

Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials

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Abstract

Objectives To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anaesthesia on postoperative morbidity and mortality. **Design** Systematic review of all trials with randomisation to intraoperative neuraxial blockade or not.

Studies 141 trials including 9559 patients for which data were available before 1 January 1997. Trials were eligible irrespective of their primary aims, concomitant use of general anaesthesia, publication status, or language. Trials were identified by extensive search methods, and substantial amounts of data were obtained or confirmed by correspondence with trialists.

Main outcome measures All cause mortality, deep vein thrombosis, pulmonary embolism, myocardial infarction, transfusion requirements, pneumonia, other infections, respiratory depression, and renal failure.

Results Overall mortality was reduced by about a third in patients allocated to neuraxial blockade (103 deaths/4871 patients versus 144/4688 patients, odds ratio = 0.70, 95% confidence interval 0.54 to 0.90, $P = 0.006$). Neuraxial blockade reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59% (all $P < 0.001$). There were also reductions in myocardial infarction and renal failure. Although there was limited power to assess subgroup effects, the proportional reductions in mortality did not clearly differ by surgical group, type of blockade (epidural or spinal), or in those trials in which neuraxial blockade was combined with general anaesthesia compared with trials in which neuraxial blockade was used alone.

Conclusions Neuraxial blockade reduces postoperative mortality and other serious complications. The size of some of these benefits remains uncertain, and further research is required to determine whether these effects are due solely to benefits of neuraxial blockade or partly to avoidance of general anaesthesia. Nevertheless, these findings support more widespread use of neuraxial blockade.

Introduction

Anaesthesia is commonly classified into two main techniques: general anaesthesia, in which gaseous or intravenous drugs achieve central neurological depression, and regional anaesthesia, in which drugs are administered directly to the spinal cord or nerves to locally block afferent and efferent nerve input.¹ Regional anaesthesia for major thoracic, abdominal, or leg surgery relies on neuraxial blockade by injection of local anaesthetic drugs into either the subarachnoid space (spinal anaesthesia) or into the epidural space surrounding the spinal fluid sac (epidural anaesthesia).

The risks of fatal or life threatening events are increased several fold after major surgery, but there is debate about whether the type of anaesthesia has any substantive effect on these risks. Neuraxial blockade has several physiological effects that provide a rationale for expecting to improve outcome with this technique.² However, the few clinical trials of epidural or spinal anaesthesia that have focused specifically on fatal or life threatening events have generally been too small to detect effects of plausible size reliably. To provide more reliable estimates of the effects of neuraxial blockade on postoperative morbidity and mortality, we conducted a systematic review of all relevant randomised trials.

Methods

Identification of trials and data collection

We sought to identify all trials in which patients were randomised to receive intraoperative neuraxial blockade (with epidural or spinal anaesthesia) or not. Eligibility was not based on whether results were published, the language of publication, or the primary aims of the trial. Trials were ineligible if they were not randomised or were quasi-randomised or if data were not available before 1 January 1997.

We searched the electronic databases Current Contents (1995-6), Embase (Excerpta Medica, 1980-96), Medline (1966-96), and the *Cochrane Library* (1998). We used the key words "regional anaesthesia," "regional anesthesia," "spinal," or "epidural" and the Cochrane Collaboration search terms for randomised trials.³ Once papers were identified, authors' names

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Table 1 Characteristics of included studies

Surgical group	No of studies	No of patients randomised		Type of NB	General anaesthesia used in NB group	NB continued postoperatively
		NB	No NB			
General	28	1065	915	2 spinal; 18 thoracic; 7 lumbar; 1 thoracic and lumbar	22 yes; 6 no	19 yes; 8 no; 1 unknown
Orthopaedics	44	1768	1849	20 spinal; 24 lumbar	5 yes; 39 no	16 yes; 27 no; 1 unknown
Urology	18	463	465	7 spinal; 10 lumbar; 1 spinal and lumbar	1 yes; 17 no	5 yes; 13 no
Vascular	22	905	806	1 spinal; 12 thoracic; 7 lumbar; 2 spinal and lumbar	17 yes; 5 no	15 yes; 7 no
Other	29	670	653	3 spinal; 5 thoracic; 16 lumbar; 1 unknown; 3 spinal and lumbar; 1 thoracic and lumbar	15 yes; 13 no; 1 unknown	11 yes; 14 no; 4 unknown
Total	141	4871	4688	33 spinal; 35 thoracic; 64 lumbar; 8 more than 1 type; 1 unknown	60 yes; 80 no; 1 unknown	66 yes; 69 no; 6 unknown

NB=neuraxial blockade, lumbar=lumbar epidural.

and study titles were used as search terms. We scrutinised the reference lists of all identified papers and also hand searched selected conference proceedings.

Two reviewers independently recorded the published findings from each study on standard data collection sheets. We did not use quality scores,⁴ and the definitions of events were those used in the original trials. A third reviewer compared the two sets of data collection sheets and any differences were resolved by discussion. We attempted to contact the authors of all trials to verify the data and obtain additional unpublished data. If there was more than one trial report, authors were also asked whether the patient groups overlapped. Lastly, we asked authors if they knew of any other relevant studies (published or unpublished).

Statistical analysis

Analysis was carried out on an intention to treat basis wherever possible. We calculated odds ratios, 95% confidence intervals, and two sided P values for each

outcome of interest using Peto's modification of the Mantel-Haenszel method.⁵ Homogeneity was assessed by a χ^2 test.

Results

Study characteristics

We identified 158 potentially eligible trials; 17 studies were excluded. The remaining 141 trials that met all the inclusion criteria included a total of 9559 patients. More than one publication was available for 18 studies but each study was counted only once. No unpublished eligible studies were identified. Table 1 shows the patient characteristics and anaesthetic methods.

Overall mortality

A total of 247 deaths within 30 days of randomisation were recorded in 35 trials. Overall mortality was about one third less in the neuraxial blockade group (odds ratio 0.70, 95% confidence interval 0.54 to 0.90, P = 0.006; fig 1) with no clear difference between different surgical groups (fig 2). The observed improvement in survival was due to trends towards reductions in deaths from pulmonary embolism, cardiac events, or stroke (0.73, 0.45 to 1.16), deaths from infection (0.68, 0.39 to 1.21), deaths from other causes (0.84, 0.44 to 1.61), and deaths from unknown causes (0.64, 0.41 to 1.01). There was about one fewer death per 100 patients in the 30 days after randomisation in the neuraxial blockade group (103/4871 (2.1%) versus 144/4688 (3.1%)).

Mortality results by type of anaesthesia

Seven trials (with 826 participants) directly randomised patients to spinal or epidural anaesthesia. Only 13 deaths occurred in these trials, four in the spinal group. However, an indirect comparison between trials of spinal and epidural anaesthesia showed no clear difference between their effects on total mortality (0.68, 0.49 to 0.95 for spinal anaesthesia and 0.68, 0.43 to 1.07 for epidural anaesthesia, P for homogeneity = 1.0; fig 2). Mortality was reduced overall whether neuraxial blockade was continued postoperatively (0.68, 0.43 to 1.08) or not (0.70, 0.51 to 0.97). The effect on total mortality was not clearly lower in trials in which neuraxial blockade was combined with general anaesthesia (0.87, 0.53 to 1.41) than in trials in which neuraxial blockade was used alone (0.64, 0.47 to 0.87; P for homogeneity = 0.3; fig 2). However, the confidence intervals were wide for the trials that used general anaesthesia.

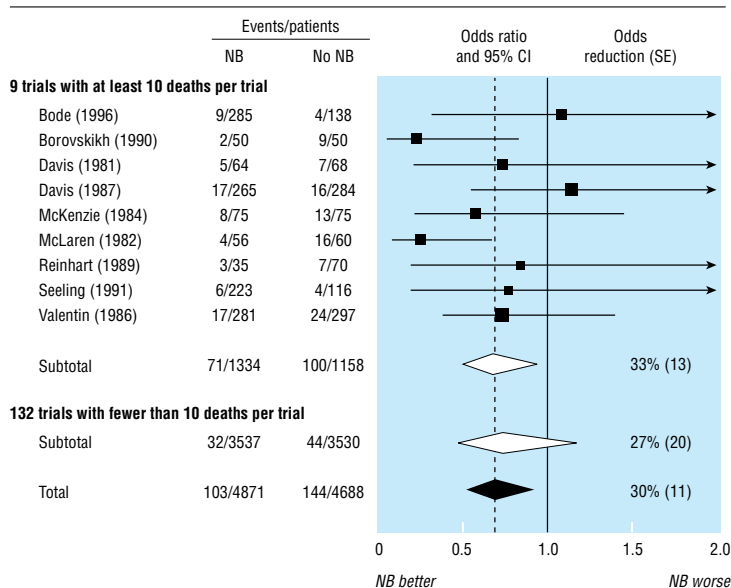


Fig 1 Effect of neuraxial blockade (NB) on postoperative mortality within 30 days of randomisation. Diamonds denote 95% confidence intervals for odds ratios of combined trial results. The vertical dashed line represents the overall pooled result. Size of shaded boxes is proportional to number of events. The overall event rates after adjusting for uneven randomisation⁶ were 113/5811 (1.9%) versus 158/5667 (2.8%). χ^2 test for heterogeneity between individual trials P=0.5

Venous thromboembolism, cardiac events, and stroke

A total of 365 deep vein thromboses were reported from 18 trials. Neuraxial blockade reduced the risk of deep vein thrombosis by almost half (0.56, 0.43 to 0.72; fig 3). Since more than 80% of deep vein thromboses were recorded in orthopaedic trials, there was limited power to detect differences between surgical groups. Outcome assessments were known to be blinded in only two trials, and deep vein thromboses were also reduced in these studies (0.46, 0.21 to 0.99). A total of 96 pulmonary emboli were reported from 23 trials, 21 (22%) of which were fatal. Overall, there were about half as many pulmonary emboli in patients allocated to neuraxial blockade (0.45, 0.29 to 0.69; fig 3).

A total of 104 myocardial infarctions were reported in 30 trials. Overall, there were about one third fewer myocardial infarctions in patients allocated to neuraxial blockade, but the confidence intervals were compatible with both no effect and a halving in risk (0.67, 0.45 to 1.00; fig 3). Only 42 strokes were reported from eight trials, and the confidence intervals were very wide for this outcome (0.85, 0.46 to 1.57; fig 3).

Bleeding

In total, 473 patients from 16 trials required transfusion of two or more units of blood and 100 patients from 12 trials had a postoperative bleed requiring a transfusion. The requirement for a transfusion of two or more units of blood was reduced by about half in patients allocated neuraxial blockade (0.50, 0.39 to 0.66; fig 3). A similar proportional reduction was found for postoperative bleeds requiring a transfusion (0.45, 0.29 to 0.70; fig 3). There was no clear difference in the proportional effects on either outcome across surgical groups.

Postoperative infection

In total, 62 wound infections were reported from 14 trials. There were fewer wound infections in those allocated to neuraxial blockade, although the confidence intervals were wide (0.79, 0.47 to 1.33; fig 3). Three hundred and eighty seven cases of pneumonia were recorded in 28 trials, of which 38 (10%) were fatal. The risk of developing pneumonia was less in patients randomised to neuraxial blockade (0.61, 0.48 to 0.76; fig 3). There was some evidence (P for homogeneity = 0.05) that the proportional reduction in pneumonia was greater after thoracic epidural anaesthesia (0.48, 0.35 to 0.67) than after lumbar epidural or spinal anaesthesia (0.76, 0.55 to 1.04). Twelve deaths due to an infective cause other than pneumonia were recorded in six trials, of which two occurred in patients allocated to neuraxial blockade (0.33, 0.10 to 1.07; fig 3).

Other postoperative events

A total of 64 cases of respiratory depression were reported from eight trials. The odds of respiratory depression were reduced by 59% in patients allocated to neuraxial blockade (0.41, 0.23 to 0.73; fig 3). The effect was present in trials with and without concomitant general anaesthesia. Fifty cases of renal failure were recorded in 10 trials. Although the risk of renal failure was reduced in patients randomised to neuraxial blockade, the confidence intervals were wide and compatible with both no effect and a two thirds reduction (0.57, 0.32 to 1.00; fig 3).

Sensitivity analyses

We conducted several analyses to assess whether the effects on total mortality were dependent on trials with

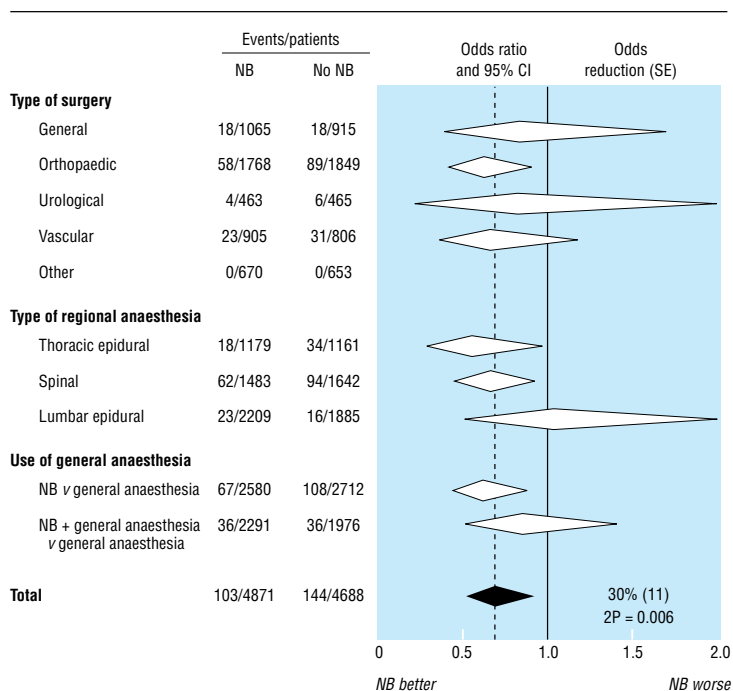


Fig 2 Effect of neuraxial blockade (NB) on postoperative mortality, by surgical group, type of neuraxial blockade, and use of general anaesthesia. Obstetrics and gynaecology trials are included with other surgery. One trial with unknown details of anaesthesia was grouped with lumbar epidural and neuraxial blockade plus general anaesthesia versus general anaesthesia comparisons. Diamonds denote 95% confidence intervals for odds ratios of combined trial results. The vertical dashed line represents the overall pooled result. χ^2 test for heterogeneity between different surgical groups, $P=0.9$

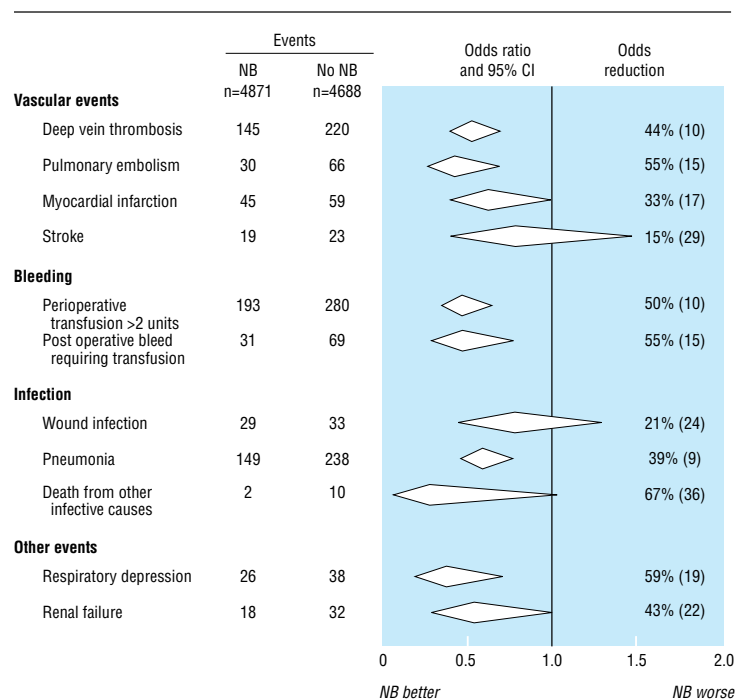


Fig 3 Effects of neuraxial blockade (NB) on postoperative complications. Diamonds denote 95% confidence intervals for odds ratios of combined trial results

methodological problems or affected by the type of anaesthesia. However, all these tests lacked power to detect moderate sized differences.

An overall reduction in mortality was still evident after we excluded studies for which the total number of patients originally randomised was not available (0.68, 0.51 to 0.91); original authors could not be contacted (0.69, 0.53 to 0.90); more than 5% of all patients were lost to follow up or excluded after randomisation (0.69, 0.51 to 0.91); or more than 5% of the neuraxial blockade group were excluded after randomisation (0.68, 0.51 to 0.91). The reduction in mortality was also evident after exclusion of two trials that were stopped before scheduled completion (0.70, 0.53 to 0.91) and exclusion of unpublished data (0.67, 0.51 to 0.88). Finally, there was no clear evidence of publication bias from tests for trend across groups defined by trial size.

Discussion

Our overview shows improved survival in patients randomised to neuraxial blockade. Additionally, we found reductions in risk of venous thromboembolism, myocardial infarction, bleeding complications, pneumonia, respiratory depression, and renal failure. There was no clear evidence that these effects, in proportional terms, differed by the type of surgical group or the type of neuraxial blockade, although there was limited power to assess subgroup effects reliably. Furthermore, there was no evidence of “catch up” mortality in the neuraxial blockade group between 30 days and 6 months (see data on *BMJ*'s website).

The benefits seen for neuraxial blockade may be conferred by multifactorial mechanisms, including altered coagulation, increased blood flow, improved ability to breathe free of pain, and reduction in surgical stress responses.² In particular, major surgery induces a “stress response” that is substantially altered by neuraxial blockade but not by general anaesthesia.² This observation, together with the subgroup comparisons shown here, suggests that these benefits are principally due to the use of neuraxial blockade rather than avoidance of general anaesthesia. Thus the key issue seems to be whether neuraxial blockade is used or not, and the way in which this is achieved is less relevant.

Validity of findings

It is unlikely that bias could explain much of the reduction in mortality. We included all randomised trials, irrespective of their initial aims or reported findings. Most trials were not designed to assess major events, but it is unlikely that we missed many deaths or major non-fatal events because we contacted the authors of trials involving 87% of patients and few patients had no outcome data. However, incidence will have been underestimated for non-fatal events that often go undiagnosed, such as deep vein thrombosis. This finding will not bias relative risk estimates⁷ unless information is selectively available from trials with extreme results. For deep vein thrombosis, at least, the proportional effect of neuraxial blockade in trials designed to assess this outcome was similar to that in other trials. With regard to other potential biases, lack of blinding may have caused some selective misdiagno-

What is already known on this topic

Neuraxial blockade with epidural or spinal anaesthesia reduces the incidence of deep vein thrombosis and one month mortality in patients with hip fractures

Insufficient evidence exists for other postoperative outcomes in this surgical group

What this study adds

Mortality was reduced by one third in patients allocated neuraxial blockade

Reductions in mortality did not differ by surgical group, type of blockade, or in trials in which neuraxial blockade was combined with general anaesthesia

Neuraxial blockade also reduced the risk of deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia, respiratory depression, myocardial infarction, and renal failure

sis of non-fatal events, but analyses did not indicate publication bias and the overall reduction in mortality was not dependent on inclusion of trials with unconfirmed data or trials for which intention to treat analyses were not possible. Lastly, even though these data represent most of the randomised evidence potentially available, the confidence intervals were wide for many outcomes and relatively little information was available about cause of death.

If the proportional effects of neuraxial blockade are consistent in different patient populations, neuraxial blockade would be expected to result in about one fewer postoperative death and several fewer major complications for every 100 patients at similar risk to those in the studies. However, even though such benefits would be widely regarded as clinically important, the largest individual trial to date,⁸ did not have the power to reliably detect effects of this size. Lack of statistical power may therefore be the principal reason why previous individual trials, editorials,⁹ and meta-analyses of trials in hip fracture patients^{10 11} have concluded that neuraxial blockade had no important effect on mortality.

Implications

Our overview indicates that neuraxial blockade reduces major postoperative complications in a wide range of patients. However, uncertainty about the net benefits of neuraxial blockade is likely to remain among some clinicians and for some patient groups. For example, opinion is divided about whether neuraxial blockade is indicated or contraindicated in patients at risk of cardiac complications,¹² and it is unclear whether the differences that we observed reflect the benefits of neuraxial blockade alone or are partly due to the avoidance of the adverse effects of general anaesthesia. Such uncertainties provide the rationale for large randomised trials, such as the ongoing multicentre Australian study of epidural anaesthesia and analgesia in major surgery.¹³ However, since serious complications associated with neuraxial blockade, such as spinal haematoma, are very rare¹⁴⁻¹⁶

and more common side effects, such as headache or urinary retention, are not life threatening, our data should result in more widespread use of spinal or epidural anaesthesia.

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Contributors: AR had the original idea for this study. All authors contributed actively to the protocol. NW and AR performed all searching for trials and AM, SS, and GS abstracted the data. NW and TC carried out all data analysis. AR, NW, AM, TC, and SS wrote the first draft of the paper and HK, AvZ, DS, MF, and SM made revisions. AR will act as guarantor for the paper.

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Competing interests: HK has received fees for consulting and speaking at meetings from AstraZeneca.

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Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia

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Abstract

Objectives To assess the feasibility of detecting new cases of heterozygous familial hypercholesterolaemia by using a nurse led genetic register.

Design Case finding among relatives of patients with familial hypercholesterolaemia.

Setting Two lipid clinics in central and south Manchester.

Subjects 259 (137 men and 122 women) probands and 285 first degree relatives.

Results Of the 200 first degree relatives tested, 121 (60%) had inherited familial hypercholesterolaemia. The newly diagnosed patients were younger than the probands and were generally detected before they had clinically overt atherosclerosis. Concentrations of serum cholesterol were, respectively, 8.4 (1.7 SD) mmol/l and 8.1 (1.9 SD) mmol/l in affected men and women and 5.6 (1.0 SD) mmol/l and 5.6 (1.1 SD) mmol/l in unaffected men and women. Screening for risk factors as recommended in recent guidelines for coronary heart disease prevention would have failed to identify most of the affected relatives in whom hypertension, diabetes mellitus, cigarette smoking, and obesity were uncommon.

Conclusions By performing cholesterol tests on 200 relatives, 121 new patients with familial

hypercholesterolaemia were discovered. Because 1 in 500 people in the United Kingdom are affected by this condition, to detect a similar number by population screening over 60 000 tests would be required, and only a few of these patients would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease. A case exists for organising a genetic register approach, linking lipid clinics nationally.

Introduction

Familial hypercholesterolaemia in its heterozygous form occurs in around 1 in 500 people in Europe and North America, making it the most common potentially lethal genetic disorder. The characteristic clinical syndrome in adulthood comprises an increased serum cholesterol concentration, tendon xanthomas, and premature coronary heart disease, the median age of onset for coronary heart disease being around 50 years in men and 59 in women.^{1,2} Statin treatment and the opportunity for prompt access to cardiological services for patients with familial hypercholesterolaemia seem to have improved survival.³ In trials using coronary angiography, cholesterol lowering treatment is at least as effective in patients with familial hypercholesterolaemia as it is in other types of

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