Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study

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Lancet 2008; 372: 562–69

Published Online August 11, 2008 DOI:10.1016/S0140-6736(08)61121-6

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Summary

Background **Although epidural anaesthesia and analgesia have numerous benefits, their effects on postoperative survival are unclear. We therefore undertook a population-based cohort study to determine whether perioperative epidural anaesthesia or analgesia is associated with improved 30-day survival.**

Methods **We used population-based linked administrative databases to do a retrospective cohort study of 259 037 patients, aged 40 years or older, who underwent selected elective intermediate-to-high risk non-cardiac surgical procedures between April 1, 1994, and March 31, 2004, in Ontario, Canada. Propensity-score methods were used to construct a matched-pairs cohort that reduced important baseline differences between patients who received epidural anaesthesia or analgesia as opposed to those that did not. We then determined the association of epidural anaesthesia with 30-day mortality within these matched-pairs.**

Findings **Of the 259 037 patients, 56 556 (22%) received epidural anaesthesia. Within the matched-pairs cohort (n=88 188), epidural anaesthesia was associated with a small reduction in 30-day mortality (1·7% *vs* 2·0%; relative risk 0·89, 95% CI 0·81–0·98, p=0·02).**

Interpretation **Epidural anaesthesia and analgesia were associated with a small improvement in 30-day survival, but this effect should be interpreted cautiously. The estimate had borderline significance, despite a large sample size. Its absolute magnitude was also small, corresponding to a number needed to treat of 477. Our study, therefore, does not provide compelling evidence that epidural anaesthesia improves postoperative survival. Nonetheless, our results support the safety of perioperative epidural anaesthesia when used for indications other than improving survival (eg, improving postoperative pain relief, preventing postoperative pulmonary complications).**

Funding **Institute for Clinical Evaluative Sciences.**

Introduction

Epidural anaesthesia or analgesia (hereafter referred to as anaesthesia) offers important advantages during major non-cardiac surgery, and provides better postoperative pain relief than parenteral opioid therapy.[1] It also attenuates the surgical stress response, which has theoretical benefits for cardiovascular, respiratory, gastrointestinal, and metabolic function.[2] Nonetheless, an important, and yet unanswered,[3] question is whether these advantages translate into improved survival.

If epidural anaesthesia does improve postoperative survival, this finding would have practical implications for perioperative medicine. First, many patients are reluctant to accept epidural anaesthesia,[4] despite the evidence for improved pain relief and prevention of pulmonary complications. Similarly, some surgeons do not favour regional anaesthesia, often because of concerns that total intervention times would be increased.[5] Both patients and surgeons might be more willing to accept epidural anaesthesia if there was evidence for improved survival. Second, epidural catheters are associated with rare, but important, complications.[6] The demonstration of improved survival would suggest that, despite these risks, epidural anaesthesia still has a favourable risk–benefit profile.

Some early randomised controlled trials (RCTs) of epidural anaesthesia,[7] as well as a subsequent quantitative systematic review,[8] concluded that it significantly improved postoperative outcomes. Nonetheless, individual RCTs have been criticised for limited external generalisability and statistical power.[9] Importantly, two subsequent larger RCTs, with sample sizes of around 900 to 1000 patients, did not find the same overall improvement in postoperative outcome.[9,10] Despite the size of these trials, they also remained underpowered to detect a plausible moderate-sized treatment effect (eg, 20% relative risk reduction).[11,12]

To address these problems of limited external generalisability and statistical power, we did a population-based cohort study in Ontario, Canada. Our objective was to establish whether epidural anaesthesia is associated with improved 30-day survival after elective intermediate-to-high risk non-cardiac surgery.

Methods

Study design

After receiving research ethics approval from Sunnybrook Health Sciences Centre, we used linked population-based administrative health-care databases in Ontario, Canada, to undertake a cohort study. These databases were: the Canadian Institute for Health Information (CIHI) Discharge Abstract database, which describes all hospital admissions; the Ontario Health Insurance Plan (OHIP)

	Epidural n=56 556	No epidural n=202 481
Demographics		
Women	24 516 (43%)	110 662 (55%)
Age in years, mean (SD)	68 (10)	68 (10)
Socioeconomic status		
Annual income, CAD$, mean (SD)	24 578 (5043)	24 771 (5084)
Procedure		
Abdominal aortic aneurysm repair	5162 (9·1%)	2769 (1·4%)
Peripheral vascular bypass	4589 (8·1%)	11 457 (5·7%)
Total hip replacement	6595 (12%)	58 096 (29%)
Total knee replacement	10 684 (31%)	75 781 (37%)
Large bowel surgery	13 238 (23%)	40 622 (20%)
Liver resection	869 (1·5%)	1065 (0·5%)
Whipple procedure	716 (1·3%)	390 (0·2%)
Pneumonectomy or lobectomy	7358 (5·7%)	2731 (2·6%)
Gastrectomy or oesophagectomy	2682 (4·7%)	2945 (1·5%)
Nephrectomy	3275 (5·8%)	5582 (2·8%)
Cystectomy	1208 (2·1%)	1043 (0·5%)
Hospital type		
Teaching hospital	21 985 (39%)	64 115 (32%)
High-volume non-teaching	12 738 (23%)	41 357 (20%)
Mid-volume non-teaching	11 473 (20%)	47 568 (23%)
Low-volume non-teaching	10 450 (18%)	49 441 (24%)
Comorbid disease		
Ischaemic heart disease	6510 (12%)	17 454 (8·6%)
Congestive heart failure	1842 (3·3%)	4715 (2·3%)
Cerebrovascular disease	1726 (3·1%)	4884 (2·4%)
Hypertension	29 116 (51%)	108 403 (54%)
Diabetes mellitus	10 516 (19%)	35 469 (18%)
Pulmonary disease	3797 (6·7%)	9435 (4·7%)
Dialysis or renal disease	828 (1·5%)	2338 (1·2%)
Malignancy	9595 (17%)	13 948 (6·9%)
Specialist consultations*		
Anaesthesiology	32 431 (57%)	65 931 (33%)
General internal medicine	10 419 (18%)	50 898 (25%)
Cardiology	5171 (9·1%)	14 049 (6·9%)
Preoperative cardiac testing†		
Echocardiogram	7039 (12%)	14 932 (7·4%)
Myocardial perfusion test	6858 (12%)	13 946 (6·7%)
Coronary angiogram	474 (0·8%)	720 (0·4%)
Intraoperative care		
Arterial line	33 569 (59%)	65 931 (33%)
Central venous line	12 670 (22%)	9157 (4·5%)
Pulmonary artery catheter	5337 (9·4%)	3369 (1·7%)

Data are number (%) unless otherwise indicated. p<0.0001 for all differences.
*Within 60 days before surgery. †Within 6 months before surgery.

Table 1: **Characteristics of entire cohort and their bivariate association with epidural anaesthesia or analgesia**

database, which describes physician billings for inpatient and outpatient services; the Registered Persons Database (RPDB), which describes demographics and vital statistics; the Corporate Providers Database (CPDB), which describes physicians' specialties; and the 2001 Canadian census. Although these databases lack physiological and laboratory measures (eg, blood pressure, serum creatinine), they have been validated for many other outcomes, exposures, and comorbidities.[13–18] Ontario residents had access to physician services and hospital services through a universal health-care programme.

Study cohort

We retrospectively identified all Ontario residents, older than 40 years, who underwent the following specific elective surgical procedures during fiscal years 1994–2003 (April 1, 1994, to March 31, 2004): abdominal aortic aneurysm repair, peripheral vascular bypass, total hip replacement, total knee replacement, large bowel surgery, liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, oesophagectomy, nephrectomy, or cystectomy. We selected these procedures because they were intermediate-to-high risk, amenable to the use of epidural anaesthesia, applicable to either sex, and previously described in research studies that used the CIHI database.[19–23] Procedure codes in the CIHI database have excellent accuracy.[18]

The principal exposure was epidural anaesthesia or analgesia, as defined by a physician billing for the insertion of an epidural catheter within 1 day of surgery. These billings included cases where: the epidural catheter was successfully inserted and functioned appropriately; the anaesthesiologist was unsuccessful at inserting the epidural catheter; and the epidural catheter was successfully inserted but subsequently removed prematurely because of inadequate analgesia. The primary outcome was all-cause death within 30 days after surgery, which was established using the CIHI (in-hospital deaths) and RPDP (out-of-hospital deaths) databases. Additionally, we used the OHIP database to identify postoperative mechanical ventilation, as well as decompression spinal laminectomy, which might be related to complications from epidural catheters (eg, spinal epidural haematoma or spinal epidural abscess).

Demographic information was obtained from the RPDB. We used validated administrative data algorithms to identify patients with diabetes mellitus or hypertension.[14,17] The OHIP database was used to identify patients who had previously needed dialysis. We used previously described methods to identify other comorbidities based on International Classification of Diseases codes (9th Revision, Clinical Modification [ICD-9-CM]; or 10th Revision [ICD-10]) within the CIHI database. These other comorbid conditions were ischaemic heart disease, congestive heart failure, cerebrovascular disease, pulmonary disease, chronic renal insufficiency, malignancy, liver disease, and dementia.[24,25] To improve sensitivity for identifying comorbidities, we used information from hospitalisations within 2 years preceding surgery.[16] The OHIP and CPDB databases were used to identify outpatient

specialist consultations (general internal medicine, cardiology, anaesthesiology) within 60 days before surgery, outpatient cardiac testing within 6 months before surgery (echocardiogram, non-invasive myocardial perfusion test, coronary angiogram), and intraoperative invasive monitoring. Procedure codes in the OHIP database have a high accuracy rate.[18] We imputed patients' incomes based on their neighbourhood (Forward Sortation Area) median income in the 2001 Canadian census.

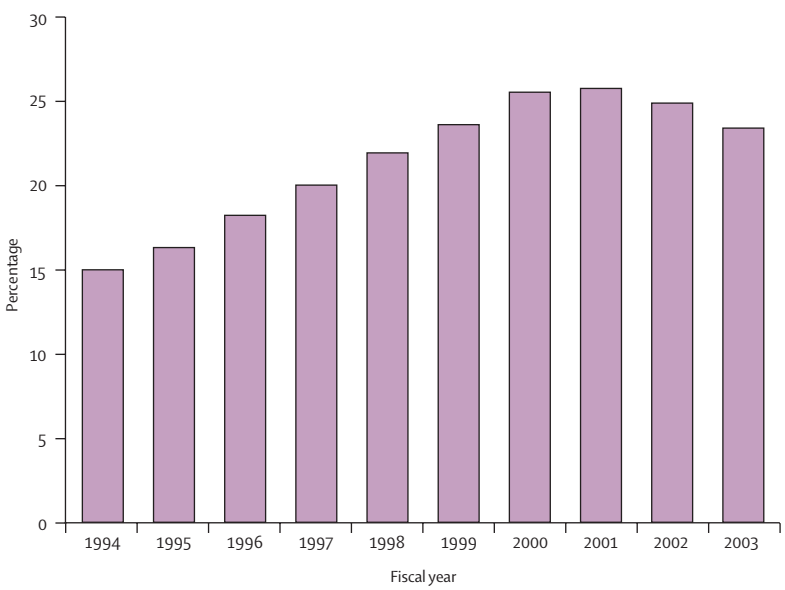

Figure 1: **Proportion of patients who received perioperative epidural anaesthesia or analgesia**

	Epidural n=44 094	No epidural n=44 094	Absolute standardised difference (%)	
			Before matching	After matching
Demographics				
Women	20 464 (46%)	20 536 (47%)	2·3	0·3
Age in years, mean (SD)	68 (11)	68 (11)	3·6	0·7
Socioeconomic status				
Annual income, CAD$, mean (SD)	24 636 (5096)	24 615 (5050)	3·8	0·4
Fiscal year				
1994	2870 (6·5%)	2810 (6·4%)	1·3	0·6
1995	3129 (7·1%)	3036 (6·9%)	1·0	0·8
1996	6856 (7·6%)	6902 (7·7%)	6·9	0·3
1997	8194 (9·1%)	8030 (8·9%)	3·6	1·0
1998	8985 (10%)	8884 (9·9%)	0·2	0·6
1999	9548 (11%)	9394 (10%)	3·5	0·9
2000	10 612 (12%)	10 518 (12%)	7·2	0·5
2001	11 541 (13%)	11 632 (13%)	7·9	0·5
2002	12 125 (13%)	12 164 (14%)	6·3	0·2
2003	12 488 (14%)	12 519 (14%)	3·3	0·2

(Continues on next page)

Patients who consent to epidural anaesthesia might be systematically more compliant with health-care recommendations. We therefore used the OHIP database to identify testing indicative of adherence to screening guidelines: mammography, colonoscopy, and faecal-occult-blood testing.

Statistical analyses

Bivariate tests were initially used to compare the characteristics of patients who did or did not receive epidural anaesthesia or analgesia (*t* test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test).

We used propensity-score matched-pairs analyses to determine the adjusted association of perioperative epidural anaesthesia with the primary outcome (30-day mortality). The rationale and methods underlying the use of propensity scores for proposed causal exposure variables have been previously described.[26,27] We developed a non-parsimonious multivariable logistic regression model to estimate a propensity score for perioperative epidural anaesthesia, irrespective of outcome. Clinical significance guided the initial choice of covariates in this model: age, sex, year, surgical procedure, hospital-type (teaching, low-volume non-teaching, mid-volume non-teaching, high-volume non-teaching), comorbid disease, specialist consultations (general internal medicine, cardiology, anaesthesiology), cardiac testing (echocardiogram, non-invasive myocardial perfusion test, coronary angiogram), intraoperative invasive monitoring, and income. We used previously described methods to categorise non-teaching hospitals into terciles[28] on the basis of the annual volume of included procedures.

We considered comorbid conditions that were present in at least 1% of the study cohort: ischaemic heart disease, congestive heart failure, cerebrovascular disease, hypertension, diabetes, pulmonary disease, renal disease, and malignancy. As suggested by recent statistical research on propensity score development, we used a structured iterative approach to refine this model, with the goal of achieving covariate balance within the matched-pairs.[29] Covariate balance was measured using the standardised difference, where an absolute standardised difference greater than 10% is suggested to represent meaningful covariate imbalance.[29] We matched epidural patients to no-epidural patients using a greedy-matching algorithm with a calliper width of 0·2 SD of the log odds of the estimated propensity score. This method involved sampling without replacement, and has been shown to remove 98% of the bias from measured covariates.[30] Within the matched pairs, we used the methods of Agresti and Min[31] to compare mortality rates.[32]

Prespecified subgroup analyses were based on procedure (abdominal, orthopaedic, thoracic, or vascular surgery), hospital (teaching or high-volume hospital versus mid-volume or low-volume hospital), and

anatomic location of the epidural catheter (thoracic versus lumbar). We did a subgroup analysis based on the level of the epidural catheter because thoracic epidural analgesia, by selectively blocking cardiac sympathetic innervation,[2] might better prevent mortality and cardiac complications.[8,33] In these subgroup analyses, we repeated the same propensity-score matching process while forcing an exact match on the subgroup characteristics. The 30-day mortality rates were then compared within the subgroup-specific matched-pairs. For each subgroup analysis, we assessed the heterogeneity of treatment effects by using a test of interaction in a conditional logistic regression model.

In a sensitivity analysis, we used multivariable logistic regression to determine the adjusted association of epidural anaesthesia with 30-day mortality in the entire sample (N=259 037). These results were similar to the propensity-score analysis, and are therefore not reported. Analyses were done using SAS version 9.1 and R 2.4.1.[34] All p values were two-tailed, with statistical significance defined by $p<0·05$.

Role of the funding source

The study sponsor had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript. The opinions, results, and conclusions are those of the authors, and no endorsement by the Ontario Ministry of Health and Long-Term Care or the Institute for Clinical Evaluative Sciences is intended, or should be inferred. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study cohort consisted of 259 037 patients, of whom 22% (56 556) received perioperative epidural anaesthesia or analgesia (table 1). The proportion of patients who received epidural anaesthesia rose gradually from fiscal years 1994 (3190 [15%] of 21278 cases) to 2001 (7391 [26%] of 28707 cases), but subsequently decreased somewhat by fiscal year 2003 (7044 [23%] of 30076; figure 1). The differences between patients who did or did not receive epidural anaesthesia were significant ($p<0·0001$) for all measured characteristics (table 1). Patients who received epidural anaesthesia were typically men who underwent surgery at teaching hospitals, and had increased burdens of comorbid disease (table 1). They were also more likely to be referred for anaesthesia or cardiology consultation before surgery, undergo preoperative cardiac testing, and require intra-operative invasive monitoring. Conversely, they were less likely to be assessed by general internists. The different surgical procedures showed substantial variation in the use of epidural anaesthesia (table 1).

	Epidural n=44 094	No epidural n=44 094	Absolute standardised difference (%)	
			Before matching	After matching
(Continued from previous page)				
Procedure				
Abdominal aortic aneurysm repair	2411 (5·5%)	2251 (5·1%)	35	1·6
Peripheral vascular bypass	3722 (8·4%)	3926 (8·9%)	9·7	1·6
Total hip replacement	6575 (15%)	6557 (15%)	43	0·1
Total knee replacement	10 539 (24%)	10 427 (24%)	42	0·6
Large bowel surgery	11 794 (27%)	12 154 (28%)	8·1	1·8
Liver resection	666 (1·5%)	642 (1·5%)	10	0·5
Whipple procedure	334 (0·8%)	339 (0·8%)	13	0·1
Pneumonectomy or lobectomy	2810 (6·4%)	2515 (5·7%)	46	2·8
Gastrectomy or oesophagectomy	1558 (3·5%)	1527 (3·5%)	19	0·4
Nephrectomy	2903 (6·6%)	2980 (6·8%)	15	0·7
Cystectomy	782 (1·8%)	776 (1·8%)	14	0·1
Hospital type				
Teaching	16 184 (37%)	16 180 (37%)	15	0·02
High-volume non-teaching	9404 (21%)	9423 (21%)	5·1	0·1
Mid-volume non-teaching	9220 (22%)	9060 (21%)	7·8	0·9
Low-volume non-teaching	9286 (21%)	9431 (21%)	15	0·8
Comorbid disease				
Ischaemic heart disease	4869 (11%)	4997 (11%)	9·6	0·9
Congestive heart failure	1407 (3·2%)	1491 (3·4%)	5·6	1·1
Cerebrovascular disease	1324 (3·0%)	1349 (3·1%)	3·9	0·3
Hypertension	23 057 (52%)	23 183 (53%)	4·1	0·6
Diabetes mellitus	8303 (19%)	8511 (19%)	2·8	1·2
Pulmonary disease	2675 (6·1%)	2775 (6·3%)	8·9	0·9
Dialysis or renal disease	671 (1·5%)	695 (1·6%)	2·7	0·4
Malignancy	6287 (14%)	6145 (14%)	31	0·9
Specialist consultations*				
Anaesthesiology	22 673 (51%)	23 472 (53%)	51	3·6
General internal medicine	8807 (20%)	8677 (20%)	16	0·7
Cardiology	3756 (8·5%)	3718 (8·4%)	8·1	0·3
Preoperative testing†				
Echocardiogram	7341 (17%)	7386 (17%)	17	0·3
Myocardial perfusion test	4487 (10%)	4291 (10%)	18	1·5
Coronary angiogram	311 (0·7%)	303 (0·7%)	6·2	0·2
Intraoperative care				
Arterial line	21 373 (48%)	21 181 (48%)	56	0·9
Central venous line	7393 (17%)	7080 (17%)	54	1·9
Pulmonary artery catheter	2766 (6·3%)	2657 (6·0%)	53	1·0

Data are number (%) unless otherwise indicated. *Within 60 days before surgery. †Within 6 months before surgery.

Table 2: **Characteristics of the propensity-matched pairs**

The rate of decompression laminectomy within 30 days after surgery was 21·2 per 100 000 [95% Poisson CI 11·0–37·1] after epidural anaesthesia. By comparison, decompression laminectomy was still done in 13·8 per 100 000 patients who did not undergo insertion of an epidural catheter (95% Poisson CI 9·2–20·0). The unadjusted difference between these rates was not significant (rate ratio 1·54, 95% CI 0·75–2·95, p=0·23).

	Epidural n=44 094	No epidural n=44 094
Previous use of recommended screening tests*		
Mammography	2804 (6·4%)	2718 (6·2%)
Colonoscopy	12 216 (27%)	11 930 (27%)
Faecal-occult-blood testing	4817 (11%)	4604 (10%)
Outcomes		
30-day mortality	768 (1·7%)	860 (2·0%)
Postoperative mechanical ventilation†	4389 (10·0%)	4238 (9·6%)
Spinal decompression laminectomy‡	8 (0·02%)	7 (0·02%)

* Within 2 years before hospital admission for surgery. †Within 5 days after surgery. ‡Within 30 days after surgery.

Table 3: **Processes-of-care and outcomes in the propensity-matched pairs**

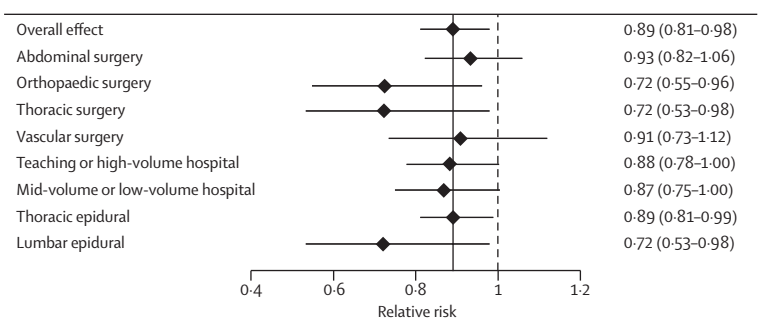

Figure 2: **Association of epidural anaesthesia or analgesia with 30-day mortality in the subgroup analyses**
Diamonds represent relative risks for 30-day mortality within each subgroup. Error bars are 95% CI. The corresponding numerical values for these point estimates and CIs are presented on right. Solid vertical line represents the overall treatment effect (relative risk 0·89). Dashed vertical line represents a null effect (relative risk 1).

Of the patients who received epidural anaesthesia, 78% (44 094) were matched to a similar patient who did not. The covariate balance between the epidural and no-epidural groups improved substantially through propensity-score matching (table 2). The mean standardised difference decreased from 16·4% (range 0·2–56·0) to 0·8% (0·02–3·6).

Within the matched cohort, the 30-day mortality rate was 1·74% (n=768) in patients who received epidural anesthesia, as opposed to 1·95% (n=860) in those who did not (relative risk [RR] 0·89, 95% CI 0·81–0·98, p=0·02). This difference corresponded to an absolute risk reduction of 0·21% (95% CI 0·03–0·39), or a number-needed-to-treat of 477 (95% CI 256–3334). The rates of postoperative mechanical ventilation were similar for patients who did or did not receive epidural anaesthesia (table 3; RR 1·04, 95% CI 0·99–1·07, p=0·08). Additionally, decompression laminectomy was rare, and occurred in similar proportions of patients within the matched-pairs (table 3). With regard to testing that could indicate compliance with screening recommendations, the rates of mammography, colonoscopy, and faecal-occult-blood testing were similar in the matched-pairs, suggesting that the matching process produced cohorts that had similar compliance with non-surgery-related screening recommendations (table 3).

The association of epidural anaesthesia with 30-day mortality was generally similar when the analyses were repeated within the prespecified subgroups (figure 2). There was no significant heterogeneity within the subgroups defined by procedure type (p=0·34), hospital type (p=0·95), or epidural level (p=0·20).

Discussion

In this population-based cohort study, epidural anaesthesia or analgesia was associated with a small improvement in 30-day postoperative survival. The improvement corresponded to a relative risk reduction of 11%, or an absolute risk reduction of 0·2%. We also found that patients who received epidural anaesthesia or analgesia had a generally higher burden of comorbid disease, and that rates of epidural anaesthesia had risen consistently from 1994 to 2001, after which they declined slightly. Notably, the slight decline occurred shortly after two negative studies of epidural anaesthesia were published.[9,10]

Despite showing a significant benefit, our study does not provide compelling data to justify using epidural anaesthesia or analgesia specifically to improve postoperative survival. The absolute magnitude of the benefit is small, corresponding to a number needed to treat of 477. In addition, the benefit has only borderline significance, despite a very large sample size. These results should, however, not be interpreted as evidence that perioperative epidural anaesthesia or analgesia should be avoided. There are other compelling reasons for using epidural anaesthesia, namely to improve postoperative pain control,[1,9,10] or prevent perioperative respiratory complications.[8–10,35] Our study would suggest that, when used for these better proven indications, epidural anaesthesia is safe, and might offer a small survival benefit.

There are several reasons why our observed small treatment effect, a relative risk of 0·89, is plausible. First, there are many physiological reasons why epidural anaesthesia might improve postoperative outcomes, namely by reducing the surgical stress response,[2] cardiac complications,[2,11] pulmonary complications,[2,8,9,35] and postoperative pain.[1,9,10] Second, postoperative mortality is multifactorial in cause; hence, epidural anaesthesia will, at best, contribute a moderate treatment effect (15–20% relative risk reduction).[12] Finally, epidural anaesthesia is not a straightforward intervention: its benefit will only occur under the ideal conditions where the epidural catheter is inserted successfully, safely secured in position, and able to provide adequate analgesia. In a substantial proportion of cases, these ideal conditions do not occur. For example, in 27% of patients randomised to epidural anaesthesia in the MASTER randomised trial,[9] the epidural catheter was not inserted, removed immediately after surgery, accidentally dislodged, or failed to provide adequate analgesia. These failures of epidural anaesthesia could, in turn, diminish

its overall population-level benefit from a moderate effect to a small effect.

The small treatment effect also raises questions about the feasibility of any future RCT designed to establish whether epidural anaesthesia reduces mortality, even if the trial recruited only high-risk patients. Based on the baseline mortality rate (4·3%) among the high-risk participants in the MASTER clinical trial,[9] around 55 000 participants will be required to detect a relative risk of 0·89 in mortality (two-tailed α of 0·05 and 80% power). If this future RCT focuses on the meaningful combined outcome of death, cardiac event, or respiratory failure, the required sample size would still be large, but potentially feasible. Based on an estimated 30% rate of this combined outcome in a high-risk sample,[9] roughly 5800 participants would be required to detect an 11% relative risk reduction (two-tailed α of 0·05 and 80% power). Future trials might instead focus on important patient-reported outcomes, such as health-related quality of life, postoperative quality of recovery, or patient satisfaction.[36] The primary purpose of these trials would be to show that reduced visual analogue scale pain scores and postoperative pulmonary complications produce clinically meaningful changes in patients' postoperative recovery, quality of life, or satisfaction. This strategy will, in turn, necessitate the development of validated patient-reported instruments to measure these outcomes.

Our study warrants comparison with another large observational study of perioperative epidural anaesthesia. Wu and colleagues[37] found that postoperative epidural analgesia was associated with moderately reduced 30-day mortality (odds ratio 0·74; 95% CI 0·63–0·89) in 68 723 Medicare beneficiaries aged over 65 years in the USA. The absolute risk reduction was roughly 0·65% (95% CI 0·27–0·92). Several reasons might explain why our results differ. We adjusted for more comorbidities, and included patients with a wider range of ages. Additionally, a different risk-adjustment technique was used in our study (propensity-score matched-pairs as opposed to logistic regression). Although results from these two analytic methods are often similar,[38] they can occasionally differ.[39]

Finally, Wu and colleagues[37] defined their exposure as a physician billing for postoperative epidural analgesia. This definition might have biased the results in favour of epidural anaesthesia. Specifically, epidurals may be discontinued early after surgery because of complications. For example, 17% of early removals of epidurals in the MASTER trial were due to postoperative complications (eg, sepsis, haemodynamic instability).[9] No specific reason was documented for another 33% of these early removals; some were possibly also due to complications. Thus, excluding these early removals could bias the results in favour of epidural anaesthesia. By contrast, our definition, a billing for insertion of an epidural catheter, is less prone to bias. It mimics the intention-to-treat approach of a RCT by including all cases where an anaesthesiologist attempted to insert an epidural catheter, irrespective of whether the catheter was inserted successfully, able to provide adequate analgesia, or continued postoperatively.

Our study had several strengths. First, our population-based sample enhanced the generalisability of our findings to other health-care systems that are reasonably similar to that in Ontario. Second, the large sample size allowed us to detect small treatment effects that would have been deemed non-significant in smaller studies. Finally, our study included only elective intermediate-to-high-risk surgical procedures. The benefits of epidural anaesthesia are likely diminished in low-risk procedures such as knee arthroscopy. The potential for haemodynamic instability or systemic infection would result in patients undergoing emergency procedures being less likely to receive epidural anaesthesia. Our study therefore focused on the patients who were most likely to benefit from epidural anaesthesia or analgesia.

Our study had several limitations. Since it was an observational study, our results showed an association between epidural anaesthesia and improved survival, but do not prove causality. However, as mentioned above, an adequately powered RCT might never be done. Additionally, administrative data sources do not adequately capture postoperative complications (eg, myocardial infarction, pneumonia) or causes of death.[40] Such information could have helped to better describe how epidural anaesthesia might alter postoperative survival. Specifically, epidural anaesthesia is more likely to prevent cardiac-related or pulmonary-related complications than surgical complications. Our data sources were also unable to differentiate between patients who received intraoperative epidural anaesthesia alone, as opposed to combined intraoperative anaesthesia with postoperative analgesia. Nonetheless, neuraxial blockade has similar effects on mortality, irrespective of whether it is continued postoperatively;[8] hence, these two different groups of patients could reasonably be combined. Finally, these administrative data were limited with respect to detailed clinical information and some processes-of-care (eg, drug administered via the epidural catheter, involvement of a Pain Service), thereby limiting our ability to adjust for some differences between those who received an epidural and those who did not. We addressed this limitation, in part, by using hospitalisation information from the 2 years before surgery,[16] including comorbidity definitions with generally high specificity and moderate-to-good sensitivity,[13–17,41] and doing the analysis using propensity scores. Furthermore, the increased burden of comorbid illness in patients who received epidural anaesthesia would suggest that our study, if anything, is biased against epidural anaesthesia.

Perioperative epidural anaesthesia or analgesia is associated with a small improvement in 30-day survival after elective intermediate-to-high risk non-cardiac surgery. Based on the large number needed to treat and borderline significance of this treatment effect, our study does not support the routine use of epidural anaesthesia to prevent postoperative mortality. Nonetheless, our results suggest that, when used for better-proven indications, such as improving postoperative pain control or preventing pulmonary complications, epidural anaesthesia is safe and might offer a small survival benefit.

Contributors

DNW took part in study conception and design, data acquisition, statistical analyses, interpretation of the results, and drafting of the manuscript. WSB and JEH took part in study conception and design, interpretation of the results, and revision of the manuscript. PCA took part in study conception and design, statistical analyses, interpretation of the results, and revision of the manuscript. AL took part in study conception and design, interpretation of the results, revision of the manuscript, and provided supervision and administrative support. All authors approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was supported in part by the Institute for Clinical Evaluative Sciences, which is itself supported in part by a grant from the Ontario Ministry of Health and Long-Term Care. DNW is supported by a Clinician-Scientist Award, and PCA by a New Investigator Award from the Canadian Institutes of Health Research. WSB is the Fraser Elliot Chair of Cardiovascular Anaesthesiology at the University Health Network.

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Research and the issue of patients' consent

As chair of the National Information Governance Board for Health and Social Care (NIGB) I do indeed welcome a public debate on the rights and wrongs of researchers looking at identifiable clinical records without consent.

However, your Editorial (Nov 29, p 1956)[1] suggests that I make assumptions about what the public think. I do not. You say there is little evidence about public attitudes. This is no longer true. I agree that public opinion is in favour of clinical research. Three recent studies bear this out. They also show that the public wants to be asked.

A Medical Research Council study[2] says that "Results indicate that a majority of the general public feels that consent should always be sought". Similarly a Wellcome Trust study[3] says "There was strong agreement...that explicitly being asked for their consent to take part in biomedical research was a good thing". An earlier study by the National Health Service (NHS) Information Authority[4] reported that patients wanted anonymisation of data for purposes other than care.

In suggesting that looking at identifiable patients records without consent is unethical and possibly without legal basis I reflect the considered views of the National Information Governance Board as set out in its Annual Report and formal response to the draft NHS constitution.

The NIGB has made clear its support for clinical research and its willingness to be part of finding a solution which respects patients and includes consent as well as confidentiality.

I declare that I have no conflict of interest.

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Epidural analgesia and postoperative outcome

Duminda Wijeysundera and colleagues (Aug 16, p 562)[1] provide large-scale data to question the efficacy of epidural analgesia on postoperative outcome, thereby supporting the findings of other randomised trials and systematic reviews.[2] The main question, however, is whether it is still relevant to analyse old clinical data.

There is general agreement that continuous thoracic epidural analgesia in major abdominal and thoracic surgery has positive physiological effects on analgesia, pulmonary function, paralytic ileus, and catabolism, all of which theoretically translate into reduced morbidity and mortality. However, during the past decade, single-modality interventions for multimodality problems such as postoperative morbidity have repeatedly been shown to have few positive effects owing to the complexity of the problem.[3] Consequently, the potential positive effect of continuous epidural analgesia on postoperative outcome might not live up to expectations unless the well documented physiological advantages are used in the perioperative care programme to facilitate early recovery with mobilisation and oral nutrition (the fast-track method).

The fast-track approach has been shown to enhance recovery and reduce medical morbidity across surgical procedures.[4,5] Since this rational and evidence-based approach has not been used in any available randomised studies of epidural analgesia,[2] nor in the study by Wijeysundera and colleagues, we question the relevance of such data without any information on perioperative care regimens.

The time has come for anaesthesiologists and surgeons to collaborate in postoperative outcome studies and combine efficient analgesic regimens with adjustment of perioperative care according to available evidence.[4,5]

I declare that I have no conflict of interest.

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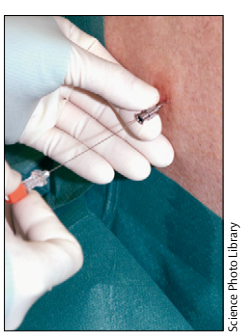
In commenting on Duminda Wijeysundera and colleagues' paper,[1] Michael Barrington and David Scott (p 514)[2] make the point well that epidural analgesia might be justified after major surgery on the grounds of analgesic efficacy alone, with or without a demonstrable benefit in terms of mortality. They start, however, from the incorrect premise that "a systematic review has shown

Published **Online** December 3, 2008
DOI:10.1016/S0140-6736(08)61819-X



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that epidural anaesthesia reduced mortality after major surgery". In fact, the meta-analysis by Rodgers and colleagues[3] did not demonstrate this, but showed decreased mortality associated with central neuraxial block in general. It is of course the very heterogeneity of the trials included in this meta-analysis that casts doubt over the validity of its conclusions, and necessitated the cohort study by Wijeysundera and colleagues.

This group is to be congratulated on showing the benefits of epidural anaesthesia, analgesia, or both on 30-day mortality. However, this study also suffers from heterogeneity: the investigators were unable to distinguish between patients who received epidural anaesthesia or analgesia, or both. The benefits of postoperative epidural analgesia might be expected to exceed those of a single-shot technique: it is thus possible that the effect on mortality would be greater if the study could have been confined to patients who benefited from postoperative analgesia, and thus that the number needed to treat for postoperative epidural analgesia might be lower.

We declare that we have no conflict of interest.

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Authors' reply

H Kehlet raises several points that warrant discussion. He is concerned about the relevance of the older clinical data in our study. We therefore assessed the presence of a temporal effect by using a test of interaction between time and the exposure (epidural anaesthesia). This test was not significant, suggesting that the benefits of epidural anaesthesia were stable over time.

We agree that no single perioperative intervention will have a large benefit because of the multifactorial cause of postoperative morbidity and mortality. It is for this very reason that we did a large cohort study with sufficient statistical power to detect plausible small-to-moderate treatment effects. Indeed, we did find that epidural anaesthesia has benefits, but they are relatively small in magnitude. These findings are important. They show that the physiological benefits of epidural anaesthesia do translate into an improvement, albeit small, in clinical outcomes. Previous research should caution us against extrapolating all beneficial physiological effects into improved clinical outcomes.[1]

Epidural analgesia is a component of the fast-track postoperative recovery programmes advocated by Kehlet.[2] The overall effectiveness of a multifactorial intervention such as fast-track postoperative recovery must necessarily depend on its individual components. Our results therefore also help assess the effectiveness and safety of an important component of fast-track recovery programmes.

We could not directly assess the effects of fast-track postoperative recovery itself in our study because our database did not capture the requisite information. We agree that this intervention has intuitive appeal, and warrants further research, especially given the relative paucity of outcome data for fast-track programmes. For example, a systematic review[2] identified only three single-centre unblinded randomised controlled trials, which did not report allocation concealment and included 128 participants. Multicentre randomised controlled trials of fast-track recovery programmes, on the scale conducted thus far for epidural anaesthesia,[3,4] might help better clarify their overall efficacy and safety.

Jeremy Nightingale and Alan Stedman suggest that postoperative epidural analgesia might confer greater benefits than intraoperative epidural anaesthesia alone. We could not address this question directly in our study because our dataset did not differentiate between these two scenarios. Nonetheless, in the meta-analysis by Rodgers and colleagues,[5] neuraxial blockade had similar effects on mortality irrespective of whether it was continued postoperatively or not. Additionally, consideration of only patients who benefit from postoperative analgesia has inherent problems. Since epidurals are sometimes discontinued early after surgery because of prognostically important complications,[4] exclusion of these early removals could lead to an inappropriate bias in favour of epidural analgesia.

We declare that we have no conflict of interest.

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Cognitive behaviour therapy for depressed Pakistani mothers

The study by Atif Rahman and colleagues (Sept 13, p 902)[1] has far-reaching implications for mother-and-child health-care models for other developing countries. We have some concerns, however, about the interpretation of the data.

Perhaps the most striking finding was the 47% and 41% remission from major depressive episodes at 6 and 12 months, respectively, in the control group. This enviable achievement, brought about by community heath workers (CHWs) with no mental-health training, and with no mention of antidepressant medication, is similar, if not superior, to major antidepressant trial results.[2]

The CHWs did not do anything additional to their routine duties except, and very importantly, paying the mothers all 16 scheduled visits, as in the intervention group. This "enhanced routine care" made almost double the impact of that seen in Rahman and colleagues' observational study from the same area, where routine visits by CHWs were far fewer.[3] Could this extra attention and time devoted to the control group produce a Hawthorne effect?[4]

Further, we are not told how much time the control-group CHWs spent with the mothers, vis-à-vis 45 min per session in the intervention group.[5] If the elements of the intervention that were not based on cognitive behaviour therapy (immunisation, breastfeeding, contraception) were discussed more thoroughly than usual, could the additional improvements noted in this group be also at least partly due to a Hawthorne effect?

These remarks are in no way meant to diminish the importance of the paper. If scheduled "routine" visits to the mother by CHWs, ensured for an adequate time with attentive discussion on several issues, can bring about important and lasting changes in maternal and child health, that would certainly be hailed as an extremely cost-effective intervention in itself.

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Atif Rahman and colleagues[1] found that cognitive behaviour therapy had positive effects on depression in mothers in Pakistan. However, some points were not clarified and this could influence the quality of the paper.

First, it is not clear how treatment allocation was concealed from the interviewers.

Second, the mechanism of monitoring is not clearly defined. The Lady Health Workers received monthly supervision, but should such regular supervision be supplemented by irregular (ie, unannounced) supervision?

Third, the geographical origin of the mothers in this study is a very important factor. Those who had immigrated must have had different feelings about their living environment from the native mothers. Such factors can have a crucial role in the development of depression.[2,3]

Finally, whether any mothers in either group took drugs to prevent or treat depression was not studied or controlled for in the study. Drug use could have confounded the effect of the cognitive behaviour therapy.

We declare that we have no conflict of interest.

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Authors' reply

To interpret correctly the results of our cluster randomised trial of treatment of depression by community health workers, one must differentiate between explanatory trials (which measure efficacy—ie, the benefit a treatment produces under ideal conditions) and pragmatic trials (which measure effectiveness—ie, the benefit the treatment produces in routine practice).[1] Ours was a pragmatic trial.

In pragmatic trials, the intervention response is the total difference

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