a reduction in the rate of respiratory failure, they did not demonstrate any advantage to thoracic epidural analgesia. Their finding reiterates the observation made by Norris *et al.* in aortic surgery.⁴

In both studies, the primary analysis was "intention-to-treat". Although this provides an estimate of effectiveness of the intervention, crossover of patients from one group to the other may compromise detection of efficacy. An "as treated" analysis might be more appropriate. Crossover rates in Park's and Rigg's studies were 7.8% and 5.4% respectively. The "as treated" analyses confirmed the results found with "intention-to-treat".

Finally, I firmly believe epidural analgesia is not a cure for preexisting morbidity that contributes to postoperative complications. One cannot reduce death from severe coronary artery disease with a short-term intervention.

For now, I will tell my patients that thoracic epidural analgesia provides them with excellent analgesia with activity, reduces respiratory complications, and provides questionable benefits with other outcomes. Will I continue to use it? You bet.

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References

- 1 Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology* 1987; 66: 729–36.
- 2 Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000; 321: 1493–7.
- 3 Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; 82: 1474–1506.
- 4 Norris EJ, Beattie C, Perler BA, et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology* 2001; 95: 1054–67.

Commentary by C.J.L. McCartney, W.S. Beattie, and V.W.S. Chan

The advantages of epidural anesthesia and analgesia are intuitive and are confirmed by the meta-analysis by Rodgers *et al.*¹ showing significant reduction in surgical morbidity and mortality with centroneuraxial blocks. Critics have argued that studies pooled in this systematic review involved many types of surgery and were conducted prior to routine use of thromboprophylaxis and perioperative β -blockade. Today, it is necessary to demonstrate the clinical advantages of epidural anesthesia and analgesia in the presence of modern medical techniques.

The recently published MASTER Trial and Veterans Affairs study,^{2,3} both large randomized controlled outcome studies (915 and 1,021 patients respectively), failed to demonstrate reduction in major morbidity and mortality up to 30 days postoperatively in patients who had epidural anesthesia and analgesia. However, both studies lacked adequate sample size and power to demonstrate a difference in overall mortality or cardiac morbidity between epidural and systemic treatments. To demonstrate a 30% reduction in myocardial infarction, as suggested by Rodgers *et al.*,¹ a study with a 5% type I error rate and 80% power would require at least 9,500 patients. In addition, in the MASTER trial, nearly 50% of patients in the epidural group were not fully compliant with the study protocol and thoracic epidural was not mandatory. Two recent meta-analyses have demonstrated that only thoracic, and not lumbar, epidural analgesia can reduce the incidence of mortality¹ or perioperative myocardial infarction.⁴

Despite a lack of power, both studies demonstrate several advantages of the use of epidural techniques. Superior postoperative analgesia was evident in both

studies despite epidural opioids alone being used in the Veterans Affairs study. The MASTER Trial demonstrated a significant reduction in respiratory failure (30.2% *vs* 23.3%, $P = 0.02$) in all patients who had epidural techniques. The Veterans Affairs study showed significantly fewer patients experiencing one or more primary postoperative complications (40 events *vs* 70 events, $P < 0.01$) in the epidural group following abdominal aortic surgery. These included lower incidences of respiratory failure and cardiovascular morbidity with the epidural technique. Importantly, both studies found significant clinical benefits of the epidural technique with no increase in adverse effects or complications.

Good quality pain relief aside, recent studies also show improved postoperative exercise tolerance, quality of life, and return of gastrointestinal function as other benefits of epidural analgesia.⁵ Unquestionably, evidence today supports the routine use of postoperative epidural analgesia in high risk surgical patients. However, as physicians, we must constantly remind ourselves that proper epidural catheter management goes beyond consideration of technique or site of catheter insertion. Furthermore, epidural analgesia is only one of many perioperative factors that can affect patient outcome.

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References

- 1 Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000; 321: 1493–7.
- 2 Rigg JR, Jamrozik K, Myles PS, et al.; MASTER Anaesthesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; 359: 1276–82.
- 3 Park WY, Thompson JS, Lee KK, and the Department of Veterans Affairs Cooperative Study #345 Study Group. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg* 2001; 234: 560–9.
- 4 Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; 93: 853–8.
- 5 Carli F, Mayo N, Klubien K, Schrickler T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* 2002; 97: 540–9.