Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial

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Summary

Background Epidural block is widely used to manage major abdominal surgery and postoperative analgesia, but its risks and benefits are uncertain. We compared adverse outcomes in high-risk patients managed for major surgery with epidural block or alternative analgesic regimens with general anaesthesia in a multicentre randomised trial.

Methods 915 patients undergoing major abdominal surgery with one of nine defined comorbid states to identify high-risk status were randomly assigned intraoperative epidural anaesthesia and postoperative epidural analgesia for 72 h with general anaesthesia (site of epidural selected to provide optimum block) or control. The primary endpoint was death at 30 days or major postsurgical morbidity. Analysis by intention to treat involved 447 patients assigned epidural and 441 control.

Findings 255 patients (57·1%) in the epidural group and 268 (60·7%) in the control group had at least one morbidity endpoint or died (p=0·29). Mortality at 30 days was low in both groups (epidural 23 [5·1%], control 19 [4·3%], p=0·67). Only one of eight categories of morbid endpoints in individual systems (respiratory failure) occurred less frequently in patients managed with epidural techniques (23% *vs* 30%, p=0·02). Postoperative epidural analgesia was associated with lower pain scores during the first 3 postoperative days. There were no major adverse consequences of epidural-catheter insertion.

Interpretation Most adverse morbid outcomes in high-risk patients undergoing major abdominal surgery are not reduced by use of combined epidural and general anaesthesia and postoperative epidural analgesia. However, the improvement in analgesia, reduction in respiratory failure, and the low risk of serious adverse consequences suggest that many high-risk patients undergoing major intra-abdominal surgery will receive substantial benefit from combined general and epidural anaesthesia intraoperatively with continuing postoperative epidural analgesia.

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Introduction

Whether epidural anaesthesia and analgesia improve the outcome of major abdominal surgery is a long-running controversy. Proponents of the technique cite beneficial effects resulting from attenuation of the surgical stress response.[1,2] The reduction, by an effective epidural block, of intraoperative sympathetic stimulation resulting from surgical trauma has putative advantages for coagulation homoeostasis and cardiovascular, respiratory, gastrointestinal, metabolic, and immune function.[1,2] These advantages are widely believed to outweigh the rare but important morbidity risks associated with the insertion of epidural catheters.[1,2] In the mid-1980s, a randomised controlled trial by Yeager and colleagues, comparing general anaesthesia with or without perioperative epidural anaesthesia and analgesia, was stopped by the ethics committee after 53 patients had been studied, because the combined technique was associated with a significant improvement in postoperative outcome.[3] Not unexpectedly, that study has generally been regarded as too small to have a significant effect on anaesthetic and surgical practice. A 1997 audit of Australian hospitals revealed a disparate pattern of practice in terms of the use of epidural techniques in four common abdominal procedures, which suggested that anaesthetists and surgeons were still divided as to the value of this approach.[4]

Review of published reports over the past 20 years shows several small trials that involved unselected patients at low risk of adverse outcomes and therefore lacked statistical power. In addition, many examined as endpoints transient postoperative abnormalities of doubtful clinical importance[5–10] and showed other flaws in experimental design.[11] However, a systematic overview of all available randomised controlled trials over the previous 30 years showed that the use of epidural and spinal block resulted in a statistically and clinically significant reduction in morbidity and mortality after surgery.[12]

Reliable and valid conclusions about therapies in controversial areas of clinical practice require not only that systematic reviews or meta-analyses indicate the likely sizes of particular effects of such therapies, but also that the findings be independently confirmed in at least one, and preferably more, major randomised controlled trials, each of which is of a size and quality to permit an effect to be detected if it is truly present.[13] This paper presents the results of the Multicentre Australian Study of Epidural Anaesthesia (the MASTER Anaesthesia Trial), which was designed to have adequate power to confirm the beneficial effect of epidural techniques shown by Yeager and colleagues,[3] while allowing for a smaller difference observed as a result of improvements in perioperative, anaesthetic, and surgical management that have probably occurred in the time since their study.

Criteria for eligibility for the MASTER Anaesthesia Trial

Risk factor	Definition
Morbid obesity	Bodyweight more than 200% of ideal weight for height and sex
Diabetes mellitus	As defined by WHO: fasting blood glucose 7·1 mmol/L or higher or blood glucose 11·1 mmol/L or higher 2 h after 75 g oral glucose load, or any patient, previously diagnosed, receiving antidiabetic medication (eg, insulin or an oral antidiabetic drug)*
Chronic renal failure	Serum creatinine more than 200 μmol/L
Respiratory insufficiency	Either type I (PaO_2 50 mm Hg or less, breathing room air, FiO_2=0·21) or type II ($PaCO_2$ more than 50 mm Hg), or severe chronic lung disease defined as severe obstructive disease (FEV_1 1·0 or less or FEV_1/VC ratio 0·30), or severe non-obstructive (restrictive) disease (VC 1·0 or less or below 30% of predicted), or a recent admission (within 2 years of surgery) for acute respiratory failure
Major hepatocellular disease	Total bilirubin 100 μmol/L or higher, or as total bilirubin 40 μmol/L or higher plus serum albumin 30 g/L or lower
Cardiac failure	Documented history within previous 2 years (symptoms and signs of left or right heart failure, and a documented effective response to therapy), or impairment of left-ventricular function indicated by a documented LVEF of 35% or less within previous 2 years
Acute myocardial infarction	Documented history within previous 2 years (two of: typical chest pain of at least 20 min duration, unless terminated by cardiac arrest or opioid analgesia; appearance of new Q waves on ECG of at least 0·04 s in duration and 1 mm or more in depth; and raised serum CPK or lactate dehydrogenase to twice the upper limit of normal or rise in CPK isoenzyme considered diagnostic of myocardial damage by the testing laboratory)
Myocardial ischaemia	Documented history within previous 2 years of myocardial ischaemia on exercise testing, thallium scanning, or as a documented history of exertional angina considered diagnostic of myocardial damage by the testing laboratory
Age 75 years or older on day of surgery, plus at least two of:	Significant respiratory disease (documented admission to hospital for management of an acute exacerbation of chronic airways disease within previous 2 years);
	Cardiac dysrhythmia (taking medication for a documented disturbance of cardiac rhythm for at least 3 of the preceding 24 months or requiring a pacemaker);
	Hypertension (either requiring two or more drugs to control blood pressure or uncontrolled hypertension† on current single-agent therapy or no therapy);
	Moderate obesity (150% or more of ideal weight for height);
	Frailty (need, in previous 12 months, for assistance with activities of daily living);
	Myocardial infarction (documented history of myocardial infarction at any time)

PaO_2=arterial pressure of oxygen; FiO_2=fraction of inspired oxygen; $PaCO_2$=arterial pressure of carbon dioxide; FEV_1=forced expiratory volume in 1 s; VC=vital capacity; LVEF=left-ventricular ejection fraction; ECG=electrocardiogram; CPK=creatine phosphokinase. *For the purpose of this definition fasting means a minimum of 4 h since any oral intake except water. Patients said to be diet controlled should be excluded only if the fasting blood sugar is less than 7·1 mmol/L or a random blood sugar within 4 h of a meal is less than 11·1 mmol/L. †Systolic blood pressure 160 mm Hg or above and/or diastolic pressure 95 mm Hg or above.

Methods

Study design

We studied the highest-risk patients undergoing major abdominal operations or oesophagectomy, procedures that themselves are more prone to serious postoperative complications and fatal outcomes. This combination of high-risk patients and high-risk procedures defines an area of practice in which major perioperative complications are concentrated, and consequently maximises statistical power for a study of given size.[10] Even large hospitals see few patients fitting these criteria, so a multicentre randomised controlled trial was essential for timely completion of the study. A detailed description of the study and the protocol has been published.[14]

We established a group of participating hospitals in Australia, East Asia, and the Middle East and limited the trial to patients who were at high risk by virtue of having one or more major adverse characteristics evident preoperatively (panel). Eligible procedures were elective, non-laparoscopic operations involving the abdomen or thorax (except cardiac and pulmonary surgery) that invariably take longer than 1 h. We excluded patients younger than 18 years, those undergoing surgery within 12 h of admission to hospital, and those with contraindications to the use of epidural block, such as sepsis, impaired coagulation status or mental state, infection at the epidural insertion site, or a neurological disorder.

Design and procedures

Our hypothesis was that combined regional and general anaesthesia by use of intraoperative epidural anaesthesia and postoperative epidural analgesia for 72 h would lower the frequency of a combined endpoint of mortality and major postoperative complications within 30 days of surgery by a fifth, from 50% to 40%, compared with general anaesthesia based on a balanced technique with intraoperative and postoperative opioids as the primary method of postoperative analgesia. The protocol specified a patient-controlled or physician-controlled opioid infusion as the first choice of analgesia for the control group. Because surgical, anaesthetic, and perioperative care were likely to have improved since the study by Yeager and colleagues,[3] we assumed a smaller difference in outcome than they reported. Our trial was designed to have 80% power to detect an absolute difference of 10% with a two-sided α of 0·05, with allowance made for two scheduled

interim analyses by an independent data-monitoring and safety committee after 260 and 460 patients had been studied. The study required a minimum of 814 patients, but we planned to randomise 910 to allow for loss of power due to cancellation or changes in operations or initiation of epidural analgesia in the control group.

The protocol for perioperative care of patients in both the epidural and control groups was sufficiently flexible to allow participating centres to achieve optimum clinical management.[14] The protocol provided guidelines for premedication, intraoperative monitoring, site of the epidural (to be selected by the attending anaesthetist to match the planned incision), epidural local anaesthetics and opioids during and after the operation, induction and maintenance of general anaesthesia, replacement of blood and fluids, optimising core temperature and respiratory and cardiac function, criteria for extubation, and immediate postoperative medical management.[14] Postoperative analgesia in the control group was primarily achieved with patient-controlled or physician-controlled intravenous opioid infusions initially, supplemented by rectal and oral non-steroidal anti-inflammatory drugs, oral opioids, and paracetamol. In the epidural group, postoperative analgesia was managed with continuous infusions of bupivacaine or ropivicaine, supplemented with pethidine or fentanyl.[14]

Detailed descriptions and definitions of outcome measurements and endpoints have been published elsewhere.[14] Eligible patients were identified preoperatively by nurses or anaesthetists in collaborating hospitals and, after informed consent had been obtained, they were allocated by a central 24 h randomisation service to control or epidural groups by permuted random blocks with stratification by study centre. Allocation concealment was not feasible for two reasons. First, because of obvious differences clinically between control and epidural patients, masking patients and clinical staff for 3 days was impossible. Secondly, we deemed masking to be unethical in very sick patients. Data were encoded, entered on to computer, and analysed centrally in the Trial Secretariat at the University of Western Australia.[14]

To provide a simple measure of the clinical efficacy of epidural block intraoperatively, we recorded, for all patients, minimum and maximum heart rates and systolic blood pressures noted during surgery. To provide a measure of the efficacy of analgesia in patients from both control and epidural groups, we recorded pain on a visual analogue scale twice daily for the first 3 postoperative days, at rest, and immediately after coughing.

Statistical methods

We compared study groups for preoperative risk factors, procedures undergone, and a range of intraoperative and postoperative intermediate variables by χ^2 or t test, as appropriate. The primary analysis for outcomes was by intention to treat, and a comparison, with the χ^2 test, of the proportions of randomised patients in each study group who had any of the defined endpoints (death or a major complication) within 30 days of surgery.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July, 1995, and May, 2001, we recruited and randomised 920 patients in 25 hospitals in six countries (figure 1). Five patients were randomised a second time for a subsequent eligible procedure, but the data for these second randomisations were excluded from analysis. From July, 1995, to October, 1999, we followed up all eligible patients, including those for whom consent to randomise was not obtained. A detailed analysis of trial participants and non-participants was published previously.[14] 23 patients whose surgery was cancelled after randomisation and four who were randomised for an ineligible procedure were also excluded from analysis. 19 patients who were listed for an eligible procedure at the time of randomisation subsequently underwent a non-eligible operation. By the intention-to-treat principle, these patients were included in the primary analysis (figure 1).

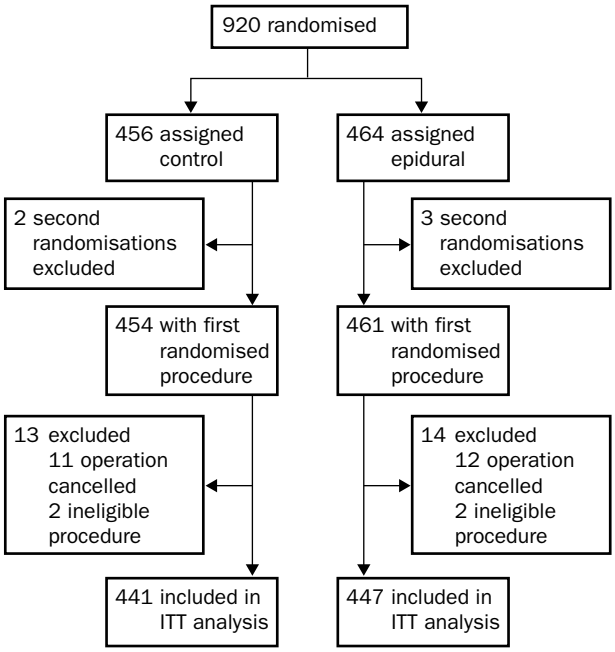

Figure 1: **Trial profile**
ITT=intention-to-treat.

The average number of patients recruited each month was 12·9, and the total number recruited in different centres varied between one and 182. Three teaching hospitals in central Melbourne randomised 466 (50·1%) participants, 16 other Australian hospitals 252 (27·5%), and six hospitals in southeast Asia and Saudi Arabia 197 (21·5%). These three subgroups of hospitals accounted for 20 (48%), 12 (28%), and ten (24%) deaths, respectively, and showed no systematic differences in patterns of operations performed or morbid endpoints

Risk factor*	Control group (n=454)	Epidural group (n=461)
Morbid obesity	19 (4%)	18 (4%)
Diabetes mellitus	209 (46%)	191 (41%)
Chronic renal failure	37 (8%)	30 (7%)
Respiratory insufficiency	36 (8%)	44 (10%)
Cardiac failure	57 (13%)	56 (12%)
Acute myocardial infarction	61 (13%)	69 (15%)
Exertional angina	88 (19%)	91 (20%)
Myocardial ischaemia	133 (29%)	115 (25%)
Severe hepatocellular disease	33 (7%)	29 (6%)
Age ⩾75 years on day of surgery, plus at least two criteria	39 (9%)	45 (10%)

Percentages in each group total more than 100 because 33% of patients in the control group and 27% of those in the epidural group had between two and five risk factors each. This difference was marginally significant (p=0·04). *See panel for detailed definitions.

Table 1: **Distribution of preoperative risk factors required for eligibility for randomisation in 915 patients recruited**

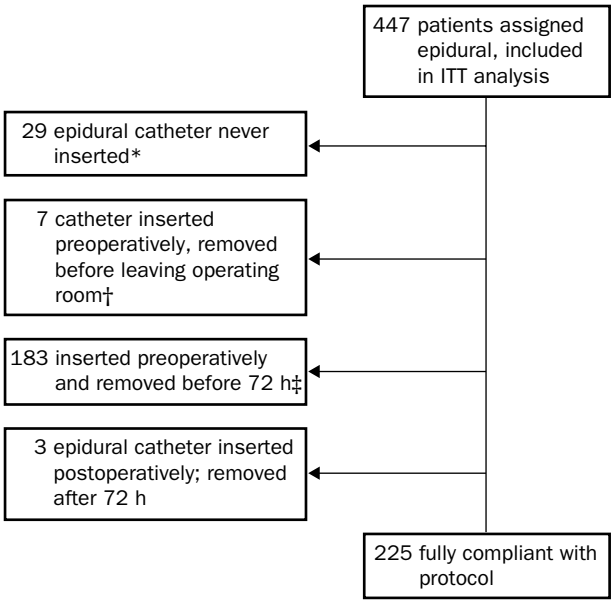

Figure 2: **Breaches of protocol for epidurals**

*Catheter could not be inserted 13, patient withdrew from trial after allocation 4, anaesthetist changed his/her mind 3, anaesthetist neglected to insert epidural 3, surgeon changed his/her mind 1, operation changed 2, contraindications after randomisation 3 (sepsis, low platelet count, aspirin therapy, 1 case each). †Reason not documented 1, inadequate analgesia intraoperatively 2 and postoperatively 1, haemodynamically unstable 1, death 1, operation changed 1. ‡Reason not documented 60, inadequate analgesia postoperatively 42, accidentally dislodged 26, medical orders 16, generalised sepsis 9, haemodynamically unstable 5, catheter leaking 5, leg weakness or numbness 4, no pain 4, death 3, no intensive-care bed or specialist nursing care available 2, operation changed 1, patient's request 2, urinary retention 1, respiratory failure 1, block too high 1, catheter blocked 1. In the nine cases in which the epidural catheter was removed before 72 h because of generalised sepsis complicating surgery, attending medical staff decided that premature removal of the catheter would be prudent to reduce the risk of infection of the epidural site. In no case was any catheter removed because of inflammation of the epidural site and in no case were there any serious complications of epidural catheter placement or adverse sequelae directly attributable to the placement of the epidural catheter.

complicating surgery. More than 95% of patients were randomised in 16 hospitals; nine hospitals randomised a total of only 41 patients because, having agreed to participate, anaesthetists in these centres found that the numbers of eligible patients were lower than expected or were unable to garner support for the trial from sufficient of their anaesthetic or surgical colleagues.

Postoperative day and observation	Mean (SD) measurement on 10 cm scale		p*
	Control (n=441)	Epidural (n=447)	
Day 1			
Rest, morning	2·4 (2·5)	1·7 (2·4)	0·0002
After coughing, morning	5·5 (2·8)	3·9 (3·3)	<0·0001
Rest, afternoon	2·1 (2·3)	1·8 (2·4)	0·08
After coughing, afternoon	5·2 (2·7)	4·0 (3·0)	<0·0001
Day 2			
Rest, morning	1·7 (2·1)	1·6 (2·2)	0·34
After coughing, morning	4·5 (2·6)	3·7 (2·9)	0·0001
Rest, afternoon	1·5 (2·1)	1·3 (2·0)	0·24
After coughing, afternoon	4·2 (2·7)	3·3 (2·5)	<0·0001
Day 3			
Rest, morning	1·2 (1·7)	1·2 (1·9)	0·85
After coughing, morning	3·8 (2·5)	3·0 (2·6)	0·0002
Rest, morning	1·2 (1·8)	1·0 (1·8)	0·18
After coughing, morning	3·5 (2·6)	2·8 (2·5)	0·0007

*t test.

Table 2: **Visual analogue scale pain scores on the first 3 postoperative days**

Two or more risk factors occurred in 33·0% of controls and 26·5% of epidural-group patients (p=0·04). Table 1 shows the distribution of preoperative risk factors in the groups as randomised. More men (59·0% control, 59·9% epidural) than women were enrolled in the study. Eligible patients ranged in age from 26 to 92 years in the control group (mean 69 [SD 11]; IQR 62–77) and 22 to 93 years in the epidural group (69 [11]; 64–77); 66% of control patients and 69% of epidural patients were aged between 60 and 79 years.

The 915 randomised patients underwent 919 surgical procedures in 14 categories (four patients were to undergo two procedures during the same period of anaesthesia): oesophagectomy 18; non-laparoscopic gastric surgery 72; non-laparoscopic biliary surgery 77; pancreatic surgery 35; bowel surgery 364; major surgery for ovarian cancer 23; surgery for aortic aneurysm 142; aorto-femoral bypass-graft surgery 28; renal-tract surgery 59; bladder surgery 12; prostate surgery seven; radical hysterectomy 44; pelvic exenteration two; other 36. The four most common procedures (bowel, aortic aneurysm, biliary, and gastric surgery) together represented 71·3% of eligible procedures. Among these groups there were no significant differences in allocation.

Of 441 patients assigned to the control group, 19 (4·3%) had epidural analgesia established pre-operatively or within 72 h of surgery. Of 447 patients

Endpoint	Definition	Frequency of endpoint (%)		p*
		Control (n=441)	Epidural (n=447)	
Postoperative death	Death from any cause within 30 days of surgery	4·3	5·2	0·67
Respiratory failure	Need for prolonged ventilation or reintubation or PaO_2 ⩽50 mm Hg or $PaCO_2$ ⩾50 mm Hg (room air)	30·2	23·3	0·02
Cardiovascular event	AMI, angina, congestive heart failure, cardiac shock, third-degree heart block or major (supra) ventricular tachyarrhythmia	24·0	25·7	0·61
Renal failure	Rise in serum creatinine of >100 μmol/L or serum creatinine ⩾300 μmol/L, or need for haemofiltration or dialysis	8·2	7·4	0·75
GI failure	GI bleeding needing transfusion of 2 units or more of blood or decision to institute total parenteral nutrition	6·8	6·5	0·95
Hepatic failure	Two of total bilirubin ⩾100 μmol/L, alkaline phosphatase ⩾3 times ULN and either lactate dehydrogenase or aspartate transaminase to >2 times ULN in absence of upper abdominal surgery	2·9	2·2	0·65
Haematological failure	Packed-cell volume ⩽20% or WCC ⩽2×10^9/L or platelets ⩽40×10^9/L	4·1	3·4	0·69
Inflammation/sepsis	Infection, pneumonia, or sepsis (all specifically defined)	46·7	42·7	0·26
At least one morbid endpoint	At least one of the above sets of criteria fulfilled	60·5	56·6	0·26
Death or at least one morbid endpoint	Death within 30 days of surgery or at least one of the above sets of criteria fulfilled	60·7	57·1	0·29

AMI=acute myocardial infarction; GI=gastrointestinal; ULN=upper limit of normal; WCC=white-cell count. *χ^2 test.

Table 3: **Endpoints**

Time of death	Number of deaths		
	Control group	Epidural group	Total
Day 0, operating room	0	1	1
<48 h after surgery	5	4	9
2–4 days after surgery	3	3	6
5–30 days after surgery	11	15	26
Overall	19	23	42

Table 4: **Summary of deaths within 30 days of surgery**

assigned to the epidural group, 29 (6·5%) did not receive an epidural. Among the remaining patients, the mean duration for which the epidural remained in situ postoperatively was 73·6 h (median 72·8). Of patients with a postoperative epidural infusion, 92·7% received a combination of local anaesthetic and opioid, 5·6% received local anaesthetic alone, and 1·7% an opioid infusion. Figure 2 summarises the epidural management of all patients allocated to the epidural group and the numbers and types of breaches of the epidural protocol. Epidural block was associated with significantly lower maximum pulse rate (p=0·01) and systolic blood pressure (p<0·0001).

Pain scores on the 10 cm visual analogue scale were significantly lower in the epidural than in the control group at rest on day 1 and after coughing on days 1–3 (table 2).

19 patients (4·3%) in the control group and 23 (5·1%) in the epidural group died within 30 days of surgery (p=0·67). In the epidural group 255 patients (57·1%) died or had at least one complication, compared with 268 (60·7%) in the control group (p=0·29). Between two and seven complications occurred in 32·0% of the epidural group and in 37·2% of the control group. Individual endpoints were analysed as eight categories: respiratory, cardiac, renal, gastric, pancreatic, hepatic, haematological, and inflammatory.[14] There were no pancreatic morbidity endpoints. Table 3 compares the proportions of patients in control and epidural groups who died or had one of the other seven categories of endpoint. Only one of these, respiratory failure, showed a significant difference, a lower proportion in patients allocated to the epidural group. We calculated that 15 patients needed to have an epidural to prevent one episode of respiratory failure.

Table 4 summarises when deaths occurred. The primary mortality endpoint was death within 30 days. A further eight patients died between 32 and 122 days after surgery but before discharge from hospital, and the attending surgical team judged that septicaemia had played a part in all of these cases. The total of 50 deaths (26 control, 24 epidural) included one patient who was discharged against medical advice on day 13 and died several hours later.

A separate "as treated" analysis, in which primary endpoints in the 19 control patients who received an epidural were counted in the epidural group, and vice versa for the 29 patients allocated epidural who did not receive one, yielded results that were similar to those from the intention-to-treat analysis.

Discussion

We observed no overall difference in mortality or major morbidity between patients randomly assigned general anaesthesia with intraoperative and postoperative epidural therapy or general anaesthesia with other anaesthetic and analgesic regimens for major abdominal or thoracic surgery. With one exception, respiratory failure, there was no significant difference in major postoperative morbidity between the control and epidural groups. We calculated that 15 patients needed to have epidural management to prevent one episode of respiratory failure.

Our results contrast strikingly with both the findings of Yeager and co-workers and the conclusions of a systematic review by Rodgers and colleagues.[12] There are several plausible explanations for these differences. The play of chance is a possibility, but there are many examples in epidemiology in which the size of statistical relations was overestimated in early, small studies compared with later, equally rigorous, but larger investigations. This pattern arises partly from publication bias but it can be related also to a shift in setting from trials that test efficacy under ideal conditions to those that assess effectiveness in everyday practice.[15]

The design and the results of the study of Yeager and colleagues[3] strongly influenced the planning of our trial. As well as cumulative mortality of 16% in their control group and no deaths in their epidural group, those investigators found large differences in cardiovascular complications (52% *vs* 14%) and in the frequency of any morbid endpoint (76% *vs* 33%). The sample size calculated for the MASTER Trial was based on a high frequency of outcomes but a more modest between-group difference, necessitating a multicentre strategy. Our rigorous inclusion criteria resulted in a control group in which 60·7% of patients experienced an adverse event. The corresponding frequency in the epidural group was 57·1%, leading to a between-group difference that was smaller than expected and not statistically significant. Most benefits of therapy shown by randomised controlled trials are small,[10,16,17] but these moderate benefits can be important clinically and economically.[10,13,18–21]

Although the report of Yeager and colleagues was the starting point for the design of our trial, there are differences between the studies that may have contributed to the contrasting results. First, their trial was a small, single-centre study (53 patients) carried out in New Hampshire, USA, over 15 years ago. The MASTER Trial took place in Australia, East Asia, and the Middle East over 5 years in the late 1990s. Such a trial is more heterogeneous in terms of mix of patients and operations, and in the detail of anaesthesia and perioperative management.[14] Greater random variation generates a bias towards the null, tending to reduce differences observed between two treatments. Second, the control group of Yeager and colleagues received an anaesthesia regimen that may have fortuitously accentuated the between-group difference in outcome observed in their trial. An accompanying editorial discussed efficacy and effectiveness, noting that generalisation from a small, single-centre trial is difficult and that low numbers of participants could lead to a type I error.[17] All these issues are important for understanding why our results could differ so much from those of the previous study.[3] We designed the MASTER Trial as a study of the effectiveness of epidural techniques as opposed to efficacy, to enhance generalisability.[14,17]

Another randomised controlled trial published in 2001[22] had results similar to those of our study. The two studies are of similar size and involved similar groups of surgical procedures, but the investigators of the trial in Veterans' Administration hospitals[22] made no attempt to select high-risk patients to maximise statistical power, which would have contributed to the fact that mortality at 30 days was only about half that in our study. Second, that study used epidural morphine postoperatively.[22] The control of pain in their epidural group was inferior to that achieved in the MASTER Trial, in which 93% of patients having an epidural infusion received a combination of local anaesthetic and opioid.

In our trial, 190 (42·5%) of the 447 patients assigned to the epidural group had their catheters removed within

72 h of surgery. In 26 cases, the catheter was accidentally dislodged, and in 43 it was removed because analgesia was inadequate. Although the management of these patients might have breached our protocol, these instances cannot be classified as failed epidurals. The true proportion of failed epidurals was only 8·7%, consisting of the 29 patients who were assigned to the epidural group but never received an epidural, seven in whom it was removed before the patient left the operating theatre, and three in whom an epidural was inserted only after surgery was completed (figure 2). The proportions and patterns of breaches of the protocol for epidurals in our trial are consistent with those described in several large case series and with the experience of anaesthetists and surgeons who manage high-risk patients undergoing major surgery.[23–27]

Recent papers have identified frequent discrepancies between meta-analyses and subsequent randomised trials,[19] the limitations of both approaches, and the reasons for contrasting results for the same experimental questions.[15,16,18,28–30] There is more agreement between our results and the findings of Rodgers and colleagues than may seem apparent.[12] They reviewed data from all types of surgery and identified five subgroups: general, orthopaedics, urology, vascular, and other types.[12] All subgroups showed a trend towards improved mortality with epidural and spinal block, but this trend was significant only in orthopaedic surgery.[12] Our study, which was limited to abdominal surgery and a few oesophagectomy cases, accrued only 42 deaths at 30 days, compared with 247 in their meta-analysis.[12] Given the modest decline in mortality in patients other than the orthopaedic group reported by Rodgers and colleagues, we are not surprised that, with less than a sixth of the number of deaths, the MASTER Trial found no significant effect on mortality.

Across all subgroups of surgery in the meta-analysis, there was significantly lower morbidity with the epidural approach in eight of ten categories of major complications.[12] By contrast, we found a significantly lower frequency only of respiratory failure. This difference may result from the lack of standard approaches to analgesia, and therefore poorer control of pain, in the control groups of the trials examined in the meta-analysis.[12] However, our finding on respiratory morbidity is consistent with the conclusion of Ballantyne and colleagues, whose cumulative meta-analyses of randomised controlled trials of the comparative effects of seven categories of analgesia regimens indicate that epidural local anaesthetic or epidural opioid therapy improves pulmonary outcomes.[31]

Large, well-designed randomised controlled trials are generally considered the gold standard in investigation of the efficacy of clinical interventions,[13–16,28–30] but allocation to treatments must be truly random. With all hospitals in the MASTER Trial being remote from the Secretariat, there was no possibility that any clinician contacting the randomisation centre could predict or influence allocation. Rigour in the assessment of outcomes is also important. Our trial used a comprehensive set of carefully defined and unambiguous outcome variables.[14] We acknowledged at the outset that, for both ethical and clinical reasons, treatment allocation could not be concealed from local investigators, research nurses, and clinical staff at participating hospitals. Thus, we designed data records for use in participating hospitals that required only objective information; no local clinical observer at any hospital was required to form a judgment as to the occurrence or absence of an endpoint. The database was established in such a way that in cases of doubt, any decision on an endpoint would be made by an expert panel, in Western Australia, independent of the study team and unaware of the allocated treatment. The computer algorithm for defining endpoints, which was written without reference to any of the clinical data, proved entirely adequate. These processes ensured that no bias could have occurred as a result of the necessarily open nature of our trial.

All clinically relevant outcomes up to 30 days of surgery were detected and reported by the system that we established to ascertain and count them.[14] Data on intermediate outcomes, such as intraoperative haemodynamics and postoperative pain, attest to the efficacy of epidural block. In line with best practice for the conduct of a large randomised controlled trial,[11,13,15–18,28–30] we used an intention-to-treat approach to analysis based on all patients randomised to have eligible surgical procedures.

It is possible that the true benefit associated with use of epidural techniques is 3·6%, as we observed. If so, our study lacked power to declare an accurately measured difference of this size statistically significant. As the examples of tamoxifen for breast cancer[19–20] and fibrinolytic therapy for acute myocardial infarction[21] remind us, approaches to clinical management of serious problems that result in small improvements in outcome can be important if the disorder is common.[16] In the case of epidural techniques for major surgery, a trial of 6000 patients at high risk would be required to give an 80% chance of declaring statistically significant an absolute difference of 3·6% in the rate of death or major complications. Such a study is of the same order of magnitude as many modern trials of novel medical treatments.

The difficulties and challenges of initiating and completing large, multicentre studies in acute multidisciplinary surgical care cannot be underestimated. Given the discrepancies between our findings and those of the previous clinical trial and meta-analysis,[3,12] clinicians may choose to use or avoid epidural techniques in high-risk patients undergoing major surgery. However, further, larger, multicentre trials may be needed to resolve outstanding issues about the use of epidural anaesthesia and analgesia in association with major abdominal surgery and oesophagectomy.[2,11,16] At present, however, we have been unable to demonstrate any significant effect of epidural management on the overall frequency of complications after major abdominal surgery, except for a modest reduction in the incidence of respiratory failure.

Contributors

All of the investigators contributed to development of the protocol, planning of the statistical analyses, interpretation of the findings, and preparation of the report. J Rigg, P Myles, B Silbert, and P Peyton took the lead in recruiting hospitals to participate in the study, K Jamrozik led design of the study forms and organised the randomisation service. K Collins coordinated day-to-day liaison with study hospitals, checked, coded, and entered data, and obtained additional information where data were missing. R Parsons developed and applied the analytical routines for ascribing endpoints and analysing the data.

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Conflict of interest statement

None of the investigators have a conflict of interest, and the report was prepared in accordance with an agreed policy on authorship that formed part of the written protocol for the trial. During the period of design and exceution of the MASTER Trial (1995–2001), J R A Rigg received sponsorship from Abbott Australasia for travel to a conference to present the findings of the study, and K Jamrozik was a member of an advisory group to SmithKline Beecham on smoking cessation. Mallinckrodt Medical, AstraZeneca, and Hoechst Pharmaceuticals each made small contributions to meeting the non-salary recurrent costs of running the secretariat for the trial. AstraZeneca and B Braun Medical assisted with meetings of trial nurses held in association with the annual scientific meetings of the Australian and New Zealand College of Anaesthetists.

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