Papers

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. We did not exclude trials in adult populations in which the group receiving neuraxial blockade group also received general anaesthesia, the general anaesthesia group received postoperative neuraxial blockade, or there was more than one type of neuraxial blockade or general anaesthesia group (in which case similar groups were combined). Eligibility was not based on whether results were published, the language of publication, or the primary aims of the trial—for example, we included a randomised trial designed to assess the effects of neuraxial blockade on cognitive function.[3] Trials were ineligible if they were not randomised or

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were quasi-randomised (such as assignment according to date of birth) or if data were not available before 1 January 1997.

We conducted a computerised search using 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.[4] Once papers were identified, authors' names and study titles were used as search terms. We scrutinised the reference lists of all identified papers and also hand searched selected conference proceedings.

We developed standard data collection sheets to record details of trial design, interventions, patient characteristics, and events. We did not use quality scores because analyses stratified by specific design characteristics are more informative.[5] The definitions of events were those used in the original trials, since patients in one trial were directly compared only with those in the same trial. Two reviewers independently recorded the published findings from each study. This process was not blinded. 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. If no events were reported in the publication or by the authors, we assumed that none occurred. This assumption will generally provide unbiased estimates of proportional effects (the entity typically combined in meta-analysis) but will underestimate absolute effects.[6] 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.[7] Homogeneity was assessed by a χ^2 test. Whenever possible, we stratified analyses of cause specific outcomes by surgical group and type of anaesthetic to determine whether these factors modified the size or direction of proportional effects. However, there were often too few trials with events for such analyses to be informative, and so subgroup analyses are mostly reported for the crude outcome of total mortality.

Results

Study characteristics

We identified 158 potentially eligible trials. Ten studies were excluded because they were quasi-randomised,[8–17] and six were excluded because not all participants were randomised and separate information on the randomised patients was not available.[18–23] One trial was excluded because the groups differed with respect to heparin treatment as well as anaesthetic technique.[24] The remaining 141 trials that met all the inclusion criteria included a total of 9559 patients.[3 25–192] More than one publication was available for 18 studies[46-49 59 60 62-65 72 73 84 85 87-92 94-96 99 100 106 107 124-128 134 135 145 146 156-158 161-163 173 174 187 188] but each study was counted only once. No unpublished eligible studies were identified.

The study authors for 107 (76%) eligible trials, including 8290 (87%) patients, verified the data collection sheets. In almost all cases, we obtained additional unpublished information from contacting the authors, mostly about trial design, but also about events (for example 18 deaths were not reported in original publications). Table 1 shows the patient characteristics and anaesthetic methods and tables 2 and 3 provide summary details of outcome events. We defined a neuraxial blockade group and a non-neuraxial blockade group for each trial, which necessitated collapsing similar groups in 15 trials with more than one randomised comparison. The neuraxial blockade group had no general anaesthesia in 79 (56%) trials and the same general anaesthesia as the non-neuraxial blockade group in 37 (26%) trials. In 22 (15%) trials the neuraxial blockade group received a general anaesthesia different from that in the non-neuraxial blockade group; the systemic opioid varied in seven trials,[28 34 43 84 120 186 192] the use of inhalational anaesthetic varied in two trials,[71 140] the type of inhalational anaesthetic varied in two trials,[148 165] the induction drug varied in one trial,[191] and more than one aspect varied in 10 trials.[42 76 80 81 97 151 161 168 169 189] For three (2%) trials details of the general anaesthesia method were unknown.

Among the 56 trials for which follow up data were available, the mean duration of follow up was about 62 days. Only 13 trials provided follow up data beyond 30 days postoperatively. No events were recorded in 80 trials involving 2941 participants, which were mostly designed to assess the physiological, biochemical, and endocrine effects of neuraxial blockade. The mean follow up in the first 30 days these trials was 11 days, compared with 21 days in trials in which events were observed.

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). A specific diagnosis was available for 162 of the deaths. Of these, 73 (45%) were due to pulmonary embolism, cardiac events, or stroke, 50 (31%) were due to infective causes, and 39 (24%) were due to other causes. 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%)). Only six intraoperative deaths were recorded, one of which was in the neuraxial blockade group (0.28, 0.06 to 1.45). Ten studies, with a total of 1371 patients, recorded 130 deaths between 30 days and six months. All but two of these studies were on orthopaedic patients. Overall, there was no clear effect of neuraxial blockade on deaths during this period (0.89, 0.61 to 1.28).

Table 1 Characteristics of included studies

First author and year of publication	No of patients randomised		No without mortality data		Mean age (years)		No of men		No with ASA status I or II		Type of NB*	General anaesthesia used in NB group	NB continued after surgery	Mean length of follow up (days)
	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB				
General														
Asoh 1983	10	10	—	—	59	57	7	7	—	—	Thoracic	No	Yes	—
Bottiglieri 1992	10	10	—	—	—	—	—	—	—	—	Thoracic	Yes	Yes	—
Cuschieri 1985	25	50	0	0	51	52	5	11	—	—	Thoracic	Yes	Yes	4
De Kock 1993	20	20	—	—	34	37	13	13	—	—	Lumbar	Yes	Yes	—
Gelman 1980	21	17	—	—	36	39	—	—	—	—	Thoracic	Yes	Yes	—
Godfrey 1981	34	34	0	0	—	—	34	34	—	—	Lumbar	No	No	30
Goertz 1993	24	12	0	0	52	44	—	—	—	—	Thoracic	Yes	Yes	—
Hendolin 1987	60	40	0	0	56	55	10	8	—	—	Thoracic	Yes	Yes	7
Hjortso 1985	50	50	6	0	66	69	23	21	42	47	Thoracic	Yes	Yes	10
Jayr 1988	75	75	1	3	60	59	44	37	—	—	Thoracic	Yes	Yes	5
Jayr 1993	82	81	4	6	58	56	43	55	—	—	Thoracic	Yes	Yes	17
Jensen 1980	6	6	0	0	51	54	6	6	6	6	Lumbar	No	No	—
Kausalya 1994	25	25	—	—	39	36	—	—	10	10	Lumbar	No	No	—
Mellbring 1983	25	25	0	0	62	61	13	19	—	—	Thoracic	Yes	Yes	—
Moiniche 1992	15	16	0	0	54	45	3	4	15	16	Thoracic	Yes	Yes	2
Naesh 1994	7	7	—	—	—	—	7	7	7	7	Lumbar	No	No	—
Naesh 1994	8	8	—	—	52	47	0	0	8	8	Lumbar	Yes	No	4
Ogata 1985	10	10	0	0	55	50	—	—	—	—	Thoracic	Yes	—	—
Rutberg 1984	16	8	0	0	43	43	0	0	16	8	Thoracic	Yes	Yes	3
Ryan 1992	57	43	12	8	65	66	—	—	—	—	Thoracic	Yes	Yes	14
Scheinin 1982	30	10	0	0	—	—	13	5	—	—	Thoracic	Yes	Yes	2
Seeling 1990	124	123	26	7	61	58	93	88	58	63	Thoracic	Yes	Yes	—
Seeling 1991	223	116	38	9	60	58	134	79	91	60	Thoracic or lumbar	Yes	Yes	—
Traynor 1982	9	9	—	—	52	49	2	1	9	9	Thoracic	Yes	No	—
Tverskoy 1990	12	24	—	—	54	56	12	24	12	24	Spinal	No	No	—
Watters 1993	12	8	—	—	64	65	4	8	—	—	Lumbar	Yes	Yes	2
Worsley 1988	47	51	0	0	53	53	—	—	—	—	Spinal	Yes	No	19
Yeager 1987	28	27	0	2	71	72	—	—	—	—	Thoracic	Yes	Yes	—
Subtotal	1065	915	87	35	58	56	466	427	274	258				11
Obstetrics and gynaecology														
Abboud 1985	32	20	0	0	28	29	0	0	—	—	Spinal or lumbar	No	No	—
Blunnie 1983	15	30	—	—	42	41	0	0	15	30	Spinal	Yes	No	—
Brandt 1978	6	6	—	—	36	40	0	0	6	6	Lumbar	No	Yes	—
Buckley 1982	6	7	0	0	38	39	0	0	6	7	Lumbar	Yes	Yes	—
Christensen 1982	12	24	—	—	—	—	0	0	—	—	Lumbar	No	—	—
Dick 1992	23	24	—	—	27	28	0	0	23	24	Lumbar	No	No	—
Halevy 1978	14	18	—	—	—	—	0	0	14	18	Lumbar	No	No	—
Holdcroft 1979	15	37	0	0	32	30	0	0	32	30	Lumbar	Yes	No	—
Jensen 1977	9	9	—	—	42	45	0	0	9	9	Lumbar	Yes	No	—
Jordanov 1985	27	20	0	0	29	31	0	0	22	20	Thoracic or lumbar	No	Yes	—
Kocknover 1982	45	45	—	—	—	—	0	0	—	—	Lumbar	Yes	No	—
Lehtinen 1987	11	13	0	0	29	38	0	0	11	13	Lumbar	No	No	—
Licker 1994	10	9	1	0	51	47	0	0	10	9	Lumbar	Yes	Yes	5
Murakami 1987	20	17	0	0	41	43	0	0	—	—	Lumbar	No	—	—
Rem 1980	6	6	—	—	38	39	0	0	6	6	Lumbar	No	No	—
Simpson 1982	6	30	0	0	44	44	0	0	6	30	Lumbar	Yes	No	8
Wallace 1995	54	26	0	0	—	—	0	0	—	—	Spinal or lumbar	No	No	—
Wattwil 1987	20	20	—	—	—	—	0	0	—	—	Lumbar	Yes	Yes	—
Wessen 1994	10	10	0	0	43	45	0	0	10	10	Lumbar	Yes	Yes	2
Subtotal	341	371	1	0	35	36	0	0	170	212				6
Orthopaedic														
Berggren 1987	28	29	—	—	78	77	4	7	—	—	Lumbar	No	No	—
Bigler 1985	20	20	0	0	80	78	2	5	17	16	Spinal	No	No	90
Bonnet 1982	5	14	—	—	60	58	1	5	—	—	Lumbar	No	No	—
Brendahl 1991	15	15	0	2	80	79	0	0	15	15	Spinal	No	No	—
Brown 1994	10	10	0	0	75	79	5	5	6	7	Spinal	No	No	2
Chin 1982	21	21	0	0	73	74	10	9	21	21	Lumbar	Yes	No	6
Christensen 1986	6	8	0	0	65	65	—	—	—	—	Lumbar	No	Yes	—
Couderc 1977	50	50	—	—	86	86	7	7	—	—	Lumbar	No	No	90
Dahl 1990	50	46	0	4	29	29	38	40	50	46	Spinal	No	No	7
Darling 1994	10	10	0	0	81	74	1	1	0	0	Spinal	No	No	360†

Table 1 contd

First author and year of publication	No of patients randomised		No without mortality data		Mean age (years)		No of men		No with ASA status I or II		Type of NB*	General anaesthesia used in NB group	NB continued after surgery	Mean length of follow up (days)
	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB				
Davis 1981	64	68	0	0	81	78	11	9	23	24	Spinal	No	No	28
Davis 1987	265	284	—	—	—	—	—	—	—	—	Spinal	No	No	28
Davis 1989‡	69	71	0	0	68	67	31	31	—	—	Spinal	No	No	14
Donadoni 1988	51	29	0	0	62	67	—	—	0	0	Lumbar	Yes	Yes	2
Fredin 1986	30	30	2	2	67	66	11	8	—	—	Lumbar	No	Yes	—
Hedenstierna 1986	8	8	0	0	64	66	6	4	—	—	Spinal	No	No	—
Hole 1980	29	31	0	0	70	72	10	11	27	29	Lumbar	No	No	300
Hole 1983	13	14	—	—	—	—	—	—	—	—	Lumbar	No	Yes	—
Hole 1984	10	10	0	0	62	64	4	1	10	9	Lumbar	No	Yes	24
Hole 1984	10	10	0	0	67	70	3	3	8	8	Lumbar	No	Yes	—
Jakobsen 1986	15	15	0	0	72	72	—	—	—	—	Lumbar	No	Yes	—
Jones 1990	76	75	2	3	—	—	20	19	—	—	Spinal	No	No	90
Jorgensen 1991	24	24	0	0	69	64	8	8	—	—	Lumbar	No	Yes	360
Keith 1977	10	17	—	—	61	64	5	3	—	—	Lumbar	No	No	—
Mann 1983	30	30	0	0	71	70	18	16	10	12	Spinal	No	No	180
Maurette 1988	18	15	0	0	81	85	—	—	18	15	Spinal	No	No	—
McKenzie 1984	75	75	6	2	75	74	8	17	38	34	Spinal	No	No	365
McLaren 1982	56	60	—	—	—	—	—	—	—	—	Spinal	No	No	30
Modig 1980	15	15	0	0	67	65	8	7	15	15	Lumbar	No	Yes	30
Modig 1986	50	50	2	4	65	66	27	22	48	46	Lumbar	No	Yes	30
Modig 1987	14	24	0	0	67	67	5	13	14	24	Lumbar	No	Yes	30
Nielsen 1989	10	20	—	—	34	38	5	10	5	10	Lumbar	No	No	—
Nielsen 1990	25	39	—	—	—	—	—	—	—	—	Spinal	No	—	—
Pedersen 1986	15	15	0	0	72	72	9	10	—	—	Lumbar	No	Yes	—
Poll 1988	24	26	0	0	—	—	—	—	—	—	Lumbar	Yes	Yes	—
Racle 1986	35	35	0	0	82	82	0	0	—	—	Spinal	No	No	30
Riis 1983	20	10	—	—	70	70	—	—	—	—	Lumbar	Yes	Yes	90
Seitz 1985	10	10	0	0	—	—	10	10	—	—	Lumbar	No	No	—
Sharrock 1992	11	10	—	—	—	—	—	—	—	—	Lumbar	No	Yes	—
Stathopoulou 1992	26	31	0	0	56	56	11	20	26	31	Spinal	No	No	—
Tulla 1992	10	10	0	0	61	59	5	5	8	10	Spinal	No	No	4
Valentin 1986§	281	297	—	—	79	79	58	59	192	182	Spinal	No	No	—
White 1980	20	40	0	4	78	79	1	7	8	18	Spinal	Yes	No	28
Williams-Russo 1995	134	128	0	0	69	69	40	38	—	—	Lumbar	No	Yes	180
Subtotal	1768	1849	12	21	71	71	382	410	559	572				84
Urology														
Asbjorn 1989§	20	20	0	0	69	69	20	20	20	20	Lumbar	No	Yes	21
Chung 1987	20	24	—	—	73	72	9	12	—	—	Spinal	No	No	—
Chung 1989	22	22	—	—	72	72	22	22	13	14	Spinal	No	No	—
Dobson 1994	11	11	—	—	77	72	11	11	11	11	Spinal	No	No	—
Edwards 1995	52	48	—	—	—	—	52	48	—	—	Spinal	No	No	—
Foate 1985	8	9	—	—	69	69	8	9	—	—	Spinal	No	No	—
Frank 1994	15	15	0	0	61	62	15	15	15	15	Lumbar	No	Yes	0
Hendolin 1981	17	21	—	—	71	67	17	21	—	—	Lumbar	No	Yes	—
Henny 1986	10	10	—	—	62	62	10	10	—	—	Lumbar	No	Yes	—
Jenkins 1983	7	8	—	—	68	68	7	8	—	—	Lumbar	No	No	—
McGowan 1980	50	100	0	0	—	—	50	100	—	—	Spinal	No	No	7
Melsen 1987	45	59	0	0	68	64	36	53	45	59	Lumbar	No	No	—
Nielsen 1987	25	20	7	2	—	—	—	—	—	—	Lumbar	No	No	—
Poikolainen 1983	17	21	—	—	—	—	—	—	—	—	Lumbar	No	No	—
Rickford 1988	53	25	—	—	45	46	31	13	31	13	Spinal or lumbar	No	No	—
Shir 1994	69	34	—	—	—	—	—	—	—	—	Lumbar	Yes	Yes	—
Stjernstrom 1985	15	10	—	—	71	66	15	10	15	10	Lumbar	No	No	—
Whelan 1982	7	8	—	—	64	66	7	8	—	—	Spinal	No	No	—
Subtotal	463	465	7	2	64	65	310	360	150	142				10
Vascular														
Baron 1991	87	86	6	0	61	62	70	81	—	—	Thoracic	Yes	Yes	—
Bode 1996	285	138	0	0	68	68	40	81	0	0	Spinal or lumbar	Yes	Yes	—
Bonnet 1989	10	11	—	—	63	64	9	11	—	—	Thoracic	Yes	No	—
Borovskikh 1990	50	50	0	0	56	55	50	50	—	—	Thoracic	No	Yes	30
Christopherson 1993	49	51	0	0	64	66	30	27	6	6	Lumbar	No	Yes	180

Table 1 contd

First author and year of publication	No of patients randomised		No without mortality data		Mean age (years)		No of men		No with ASA status I or II		Type of NB*	General anaesthesia used in NB group	NB continued after surgery	Mean length of follow up (days)
	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB				
Cook 1986	50	51	0	0	66	67	35	36	19	20	Spinal	No	No	365
Damask 1990	9	10	—	—	71	64	6	8	—	—	Lumbar	No	No	—
Davies 1993	25	25	0	0	65	67	23	21	—	—	Thoracic	Yes	Yes	7
Garnett 1996	55	56	7	5	68	69	37	43	0	0	Lumbar	Yes	Yes	—
Gold 1994	12	12	0	0	73	71	9	9	0	0	Lumbar	Yes	Yes	8
Gottlieb 1988	20	15	—	—	—	—	—	—	—	—	Lumbar	Yes	Yes	—
Haljamae 1988	27	28	—	—	65	60	19	20	—	—	Lumbar	Yes	No	—
Homann 1984	19	38	—	—	46	41	8	13	—	—	Lumbar	No	No	—
Houweling 1993	40	20	0	0	65	65	32	15	—	—	Spinal or lumbar	Yes	Yes	10
Kossman 1982	9	10	—	—	—	—	—	—	—	—	Thoracic	Yes	Yes	—
Reinhart 1989	35	70	—	—	63	61	25	52	13	28	Thoracic	Yes	Yes	5
Rosseel 1985	9	9	—	—	67	65	8	8	0	0	Thoracic	Yes	No	—
Seeling 1985	25	26	1	0	62	62	22	24	11	14	Thoracic	Yes	Yes	—
Smeets 1993	6	5	1	0	62	65	6	5	—	—	Thoracic	Yes	Yes	—
Stenseth 1994	20	10	0	0	55	54	20	10	0	0	Thoracic	Yes	Yes	6
Truman 1991	40	40	0	0	70	66	17	15	0	0	Thoracic	Yes	Yes	20
Wust 1980	23	45	—	—	58	60	20	41	12	18	Thoracic	Yes	No	—
Subtotal	905	806	15	5	65	63	486	570	61	86				94
Other surgery														
Brichon 1994	46	33	—	—	53	45	—	—	—	—	Thoracic	Yes	Yes	—
Bromage 1971	22	22	—	—	43	48	—	—	—	—	Thoracic	Yes	Yes	—
Ghoneim 1988	52	53	—	—	62	60	35	35	—	—	Spinal or lumbar	No	No	90
Hasenbos 1985	83	80	0	0	42	36	65	60	21	14	Thoracic	Yes	Yes	4
Jia 1985	67	31	—	—	—	—	—	—	—	—	—	—	—	—
Merhav 1993	16	15	—	—	40	46	14	11	—	—	Spinal	No	No	—
Ogata 1988	8	13	—	—	—	—	—	—	—	—	Thoracic	Yes	—	—
Ravin 1971	10	10	—	—	71	70	—	—	—	—	Spinal	No	No	—
Slinger 1995	15	15	—	—	65	62	12	11	—	—	Lumbar	Yes	Yes	3
Zwarts 1989	10	10	—	—	38	50	5	8	—	—	Thoracic	Yes	Yes	—
Subtotal	329	282	0	0	50	48	131	125	21	14				34
Total	4871	4688	122	63	63	62	1775	1892	1235	1284				62

*NB=neuraxial blockade.
†In excluded patients only.
‡11 patients were entered twice into this study.
§=The total number randomised was not available.Those presented are the numbers included in the study after exclusions and losses to follow up.

Mortality results by type of anaesthesia

Seven trials (with 826 participants) directly randomised patients to spinal or epidural anaesthesia.[25 32 77 104 153 181] 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. Forty four (18%) deaths occurred in the 22 trials in which the neuraxial blockade group had a different general anaesthesia to that used in the group not allocated neuraxial blockade. The overall effect in this group of trials (0.92, 0.49 to 1.71) was not clearly different (P for homogeneity = 0.3) from that in other trials (0.66, 0.49 to 0.88).

Table 2 Summary of vascular events and bleeding

	Vascular events												Bleeding			
	Deep vein thrombosis		Pulmonary embolism		Myocardial infarction		Cardiac arrhythmia		Other fatal cardiac event		Stroke		Perioperative transfusion requiring >2 units red cells		Postoperative bleed requiring transfusion	
Group	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB
General	26	24	3	5	0	4	3	4	0	0	0	0	61	80	0	0
Orthopaedics	117	184	27	59	7	19	36	41	6	3	17	16	81	125	21	57
Urology	2	11	0	1	3	6	1	0	0	0	0	2	12	32	0	0
Vascular	0	0	0	1	35	30	19	31	3	1	2	5	38	41	9	11
Other	0	1	0	0	0	0	0	0	0	0	0	0	1	2	1	1
Total	145	220	30	66	45	59	59	76	9	4	19	23	193	280	31	69

NB=neuraxial blockade.

Table 3 Summary of infection, other events, and mortality

	Infection						Other events				Mortality					
	Wound infection		Pneumonia		Death from other infective cause		Respiratory depression		Renal failure		Total mortality		No of intraoperative deaths		No of deaths between 30 days and 6 months	
Group	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB	NB	No NB
General	17	13	64	99	2	1	16	14	1	3	18	18	0	0	0	1
Orthopaedics	9	14	63	84	0	1	0	1	10	14	58	89	0	1	57	66
Urology	0	0	0	0	0	0	0	1	0	0	4	6	0	0	0	0
Vascular	2	4	22	55	0	8	10	22	7	15	23	31	1	4	3	3
Other	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	29	33	149	238	2	10	26	38	18	32	103	144	1	5	60	70

NB= neuraxial blockade.

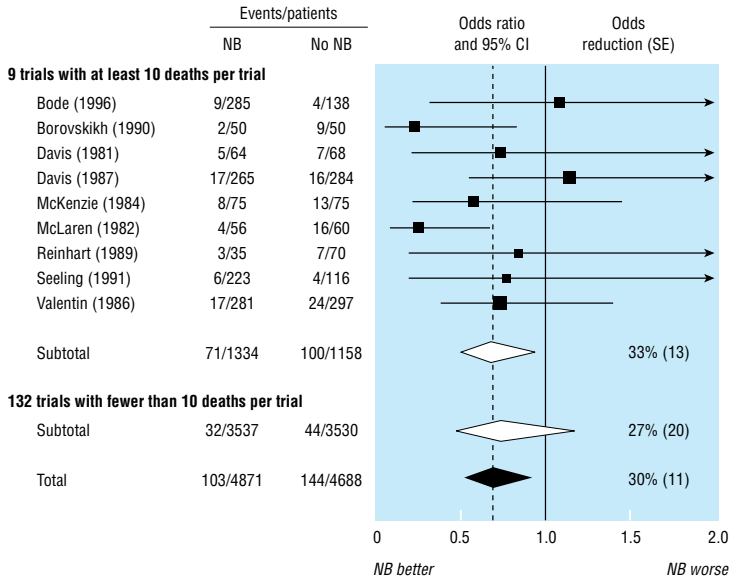

Fig 1 Effect of neuraxial blockade (NB) on postoperative mortality within 30 days of randomisation. Diamonds denote 95% confidence intervals for odds ratios of combined trial results. The vertical dashed line represents the overall pooled result. Size of shaded boxes is proportional to number of events. The overall event rates after adjusting for uneven randomisation[193] 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. In nine trials all patients were screened for deep vein thromboses by fibrinogen scanning,[59 87 129] venography,[74 114 132 187] or a combination of methods.[62 94] Proportional reductions in deep vein thromboses were similar in the trials with screening (0.56, 0.42 to 0.75) compared with other trials (0.54, 0.30 to 0.96). Therefore, absolute differences were much greater in the trials with screening (121/463 (26%) for neuraxial blockade versus 178/467 (38%) for no neuroaxial blockade) than in other trials (24/4408 (0.5%) versus 42/4221 (1.0%)). 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).[66 98] 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 no clear difference in the proportional effects with the use of concomitant general anaesthesia (neuraxial blockade versus general anaesthesia: 0.63, 0.46 to 0.87; neuraxial blockade plus general anaesthesia versus general anaesthesia: 0.59, 0.42 to 0.81). However, 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 (neuraxial blockade alone versus general anaesthesia 0.37, 0.11 to 1.21; neuraxial blockade plus general anaesthesia versus general anaesthesia 0.43, 0.22 to 0.81). 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 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)[26 180]; original authors could not be contacted (0.69, 0.53 to 0.90)[36 38 40 82 83 86 103 115 118 131 137-144 147 150 153 155 166 171 172 179 181 185 190]; more than 5% of all patients were lost to follow up or excluded after randomisation (0.69, 0.51 to 0.91) [3 14 32 38 57 62 71 74 75 94 108 113 114 120 129 130 140 159 164 165 171 173 181 187]; or more than 5% of the neuraxial blockade group were excluded after randomisation (0.68, 0.51 to 0.91).[28 32 57 75 94 113 120 129 130 140 159 164 165 171 173] 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).[28 46 94 109 130 165] 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.

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.

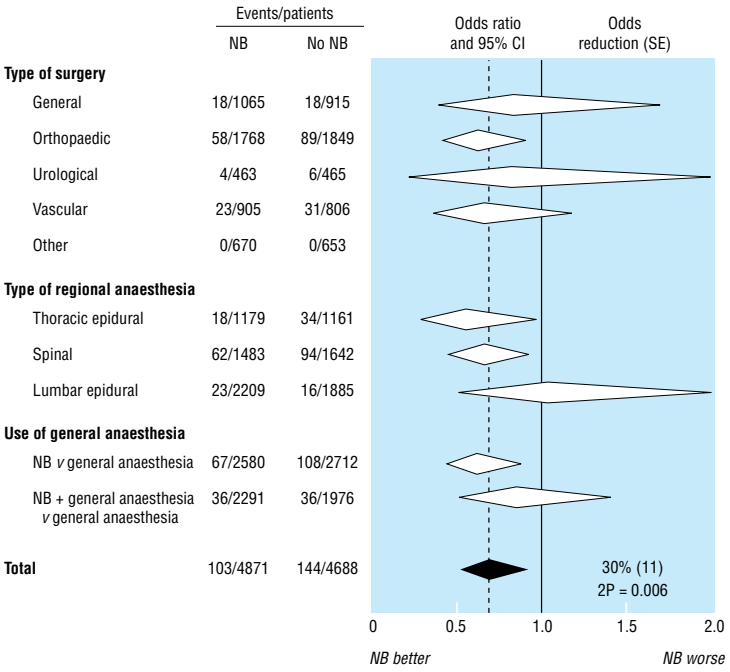

Fig 2 Effect of neuraxial blockade (NB) on postoperative mortality, by surgical group, type of neuraxial blockade, and use of general anaesthesia. Obstetrics and gynaecology trials are included with other surgery. One trial with unknown details of anaesthesia was grouped with lumbar epidural and neuraxial 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. Size of shaded boxes is proportional to number of events. χ^2 test for heterogeneity between different surgical groups, P=0.9

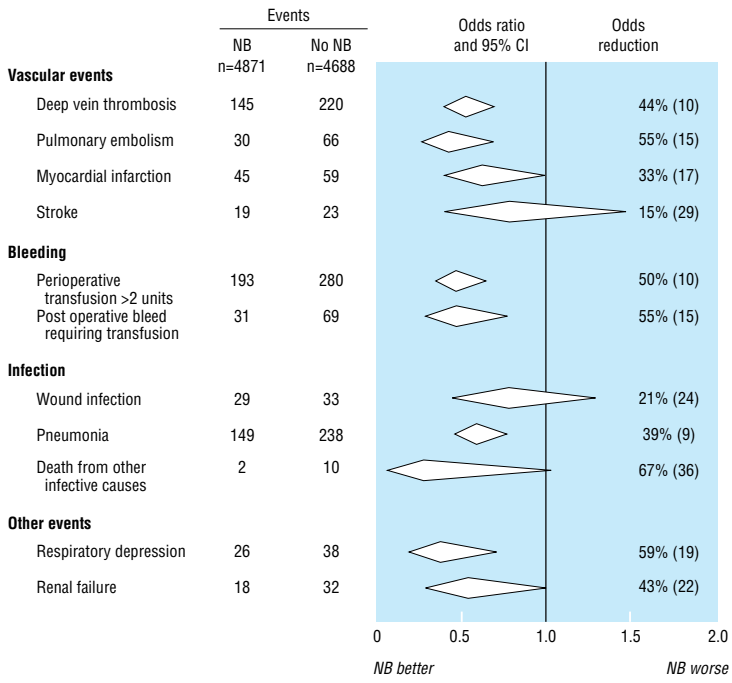

Fig 3 Effects of neuraxial blockade (NB) on postoperative complications. Diamonds denote 95% confidence intervals for odds ratios of combined trial results. The vertical dashed line represents the overall pooled result. Size of shaded boxes is proportional to number of events

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 estimates[6] 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 misdiagnosis 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[180] 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,[194] and meta-analyses of trials in hip fracture patients[195 196] 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,[197] 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.[198] However, since serious complications associated with neuraxial blockade, such as spinal haematoma, are very rare[199-201] and more common side effects, such as headache or urinary retention, are not life threatening, our data support recent trends towards increased use of neuraxial blockade. Furthermore, although we focused on intraoperative anaesthetic techniques, postoperative neuraxial blockade has been shown to have additional benefits, at least for pulmonary complications.[202] Overall, therefore our data should result in more widespread use of spinal or epidural anaesthesia.

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 hip fracture patients

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

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