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The benefits of adding epidural analgesia to general anesthesia: a metaanalysis

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Abstract
The purpose of this metaanalysis was to determine the benefits of postoperative epidural analgesia in patients operated on under general anesthesia. By searching the American National Library of Medicine's Pubmed database from 1966 to July 10, 2004, 70 studies were identified. These included 5402 patients, of which 2660 had had epidural analgesia. Epidural analgesia reduces the incidence of arrhythmia, odds ratio (OR) = 0.59 (95%CI = 0.42, 0.81, P = 0.001); time to tracheal extubation, OR = –3.90 h (95%CI = –6.37, –1.42, P = 0.002); intensive care unit stay, OR = –2.94 h (95%CI = –5.66, –0.22, P = 0.03); visual analogical pain (VAS) scores at rest, OR = –0.78 (95%CI = –0.99, –0.57, P < 0.00001) and during movement, OR = –1.28 (95%CI = –1.81, –0.75, P < 0.00001); maximal blood epinephrine, OR = –165.70 pg·ml^{-1} (95%CI = –252.18, –79.23, P = 0.0002); norepinephrine, OR = –134.24 pg·ml^{-1} (95%CI = –247.92, –20.57, P = 0.02); cortisol, OR = –55.81 nmol·l^{-1} (95%CI = –79.28, –32.34, P < 0.00001); and glucose concentrations achieved, OR = –0.87 nmol·l^{-1} (95%CI = –1.37, –0.37, P = 0.0006). It also reduces the first 24-h morphine consumption, OR = –13.62 mg (95%CI = –22.70, –4.54, P = 0.003), and improves the forced vital capacity (FVC), OR = 0.231 (95%CI = 0.09, 0.37, P = 0.001) at 24 h. A thoracic epidural containing a local anesthetic reduces the incidence of renal failure: OR = 0.34 (95%CI = 0.14, 0.81, P = 0.01). Epidural analgesia may thus offer many advantages over other modes of postoperative analgesia.

Key words Epidural analgesia · Benefits · Metaanalysis

Since it has recently been suggested that major complications associated with epidural analgesia might be more common than once thought, it is of the utmost importance to have a clear view of the real benefits associated with its use [1]. An updated reappraisal of the benefits associated with epidural analgesia could help the clinician to decide when the benefits of an epidural catheter insertion outweigh its inherent risks in a specific patient. The aim of this review is to sum up the benefits of adding epidural analgesia for patients operated on under general anesthesia, as found from all the randomized prospective clinical trials published in the English-language medical literature.

The studies were identified by searching the American National Library of Medicine's PubMed database from 1966 to July 10, 2004, using the following keywords: "epidural," "myocardial infarction," "vital capacity," "rehabilitation," "thrombosis," and "stress." A total of 1275 studies were screened for potential relevance, of which 117 were retrieved, and 70 [2–71] were retained for analysis using the following criteria: prospective randomized study, article published in English, all patients had their procedure performed under general anesthesia, one group of patients with an epidural for postoperative analgesia and one without, and a follow-up period of at least 1 week after surgery. When follow-up was available for a longer period, data were taken as long as possible after the surgery, but no later than 30 days. The following data were extracted from text, tables, or figures: number of patients included in each group, type of surgery performed, site of catheter insertion (thoracic vs. lumbar region), catheter insertion in the control group or not, use of local anesthetic or not (except the equivalent of 100 mg lidocaine or less as a test dose), deaths, deep venous thrombosis, pulmonary emboli, cerebrovascular accident, arrhythmia, myocardial infarction, acute pulmonary edema (or congestive heart failure), respiratory complications (pneumonia or atelectasis requiring an intervention or tracheal reintubation), wound infection, reoperation, time to tracheal extubation (h), intensive care unit stay (h), time to first bowel movement (h), hospital stay (days), forced vital capacity (FVC) 24 h postoperatively, visual or verbal analogical pain score (VAS) (0–10) at rest and

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during movement (or coughing) 24 h postoperatively, maximal blood epinephrine, norepinephrine, cortisol and glucose concentrations measured during the entire study and the first 24 h morphine consumption. If the patients included in the control group received more than the equivalent of 100 mg lidocaine as a test dose just prior to surgery, those patients were considered to have had an epidural and the study was excluded. All data were entered in the Review Manager software (RevMan for Windows version 4.2.7, The Cochrane Collaboration, Oxford, UK) and tested for heterogeneity. Data with a P value <0.05 for heterogeneity were analyzed with a random effects model, and those with a P value for heterogeneity ≥0.05 were analyzed with a fixed model. For the results, $P < 0.05$ was considered to be significant.

Of the 70 studies finally kept for analysis, only eight of them could be considered truly blind. In the control group in these eight studies, a catheter was inserted either into the epidural space [5,18,25,32,36,48] or subcutaneously [33,34] to mimic an epidural catheter. The 70 studies included 5402 patients, of which 2660 had epidural analgesia. These were distributed as follows: cardiac surgery 18.1% [14,19,20,22,40,45,50,55,59,64,65, 67,68,71], peripheral vascular surgery 5.5% [47,48,63, 69], thoracic surgery 11.5% [3,5–7,16,24–26,32,36,42,53, 57,62], abdominal surgery 20.7% [2,4,8,13,18,23,27–31,33,34,37,38,41,43,51,52,56,58,60], gynecological surgery 2.2% [9,11,12,21,39,44,46], urological surgery 1.3% [10,66], mixed major surgery 35.3% [49,54], and orthopedic surgery 5.3% [15,17,35,61,70].

Adding epidural analgesia to general anesthesia reduced the incidence of arrhythmia, odds ratio (OR) = 0.59 (95% CI = 0.42, 0.81, $P = 0.001$); time to tracheal extubation, OR = –3.90 h (95% CI = –6.37, –1.42, $P = 0.002$); intensive care unit stay, OR = –2.94 h (95% CI = –5.66, –0.22, $P = 0.03$); VAS scores at rest, OR = –0.78 (95% CI = –0.99, –0.57, $P < 0.00001$) and during movement, OR = –1.28 (95% CI = –1.81, –0.75, $P < 0.00001$); maximal blood epinephrine, OR = –165.70 pg·ml^{-1} (95% CI = –252.18, –79.23, $P = 0.0002$); norepinephrine, OR = –134.24 pg·ml^{-1} (95% CI = –247.92, –20.57, $P = 0.02$); cortisol, OR = –55.81 nmol·l^{-1} (95% CI = –79.28, –32.34, $P < 0.00001$); and glucose, OR = –0.87 nmol·l^{-1} (95% CI = –1.37, –0.37, $P = 0.0006$) measured during the study; and also morphine consumption during the first 24 h OR = –13.62 mg (95% CI = –22.70, –4.54, $P = 0.003$) (Tables 1 and 2). Epidural analgesia also improved the FVC at 24 h: OR = 0.231 (95% CI = 0.09, 0.37, $P = 0.001$) (Table 2). When the studies where a thoracic epidural or an epidural containing a local anesthetic, or both, were analyzed separately, the incidence of renal failure was reduced by the use of a thoracic epidural containing a local anesthetic: OR = 0.34 (95% CI = 0.14, 0.81, $P = 0.01$). Thirty-one studies were used for measurements of epinephrine, norepinephrine, cortisol, and glucose blood concentrations; for 13 studies there was no information available on blood loss and/or blood transfusion; for nine studies, no patient was transfused; for one study there was no difference in the number of units transfused; and for five studies there was no statistical difference in the amount of estimated blood loss. For three studies there was a statistical difference either in estimated blood loss [10,64] or in intraoperative hematocrit [45]. If these last three studies were excluded from the analysis, the

Table 1. Benefits of adding epidural analgesia to general anesthesia: results from binary data

Outcome	References	Number of patients with/without epidural analgesia	Odds ratio	95% confidence interval	P value
Mortality	7, 29, 30, 40, 41, 47–50, 53–56, 58, 65, 68, 69	1724/1643	1.07	0.73, 1.56	0.72
Deep venous thrombosis	10, 15, 17, 27, 29, 30, 41, 56, 66, 69	294/344	0.94	0.54, 1.62	0.82
Pulmonary emboli	10, 29, 41, 43, 49, 56	635/631	0.49	0.10, 2.26	0.36
Myocardial infarction	7, 10, 15, 19, 29, 48–50, 53, 59, 65, 68, 69	1137/1083	0.68	0.43, 1.06	0.09
Cerebrovascular accident	15, 48, 49, 53, 55, 59, 62, 65, 69	1033/972	0.59	0.30, 1.14	0.12
Acute pulmonary edema	48, 49, 69	670/582	0.77	0.42, 1.43	0.41
Arrhythmia	7, 10, 17, 29, 30, 48–50, 53, 55, 59, 62, 69	1163/1083	0.59	0.42, 0.81	0.001*
Renal failure	47–49, 54, 59, 69	1343/1244	0.74	0.51, 1.09	0.12
Respiratory complications	6, 7, 8, 10, 15, 20, 26, 28–30, 33, 34, 43, 48–50, 53, 56, 59, 62, 69	1462/1404	0.83	0.57, 1.19	0.31
Wound infection	15, 29, 53, 55, 56	191/222	1.43	0.59, 3.45	0.43
Reoperation	5, 10, 48–50, 63, 66, 67, 69	792/707	0.77	0.52, 1.16	0.21

* $P < 0.05$. When the odds ratio and the upper limit of its 95% confidence interval are smaller than the number 1, it means that epidural analgesia reduces the incidence of this specific complication. Conversely, if the odds ratio and the lower limit of its 95% confidence interval are higher than the number 1, it means that epidural analgesia increases the risk of this specific complication. If the number 1 is included in the 95% confidence interval, no significant effect could be demonstrated

Table 2. Benefits of adding epidural analgesia to general anesthesia: results from continuous data

Outcome	References	Number of patients with/without epidural analgesia	Odds ratio	95% confidence interval	*P* value
Time to tracheal extubation (h)	19, 20, 34, 36, 40, 48, 55, 65	340/279	–3.90	–6.37, –1.42	0.002*
Intensive care unit stay (h)	36, 48, 55, 69	202/124	–2.94	–5.66, –0.22	0.03*
Time to first bowel movement (h)	10, 26, 30, 33, 48, 66	300/209	–1.42	–10.80, 7.97	0.77
Hospital stay (days)	7, 8, 26, 34, 36, 43, 47, 48, 55, 61, 62, 66, 69	427/345	–0.11	–0.22, 0.01	0.06
Forced vital capacity at 24 h (l)	5, 7, 8, 16, 22, 25, 26, 28, 33, 50, 51, 55, 65, 67	358/353	0.23	0.09, 0.37	0.001*
Forced vital capacity at 24 h (in % of preoperative value)	23, 26, 36, 42, 43	82/88	1.90	–0.20, 4.00	0.08
Visual or verbal analogical pain score at rest at 24 h (0–10 cm)	4, 5, 7, 12, 20, 24–26, 33–36, 39, 40, 42, 49, 51, 54, 55, 57, 60–62, 70	1510/1604	–0.78	–0.99, –0.57	<0.00001*
Visual or verbal analogical pain score during movement or coughing at 24 h (0–10 cm)	4, 5, 7, 10, 25, 26, 34, 35, 40, 54, 55, 61	761/829	–1.28	–1.81, –0.75	<0.00001*
Maximal blood epinephrine value measured during the study ($pg \cdot ml^{-1}$)	2, 10, 12, 21, 22, 31, 32, 40, 45, 52, 57, 64, 71	175/214	–165.70	–252.18, –79.23	0.0002*
Maximal blood norepinephrine value measured during the study ($pg \cdot ml^{-1}$)	2, 10, 12, 21, 22, 31, 32, 40, 45, 52, 57, 64, 71	175/214	–134.24	–247.92, –20.57	0.02*
Maximal blood cortisol value measured during the study ($nmol \cdot l^{-1}$)	2, 9–14, 20, 21, 29, 31, 35, 37, 38, 40, 44, 45, 47, 51, 58, 63, 64, 70, 71	319/384	–55.81	–79.28, –32.34	<0.00001*
Maximal blood glucose value measured during the study ($nmol \cdot l^{-1}$)	3, 9, 11, 13, 29, 31, 35, 37–39, 44–46, 51, 58, 64	184/234	–0.87	–1.37, –0.37	0.0006*
Morphine consumption during the first 24 h (mg)	18, 20, 32, 35, 39, 49, 60, 62, 65, 66	677/694	–13.62	–22.70, –4.54	0.003*

* $P < 0.05$. When the odds ratio and the upper limit of its 95% confidence interval are smaller than the number 1, it means that epidural analgesia improves this specific parameter. Conversely, if the odds ratio and the lower limit of its 95% confidence interval are higher than the number 1, it means that the epidural analgesia deteriorates this specific parameter. If the number 1 is included in the 95% confidence interval, no significant effect could be demonstrated

P values for the difference between the groups would be 0.003 for epinephrine, 0.14 for norepinephrine, <0.00001 for cortisol, and <0.0001 for glucose.

Epidural analgesia clearly improves postoperative pain control, as demonstrated by reduced VAS scores both at rest (OR = –0.78; 95%CI = –0.99, –0.57, $P <$ 0.00001) and during movement or coughing (OR = –1.28; 95%CI = –1.81, –0.75, $P < 0.00001$) at 24 h postoperatively. This is in agreement with the studies of Block et al. [72] in mixed types of surgery, and the study of Liu et al. [73] in patients undergoing coronary artery bypass grafts. The reduced VAS scores during coughing might explain the better preservation of the FVC at the same time (24 h postoperatively) (OR = 0.231; 95%CI = 0.09, 0.37, $P = 0.001$). However, the amplitude of this effect was insufficient to induce a reduced rate of pulmonary complications (pneumonia or atelectasis requiring an intervention or reintubation) (OR = 0.83; 95%CI = 0.57, 1.19, $P = 0.31$). Nevertheless, it did allow faster tracheal extubation (OR = –3.90 h; 95%CI = –6.37, –1.42, $P =$ 0.002) and a shorter intensive care unit stay (OR = –2.94 h; 95%CI = –5.66, –0.22, $P = 0.03$). However, a reduced rate of pulmonary complications with epidural analgesia has been demonstrated by others in some specific types of surgery, for instance, by Liu et al. [73] in patients undergoing coronary artery bypass grafts (OR = 0.41; 95%CI = 0.27, 0.60, $P < 0.00001$).

Epidural analgesia also markedly reduced the stress response to surgery, as demonstrated by decreased maximal blood concentrations of epinephrine (OR = $-165.70\,pg{\cdot}ml^{-1}$; 95%CI = –258.18, –79.23, $P =$ 0.0002), norepinephrine (OR = $-134.24\,pg\cdot ml^{-1}$; 95%CI = –247.92, –20.57, $P = 0.02$), cortisol (OR = $-55.81\,nmol{\cdot}l^{-1}$; 95%CI = –79.28, –32.34, $P < 0.00001$), and glucose (OR = $-0.87\,nmol{\cdot}l^{-1}$; 95%CI = –1.37, –0.37, $P = 0.0006$). The reduced circulating catecholamines might explain the reduced incidence of arrhythmia (OR = 0.59; 95%CI = 0.42, 0.81, $P = 0.001$). However, this effect did not bring an overall reduced incidence of myocardial infarction (OR = 0.68; 95%CI = 0.43, 1.06, $P = 0.09$) in the present study. This finding is different from the conclusions of Beattie et al. [74], who were able to demonstrate a reduced rate of myocardial infarction in a mixed population (OR = 0.64; 95%CI = 0.42, 0.97, $P = 0.03$). It is notable, however, that the results of these two metaanalyses (the one from Beattie et al. and the present one) are not very different from each other. Indeed, the upper limit of the 95% confidence limits of Beatties's study was 0.97 (close to the number one, or at the limit to be considered significant), while the one from the present study is 1.06 with a *P* value of 0.09 (at the limit to become statistically significant). The effects of epidural analgesia on blood loss and on the number of patients who will require blood transfusions have not been evaluated in the present study, but a metaanalysis done on this specific topic demonstrates that epidural analgesia has a clear and definite impact on those two issues [75].

However, the risk/benefit ratio for each patient must be considered before choosing this specific mode of analgesia. Epidural analgesia carries definite risks (spinal hematoma, cauda equina syndrome, purulent meningitis, epidural abscess, traumatic cord lesion, cranial subdural hematoma, paraparesis, etc.), and these risks may vary according to sex and to the specific surgical population: epidural hematoma, 1:10300 (1:3600–1:200000); all complications, 1:3600 (1:1800–1:25000) [1].

In summary, this metaanalysis shows that epidural analgesia reduces the incidence of arrhythmia, the time to tracheal extubation, the intensive care unit stay, the decrease in forced vital capacity on postoperative day 1, the visual analogical pain scores at rest and during movement on postoperative day 1, the maximal epinephrine, norepinephrine, glucose, and cortisol blood concentrations, and the morphine consumption during the first 24 h.

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