Papers

Rates of caesarean section and instrumental vaginal delivery in nulliparous women after low concentration epidural infusions or opioid analgesia: systematic review

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Abstract

Objective To compare the effects of low concentration epidural infusions of bupivacaine with parenteral opioid analgesia on rates of caesarean section and instrumental vaginal delivery in nulliparous women.

Data sources Medline, Embase, the Cochrane controlled trials register, and handsearching of the *International Journal of Obstetric Anesthesia*.

Study selection Randomised controlled trials comparing low concentration epidural infusions with parenteral opioids. Data synthesis Seven trials fulfilled the inclusion criteria for meta-analysis. Epidural analgesia does not seem to be associated with an increased risk of caesarean section (odds ratio 1.03, 95% confidence interval 0.71 to 1.48) but may be associated with an increased risk of instrumental vaginal delivery (2.11, 0.95 to 4.65). Epidural analgesia was associated with a longer second stage of labour (weighted mean difference 15.2 minutes, 2.1 to 28.2 minutes). More women randomised to receive epidural analgesia had adequate pain relief, with fewer changing to parenteral opioids than vice versa (odds ratio 0.1, 0.05 to 0.22).

Conclusions Epidural analgesia using low concentration infusions of bupivacaine is unlikely to increase the risk of caesarean section but may increase the risk of instrumental vaginal delivery. Although women receiving epidural analgesia had a longer second stage of labour, they had better pain relief.

Introduction

It was not until the second half of the 20th century that effective analgesia for labour pain was introduced in the form of indwelling epidural catheters, providing continuous effective pain relief. Currently over half of parturient women in the United States and about a fifth in England and Wales receive epidural analgesia. $^{\!1}$ 2 The dose of anaesthetic can be adjusted for deliveries by forceps or caesarean, thus avoiding general anaesthesia.

Although regional anaesthesia has been associated with a reduction in anaesthesia related maternal mortality, there is continuing controversy over whether epidural analgesia impedes the progress of labour by causing dystocia and increasing operative delivery rates.³⁻⁵ Evidence is unclear as previous reviews have included disparate regimens for epidural analgesia and women of mixed parity.⁶⁻⁸

We focused on epidural infusions containing low concentrations of local anaesthetic as these are associated with a lower risk of operative delivery. To overcome the confounding effect of parity, we selected nulliparous women, who have a higher risk of dystocia. We assessed all operative deliveries (caesarean section, forceps, vacuum assisted) because limiting analysis to caesarean section would disguise the impact of epidural analgesia on mode of delivery.

Methods

We searched Medline, Embase, and the Cochrane controlled trials register for all relevant clinical reports published before June 2003 using thesaurus and MeSH terms for epidural analgesia, labour, forceps, vacuum assisted delivery, caesarean section, and instrumental delivery. Titles and abstracts of references were reviewed online. The contents of the *International Journal of Obstetric Anesthesia* were hand searched. Relevant studies were those where abstracts described women treated with epidural analgesia and mode of delivery. We searched the bibliographies of these studies for other reports.

Selection and validity assessment

We identified potentially relevant randomised controlled trials, excluding retrospective studies. Trials were selected for evaluation that specifically addressed whether epidural analgesia affected the risk of instrumental delivery. We then selected trials in which epidural infusions of low concentration local anaesthetic were compared with parenteral opioids and where the epidural infusions were continued during the second stage of labour. Trials using high concentration boluses of anaesthetic instead of infusions were excluded.

Trial validity was assessed using the Scottish Intercollegiate Guideline Network checklist.¹⁰ Criteria included randomisation, allocation concealment, blinding, similarity of groups at the start of the study, equal treatment of groups, measurement of outcomes, losses to follow up, and intention to treat analysis. The authors independently assessed and scored each article. Trials for data abstraction were selected only when all or most of the criteria for validity had been fulfilled, and when those not fulfilled were unlikely to alter the conclusions.

Data abstraction and synthesis and study characteristics

The authors independently abstracted data in duplicate and cross checked for transcription errors and discrepancies. Trials included for meta-analysis used low concentrations of bupivacaine ($\leq 0.125\%$) in continuous epidural infusions during the first two stages of labour in nulliparous women. All the trials had outcomes for caesarean section and instrumental vaginal delivery.

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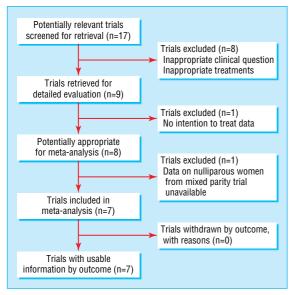


Fig 1 Flow of randomised controlled trials in meta-analysis

Results of the trials were combined using the Comprehensive Meta-Analysis Program (Biostat, Englewood, NJ, USA). We used odds ratios and 95% confidence intervals for categorical outcomes and weighted mean differences for continuous outcomes. Random effects models were used for all analyses, and heterogeneity was assessed. Sensitivity analyses were carried out if there was heterogeneity in the outcome measures.

Results

Our search identified 17 potentially relevant randomised controlled trials (fig 1 and table 1). Two trials assessed whether continuing epidural analgesia in the second stage of labour influenced the mode of delivery, and these compared local anaesthetic with saline epidural infusions during the second stage of labour. One trial compared starting epidural analgesia early in labour with starting it late. As these three trials addressed different questions and had no parenteral opioid comparator, we excluded them from the meta-analysis. We also excluded four trials using high concentration bupivacaine boluses (0.375% and 0.5% high concentration bupivacaine 0.25% boluses.

One trial with women of mixed parity did not provide intention to treat data. ¹⁹ The remaining eight trials fulfilled the criteria for inclusion in the meta-analysis. ²⁰⁻²⁷ Two of these were trials with women of mixed parity. ²⁰⁻²¹ After contacting the authors, we were able to obtain data on overall caesarean section rate for only one of these trials. ²⁰

All seven included trials had adequate allocation concealment. Treatment groups were similar at the start of the trials and seemed to have been treated equally. Intention to treat analyses were performed, and there were no losses to follow up. In none of the trials were the patients or investigators blinded.

These seven trials used low concentration bupivacaine infusions (0.125% or 0.0625%) but varied in the addition of opioids (table 2). They included women only with full term uncomplicated pregnancies with cephalic presentation. One trial included patients in both spontaneous and induced labour, with separate data for those in spontaneous labour. 27

Table 1 Randomised controlled trials comparing risk of instrumental vaginal delivery associated with epidural analgesia or parenteral opioids

Trial; country	Scottish Intercollegiate Guideline Network score*	Comments
Bofill et al, 1997 ²³ ; United States	+, not blinded	Nulliparous women; included in meta-analysis
Chestnut et al, 1987 ¹¹ ; United States	NA	Nulliparous women; excluded, as study compared 0.75% lignocaine with saline epidural infusions during second stage labour
Chestnut et al 1987 ¹² , United States	NA	Nulliparous women; excluded, as study compared 0.125% bupivacaine with saline epidural infusions during second stage labour
Chestnut et al, 1994 ¹³ ; United States	NA	Nulliparous women; excluded as study compared early with late institution of bupivacaine epidural analgesia
Clark et al, 1998 ²⁴ ; United States	+, not blinded	Nulliparous women; included in meta-analysis
Dickinson et al, 2002 ²⁷ ; Australia	+, not blinded	Nulliparous women; included in meta-analysis, separate data available for women with spontaneous and induced labour
Gambling et al, 1998 ²¹ ; United States	+, not blinded	Mixed parity women; nulliparous data not available
Howell et al, 2001 ¹⁸ ; United Kingdom	NA	Nulliparous women; excluded as study used bupivacaine 0.25% boluses
Loughnan et al, 2000 ²⁵ ; United Kingdom	+, not blinded	Nulliparous women; included in meta-analysis
Nikkola et al, 1997 ¹⁷ ; Finland	NA	Nulliparous women; excluded as study used bupivacaine 0.5% boluses, which were stopped in second stage labour
Noble et al, 1971 ¹⁶ ; United Kingdom	NA	Mixed parity women; excluded as study used bupivacaine 0.5% boluses
Philipsen and Jensen, 1989 ¹⁴ ; Denmark	NA	Mixed parity women; excluded as study used bupivacaine 0.375% boluses
Ramin et al, 1995 ¹⁹ ; United States	-, not blinded, no intention to treat data	Mixed parity women; nulliparous data not available
Robinson et al, 1980 ¹⁵ ; United Kingdom	NA	Mixed parity women; excluded as study used bupivacaine 0.5% boluses
Sharma et al, 1997 ²⁰ ; United States	+, not blinded	Mixed parity women; data or nulliparous women available only for caesarean section meta-analysis
Sharma et al, 2002 ²⁶ ; United States	+, not blinded	Nulliparous women; included in meta-analysis
Thorp et al, 1993 ²² ; United States	+, not blinded	Nulliparous women; included in meta-analysis

NA=not assessed

Quantitative data analysis

Caesarean section

Data were analysed for 2962 nulliparous women (table 3).²⁰ ²²⁻²⁷ We found no statistically significant difference in the rates of caesarean section between women receiving epidural analgesia and those receiving parenteral opioids (odds ratio 1.03, 95% confidence interval 0.71 to 1.48; fig 2). One trial showed a greatly increased risk of caesarean section with epidural analgesia.²² This small trial caused heterogeneity in the meta-analysis; when we excluded it from sensitivity analysis, the risk was slightly changed (1.01, 0.80 to 1.28) and there was no heterogeneity. Separate analyses of caesarean section rates for dystocia and for fetal distress also showed no significant differences (1.00, 0.64 to 1.58)

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^{*}Positive and minus signs indicate how well study minimised bias.

Table 2 Details of included trials of women receiving epidural infusions of low concentration local anaesthetic or parenteral opioids

	Protocol		Criteria for operative	Analgesia protocol		
Trial	Labour	Oxytocin	intervention	Epidural	Parenteral opioids	Crossover rate
Bofill et al, 1997 ²³	Spontaneous labour; active management of labour; early amniotomy and hourly pelvic examinations	6 mU/min, increased by 6 mU every 30 minutes up to maximum 42 mU/min if cervical dilation <1 cm/h	Decision for caesarean section made after consulting perinatologist blinded to treatment allocation; elective forceps delivery allowed	Induction: epidural 3 ml 1.5% lignocaine with 1:200 000 adrenaline and 3-5 ml 0.25% bupivacaine with or without 50-100 µg fentanyl; maintenance: infusion 0.125% bupivacaine and1.5 µg/ml fentanyl to maintain T10 level	Intravenous 1 or 2 mg butorphanol as required	0/49 in epidural group; 12/51 in opioid group
Clark et al, 1998 ²⁴	Spontaneous labour; intrauterine pressure catheter and fetal scalp electrode placed at amniotomy	6 mU/min, increased by 6 mU every 15 minutes until seven contractions in 15 minutes or until cervix dilation >1 cm/h	Criteria for caesarean section defined; elective forceps delivery allowed	Induction: epidural 3 ml 1% lignocaine and adrenaline, then 9 ml 0.25% bupivacaine with 50 µg fentanyl; maintenance: infusion 0.125% bupivacaine and 1 µg/ml fentanyl at 12 ml/h to achieve T10 block	Intravenous pethidine 50-75 mg as required every 90 minutes	5/156 in epidural group; 84/162 in opioid group
Dickinson et al, 2002 ²⁷	Spontaneous and induced labour; electronic fetal heart and intrauterine pressure transducers not routinely used; dystocia defined as failure of progress of cervical dilation in 2-4 hours	2 mU/min if cervix dilation <1 cm/h, increased by 2 mU/min at 30 minute intervals to maximum 36 mU/min	Not specified	Induction: combined spinal 25 µg fentanyl and bupivacaine 2 mg with epidural 0.125% bupivacaine 6 ml; or epidural 0.125% bupivacaine 10 ml and fentanyl 5 µg/ml; maintenance: patient controlled epidural analgesia 0.1% bupivacaine and fentanyl 2 µg/ml, 4 ml bolus, 15 minute lockout	Intramuscular pethidine 1.5 mg/kg	137/493 epidural group; 306/499 opioid group
Loughnan et al, 2000 ²⁵	Spontaneous and induced labour; active management; written protocol; pelvic examinations every two hours; all women given nitrous oxide for pain relief	4 mU/min, increased every 15 minutes up to maximum of 40 mU/min if cervix dilation <1 cm/h	Not specified	Induction: epidural 0.125% bupivacaine 10-15 ml; maintenance infusion: 0.125% bupivacaine at 10-15 ml/h	Intramuscular pethidine 100 mg every two hours up to 300 mg	44/304 in epidural group; 175/310 in opioid group
Sharma et al, 1997 ²⁰	Mixed parity; spontaneous labour; written protocol; cervical examinations every two hours; continuous internal monitoring for high risk cases; intrauterine pressure monitoring before starting oxytocin	6 mU/min if cervix dilation <1 cm/h, increased by 6 mU/min every 40 minutes up to 42 mU/min	Criteria defined for inadequate progress, low forceps if inadequate voluntary pushing or fetal heart rate abnormalities	Induction: epidural 0.25% bupivacaine in 3 ml increments until T10 block; maintenance: infusion 0.125% bupivacaine and fentanyl 2 µg/ml at 8-10 ml/h	Intravenous bolus pethidine 50mg and promethazine 25 mg, then patient controlled pethidine 10 mg every 10 minutes in first hour, then 15 mg every 10 minutes, additional 25 mg boluses on request	8/358 epidural group; 5/357 opioid group
Sharma et al, 2002 ²⁶	Spontaneous labour; written protocol; cervical examinations every two hours; continuous internal monitoring for high risk cases; intrauterine pressure monitoring before starting oxytocin	6 mU/min if cervix dilation <1 cm/h, increased by 6 mU/min every 40 minutes up to 42 mU/min	Criteria defined for inadequate progress, low forceps if inadequate voluntary pushing or fetal heart rate abnormalities	Induction: epidural 3 ml 1.5% lignocaine and 0.25% bupivacaine in 3 ml increments until T10 block; maintenance: infusion 0.0625% bupivacaine and fentanyl 2 µg/ml at 6 ml/h, and patient controlled epidural analgesia 5 ml bolus, 15 minute lockout	Intravenous bolus pethidine 50 mg and promethazine 25 mg, then patient controlled pethidine 15 mg every 10 minutes up to maximum 100 mg in two hours	0/226 epidural group; 14/233 opioid group
Thorp et al, 1993 ²²	Spontaneous labour; electronic fetal monitoring in all patients; fetal distress diagnosed from abnormal tracing or scalp pH; internal uterine pressure monitoring undertaken	1 mU/min, increased by 1 mU/min every 30-45 minutes	Criteria defined, caesarean for fetal distress if abnormal scalp pH or ominous heart rate tracing, caesarean for dystocia if arrest of cervical dilation in 1st stage of labour or arrest of descent in 2nd stage	Induction: epidural 0.25% bupivacaine bolus; maintenance: infusion 0.125% bupivacaine to maintain T10 block	Intravenous pethidine 75 mg and promethazine 25 mg every 90 minutes as required	0/48 in epidural group; 1/45 in opioid group

and 1.15, 0.79 to 1.67, respectively). Analysis including only women in spontaneous labour also showed no significant difference (1.08, 0.65 to 1.82).

Other maternal outcomes

We found a statistically significant increase in rates of instrumental vaginal delivery with epidural analgesia (1.63, 1.12 to 2.37). However, two trials included elective forceps delivery and forceps deliveries for training purposes, ²³ ²⁴ and two other trials included women who had their labour induced. ²⁵ ²⁷ When we excluded data for women who had labour induced and those who had elective forceps delivery, the risk was higher but not significant (2.11, 0.96 to 4.65; fig 3). Total operative delivery was higher with

epidural analgesia (1.63, 1.09 to 2.42). This risk was slightly reduced when we excluded the two trials with elective forceps deliveries and forceps deliveries for training purposes (1.55, 1.03 to 2.32). Epidural analgesia was associated with a longer second stage of labour (weighted mean difference 15.2 minutes, 2.1 to 28.2 minutes). Non-compliance with allocated analgesia was much less with epidural analgesia (0.19, 0.11 to 0.33). Fewer women changed from the epidural group to the opioid group than vice versa (0.10, 0.05 to 0.22).

Neonatal outcomes

Fewer neonates in the epidural groups had Apgar scores of less than 7 at five minutes and umbilical artery pHs of less than 7.2,

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Table 3 Outcomes of trials of women receiving epidural infusions of low concentration local anaesthetic or parenteral opioids

		No (total No) in epidural	No (total No) in opioid		
Outcome	References of trials	group	group	Odds ratio (95% CI)	% rate difference (95% CI)
Caesarean section:					
Overall	20; 22-27	178/1473	168/1489	1.03 (0.71 to 1.48)	1.18 (-2.66 to 5.01)
Excluding Thorp 1993	20; 23-27	166/1425	167/1444	1.01 (0.80 to 1.28)	-0.29 (-2.49 to 1.90)
Dystocia	22-27	102/1276	99/1300	1.00 (0.64 to 1.58)	0.42 (-2.91 to 3.74)
Fetal distress	22-27	64/1276	55/1300	1.15 (0.79 to 1.67)	0.59 (-0.79 to 1.97)
Patients in spontaneous labour	22-24; 26; 27	87/942	82/954	1.08 (0.65 to 1.82)	1.65 (-2.99 to 6.29)
Instrumental vaginal delivery:					
Overall	22-27	355/1276	289/1300	1.63 (1.12 to 2.37)	6.19 (2.46 to 9.91)
Excluding elective forceps	22; 25-27	292/1071	241/1087	1.56 (0.99 to 2.46)	6.16 (3.00 to 9.33)
Excluding elective forceps and induced labour	22; 26; 27	132/540	92/552	2.11 (0.95 to 4.65)	8.14 (4.25 to 12.03)
Total operative delivery:					
Caesarean section, forceps, and vacuum assisted deliveries	22-27	524/1276	446/1300	1.63 (1.09 to 2.42)	9.70 (2.40 to 17.00)
Excluding elective forceps	22; 25-27	441/1071	373/1087	1.55 (1.03 to 2.32)	8.57 (1.48 to 15.65)
Mean duration of second stage (minutes)	22-24; 26	64.5	49.3	15.2* (2.1 to 28.2)	_
Non-compliance with treatment allocation	22-27	221/1276	607/1300	0.19 (0.11 to 0.33)	-23.73 (-41.40 to -6.03)
Cross over to other treatment	22-27	186/1276	592/1300	0.10 (0.05 to 0.22)	-25.83 (-46.65 to -5.01)
Oxytocin:					
Required after analgesia	22; 26	121/274	87/278	1.75 (1.23 to 2.48)	13.19 (5.22 to 21.16)
Use overall	22-24; 26; 27	467/783	424/799	1.35 (0.88 to 2.07)	6.72 (-2.72 to 16.17)
Neonate details:					
Apgar score <7 at 5 minutes	22; 24; 26; 27	13/923	17/939	0.72 (0.26 to 2.04)	-0.55 (-2.21 to 1.12)
Umbilical artery pH <7.2	22; 24; 26	23/423	31/418	0.72 (0.40 to 1.27)	-2.45 (-5.51 to 0.61)
Required naloxone	23; 26	0/275	14/284	0.10 (0.01 to 0.89)	-4.38 (-7.77 to -0.99)

Mantel-Haenszel random effects models used in all analyses.

but these differences were not statistically significant (0.72, 0.26 to 2.04 and 0.72, 0.40 to 1.27, respectively). Although only two trials provided data on requirement of nalaxone by neonates, it was lower in neonates whose mothers had had epidural analgesia (0.1, 0.01 to 0.89).

Discussion

Nulliparous women who receive epidural analgesia during labour do not seem to be at an increased risk of delivery by caesarean section; the wide confidence intervals introduce some uncertainty. Epidural analgesia may be associated with a higher risk of instrumental vaginal delivery. Although epidural analgesia was associated with a longer second stage of labour, neonates seemed unharmed. We found no worsening of Apgar

scores or umbilical acid-base status in neonates whose mothers had received epidural analgesia, despite the increased risk of instrumental vaginal delivery. These neonates were also less likely to need naloxone than neonates whose mothers received opioid analgesia.

One limitation of these trials is the disparity in the quality of pain relief between epidural analgesia and parenteral opioids, which would have made blinding of clinicians difficult. Bias may have been present owing to a lower threshold for performing instrumental vaginal delivery in the presence of epidural analgesia. Two trials did not have strict indications for instrumental vaginal delivery. These permitted elective forceps delivery or assisted vaginal delivery for training purposes and had to be excluded from analysis of risk of instrumental vaginal delivery.²³ ²⁴ Even then there was a clinically important increase

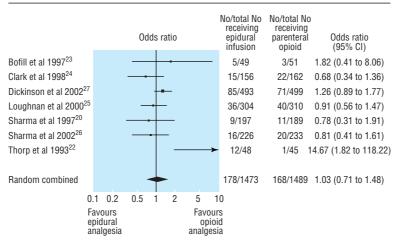


Fig 2 Rates of caesarean section in trials of nulliparous women receiving epidural analgesia or parenteral opioids

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^{*}Weighted mean difference.

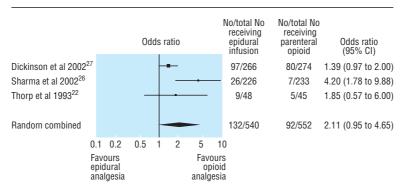


Fig 3 Rates of instrumental vaginal delivery and odds ratios in trials of nulliparous women receiving epidural analgesia or parenteral opioids; trials were excluded when elective forceps were permitted or where labour was induced

in risk. Differences in protocols for management of labour could have contributed to the differences in rates of instrumental vaginal delivery.

Another limitation was the large number of women who changed to epidural analgesia despite being randomised to parenteral opioids. Our intention to treat approach would likely render any estimation of the effects of epidural analgesia more conservative, but it was necessary to prevent selection bias. Comparing a policy of offering epidural analgesia with one of offering parenteral opioids reflects real life. In contrast, analysing data from participants who are compliant with allocation would bias the epidural group to have mainly patients with more severe pain and presumably more complicated labour, whereas the opposite would be the case for the opioid group.

As the definitions of stages of labour varied between trials, we were unable to determine if epidural analgesia prolonged the first stage, and the actual duration can only be estimated.

Unlike previous reviews, we focused on nulliparous women because the indications for, and risks of, caesarean section differ with parity. The major indication in nulliparous women is dystocia, whereas in multiparous women it is previous caesarean section.²⁷ Our analysis does not support an association between epidural analgesia and an increased risk of caesarean delivery for dystocia. But the analysis does support an association with an increased risk of instrumental vaginal delivery, which can cause maternal dissatisfaction and trauma and fetal trauma and can have a substantial impact on workload and safety.

We limited our analysis to trials that used infusions of bupivacaine with concentrations of 0.125% or less, to reflect current practice. In a randomised controlled trial, low concentrations have been shown to reduce the rate of instrumental delivery.9

Epidural analgesia may increase the risk of instrumental delivery by several mechanisms. Reduction of serum oxytocin levels can result in a weakening of uterine activity.²⁸ ²⁹ This may be due in part to intravenous fluid infusions being given before epidural analgesia, reducing oxytocin secretion.³⁰ The increased use of oxytocin after starting epidural analgesia may indicate attempts at speeding up labour. Maternal efforts at expulsion can also be impaired, causing fetal malposition during descent.³¹ Previously, the association of neonatal morbidity and mortality with longer labour (second stage longer than two hours) had justified expediting delivery, leading to increased rates of instrumental delivery.35

Delaying maternal pushing until the fetus's head is visible or until one hour after reaching full cervical dilation may reduce the incidence of instrumental delivery and its attendant morbidity.³² Although patients receiving epidural analgesia had a longer second stage labour, this was not associated with poorer neonatal outcome in our analysis. With increasing use of continuous electronic fetal monitoring, a longer but more comfortable labour may cause little harm to the neonate.

It is doubtful whether epidural analgesia with low concentration bupivacaine increases the risk of caesarean section or harms neonates. Fears about an increased risk of caesarean section should not be used to discourage epidural analgesia in nulliparous women if requested.

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Contributors: EL conceptualised the review. EL and AS independently searched for, collated, assessed, and analysed the data, and cowrote the paper. EL will act as guarantor for the paper.

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Ethical approval: Not required.

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What is already known on this topic

Epidural analgesia during labour is effective but has been associated with increased rates of instrumental delivery

Studies have included women of mixed parity and high concentrations of epidural anaesthetic

What this study adds

Epidural infusions with low concentration local anaesthetics are unlikely to increase the risk of caesarean section in nulliparous women

Although epidural analgesia is associated with an increased risk of instrumental vaginal delivery, operator bias cannot

Epidural analgesia is associated with a longer second stage labour and increased oxytocin requirement, but the importance of these is unclear as maternal analgesia and neonatal outcome may be better with epidural analgesia

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