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Dural Puncture Epidural: to puncture or not to puncture?

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Abstract: *Objective:* The aim of this systematic review is to compare the evidence derived from randomised controlled trials (RCT) regarding the use of dural puncture epidural (DPE) versus conventional epidural analgesia (EA) or combined spinal epidural analgesia (CSE) for labouring patients.
Background: DPE is a modification of the conventional epidural technique which implicates the intended puncture of the dura mater with a spinal needle but without administering drugs intrathecally. The potential benefits and risks of this technique remain debated.
Methods: A systematic literature search, retrieved from PubMed, Cochrane Library, Science direct and Web of Science, was performed to identify RCT comparing DPE with epidural or CSE analgesia.
Results: Seven RCTs were identified for final analysis. Their collective results showed no significant difference in quality of analgesia, catheter reliability and adverse outcomes.
Conclusion: Although a trend towards better analgesic outcome and a more favourable risk- benefit profile was observed, the significance of current evidence regarding DPE in labouring patients remains unclear. Further research is warranted and should focus on elucidating the optimal spinal needle size as well as the elements governing the flux of drugs over the meninges in the presence of a dural hole.

Keywords: Dural puncture; epidural; labour; analgesia.

Introduction

Childbirth can be a very painful experience for which women often request analgesic support (1, 2). A Cochrane review showed that neuraxial analgesia is effective in diminishing pain during labour (3). Various methods are available for the initiation and maintenance of neuraxial labour analgesia. Currently, epidural analgesia (EA) and combined spinal-epidural analgesia (CSE) are the most frequently used methods to initiate analgesia (3-6). In both techniques the epidural space is identified using a loss of resistance technique. In EA, a catheter is inserted epidurally and the dura is not punctured. Initiation and maintenance of analgesia is achieved through the epidural catheter. In CSE, after identification of the epidural space, a spinal needle is inserted through the dura and an initial spinal dose produces rapid onset analgesia. After removal of the spinal needle, a catheter is left in the epidural space, allowing prolonged labour analgesia (4-7). Both EA and CSE have side-effects such as pruritus, nausea and vomiting and motor block. A side effect of more concern in both techniques is uterine hypertonus leading to non-reassuring foetal heart rate tracings (2, 5, 6, 8). Additionally, the use of intrathecal drugs in the CSE technique makes it difficult to exclude unintended subarachnoid placement of the epidural catheter by obscuring the response to an epidural test dose (9, 10).

Dural puncture epidural analgesia (DPE) has been proposed as a modification of the current neuraxial initiation technique and aims to retain the advantages of a CSE while reducing its side effects. DPE involves creating a dural hole with a spinal needle, inserted through the epidural needle, but without intrathecal injection of drugs. Analgesic drugs are only given through the catheter in the epidural space, and the dural hole allows intrathecal migration of some of the epidural drugs. This could result in a faster onset of analgesia and a better sacral spread when comparing DPE to EA and in a lower incidence of side effects (such as hypotension and pruritus) in comparison to CSE (11-13). Moreover, as in the CSE technique, the

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DPE technique allows to verify the correct, midline position of the epidural needle in the epidural space: the flow of cerebrospinal fluid through the spinal needle is a clear endpoint that reflects correct (midline) positioning of the spinal needle as well as the epidural needle. This proof of correct positioning will lead to a higher reliability of the catheter with a lower rate of unilateral blockade or failed epidural analgesia (7, 12). Furthermore, by avoiding administration of intrathecal medication, testing of the epidural catheter for mispositioning remains possible (14).

The objective of this systematic review is to identify all relevant randomized controlled trials investigating DPE in obstetric patients and to analyse the data for potential benefits and side-effects of this technique as compared to EA or CSE.

Methods

Our systematic search was performed on December 8th 2020. Several databases (PubMed, Cochrane Library, Science direct and Web of Science) were screened from 1960 to December 8th 2020 in order to identify trials comparing DPE with EA or CSE in the English or Dutch language. Dural puncture epidural does not exist as a MESH term, therefore it was queried as keywords. The following search strategy was used: "[(Dural Puncture Epidural) or (Analgesia, Epidural) or (Analgesia, Obstetrical) or (Analgesics) or (Injections, Epidural) or (Spinal Puncture) and (Labour Pain) or (Pregnancy)]". Full details are provided in the supplemental content. Reference lists of the retrieved articles were also scanned to identify additional studies. Reporting was according to PRISMA guidelines (15). No protocol was registered for this study. The identified studies were entered into EndNote. Duplicates were removed and then studies were screened and evaluated for eligibility based on title, abstract and full manuscript. Inclusion and exclusion criteria were defined a priori by using the PICO acronym. Patients: Female, receiving analgesia for labour, primi- or multiparous; Intervention: dural puncture epidural analgesia; Comparator: conventional epidural technique or combined spinal epidural analgesia; Outcome: onset time of analgesia, quality of pain relief, epidural catheter reliability, complications, progress of labour and fetal heart rate changes. These outcomes are not universally defined. Therefore, the definitions reported by the authors were used. Exclusion criteria were: patient age < 18 years, non-randomized studies, language other than English or Dutch.

Data extraction was carried out and included the year of publication, the method of randomization, the study's sample size, the presence of blinded assessment, the definition of the primary outcome, sample size justification and trial registration. The validity of each trial was further assessed by use of the Cochrane Risk of Bias tool (16). Each domain in the tool is categorized as green (low risk of bias), yellow (some concern) or red (high risk of bias) (16).

To perform a meta-analysis, continuous and binary variables were extracted. If a randomized controlled trial reported a zero which caused problems with computation of the risk ratio (RR), 1 was added to each arm to calculate a relative risk (17). When only median and interquartile range were available, estimates were made of the mean and standard deviation by using the technique proposed by Hozo et al. (18). The computer program Review Manager was used. Due to clinical and methodological heterogeneity the random effects model was applied. Pooled RR, standardized mean difference (SMD) and 95% CI were computed. When the 95% CI includes 1, the estimate is considered non-significant in the case of RR. When SMD was used, the 95% CI is considered non-significant when it includes 0. To measure heterogeneity, the I^2 statistic was used. This measurement checks the percentage of variation across studies that is caused by heterogeneity rather than by chance, I^2 values >50% were considered as indicative of significant heterogeneity. Values of $p < 0.05$ were viewed as statistically significant. Song et al. (13) had two DPE groups; both used a 25 gauge spinal needle but for maintenance of labour analgesia one group used a continuous epidural infusion(CEI) and the other used programmed intermittent epidural bolus(PIEB). The events and means of both DPE groups were combined according to the Cochrane Handbook[16] in order to perform an analysis between patients exposed to dural puncture and those who were not.

Results

Our systematic search yielded 2419 hits of which finally seven RCT (9, 11-14, 19, 20) were eligible for inclusion. The results of our search are shown in figure 1. As stated in the methods, validity of each trial was assessed by using the Cochrane Risk of Bias tool. These results can be seen in figures 2 and 3. These trials provided data of 797 obstetric patients and details of the studies are provided in table 1.

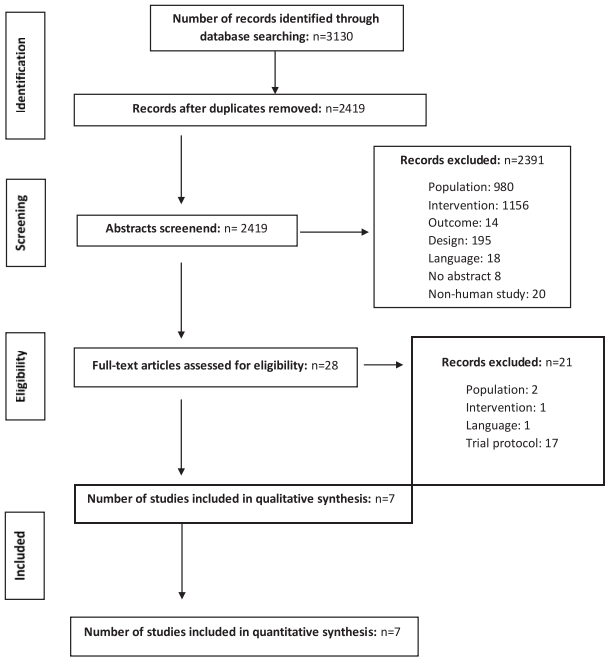

Fig. 1. — Flow chart of selection process for the systematic review.

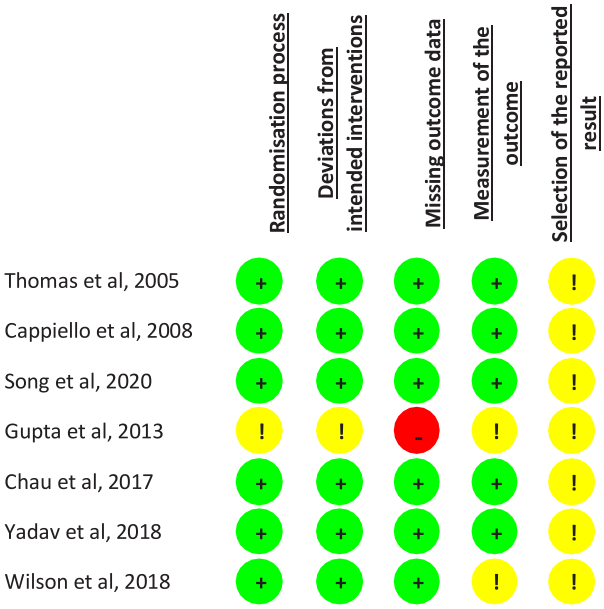

Fig. 2. — Risk of Bias assessment of included trials.

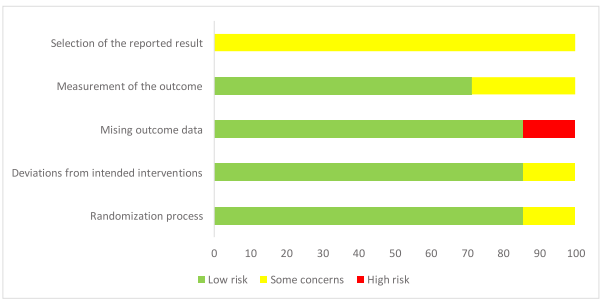

Fig. 3. — Risk of Bias graph.

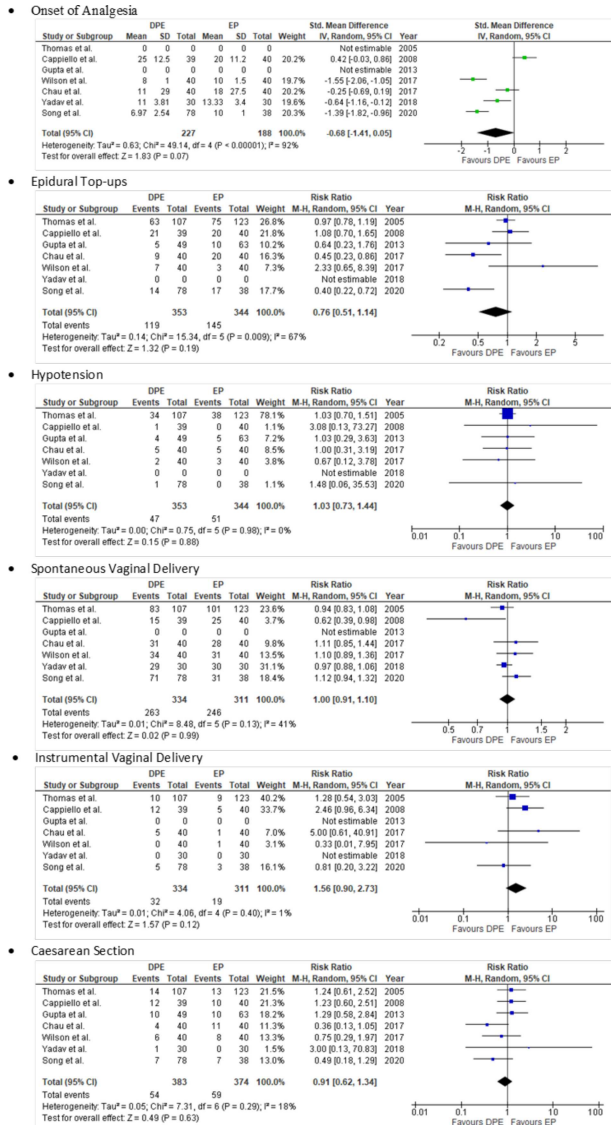

Fig. 4. — Outcomes of DPE vs EA eligible for meta-analysis.

A meta-analysis was not performed for all outcomes because for some outcomes the number of events was low whilst only a low number of studies reported on these outcomes. Additionally, different needle sizes are used for dural puncture, namely 25-, 26- and 27-gauge, which causes heterogeneity. This is discussed in more detail in the discussion section. Outcomes are shown in Figure 4 and Table 2.

Data on onset of analgesia were provided in 5 studies (11-13, 19, 20). The standardized mean difference was -0.68 (95%CI -1.41 to 0.05) with more rapid analgesia in the DPE group vs. EA; however, there was significant heterogeneity between studies ($I^2 = 92\%$, $p < 0.00001$).

Quality of analgesia, assessed by achieving a VAS score at a certain time, was reported by 5 studies (11-13, 19, 20). Chau et al. (12) and Cappiello et al. (19), both using a 25-gauge spinal needle with

Table 1

Details of included studies

Study	N	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Study Group	Control Group/LA bolus/ LA Infusion	Results
Thomas et al. 2005[9]	230	Healthy labouring parturient with uncomplicated pregnancies and with cervical dilation <6cm	No data	Instances of catheter manipulation	Dural puncture with 27G Whitacre spinal needle	L3-4 or L4-5; 17G Weiss needle; 19G multiport catheter advanced 4-6cm. Initial bolus: 2 +5 +3ml Lidocaine 2% PCEA Bupivacaine 0,11%-Fentanyl 2µg/ml: 10ml/h + 5ml q 10min PRN.	No intergroup differences in rates of catheter manipulation: 28-37%; No intergroup differences in sacral sparing, unilateral block, peak block level, number of top-up doses, average hourly epidural drug consumption, quality of analgesia, duration of labour, rate of instrument-assisted vaginal delivery and incidence of CS.
Cappiello et al. 2008[19]	79	Nulliparous parturient with single-ton, vertex presentation foetuses at 38-42 weeks' gestation and in active labour with cervical dilation <5cm	Clinically significant diseases of pregnancy, contraindications to neuraxial analgesia, conditions associate with increased risk of a caesarean delivery and know fetal anomalies.	Presence of S1 blockade with VAS<10 within 20min after the block	Dural puncture with 25G Whitacre needle	Level not specified. 17G Weiss needle; 20G polyamide multiport catheter advanced 5cm. Initial bolus: 12ml Bupivacaine 0,25% PCEA: Bupivacaine 0,125%-Fentanyl 2µg/ml: 6ml/h + 6ml q 15min PRN.	DPE: more patients with pain <10 at 20min, more patients with S1 block at any time during study, lower rate of unilateral block, lower rate of spontaneous vaginal delivery. No intergroup differences in pain at 30min, S1 block at 20 min, S2 blockade, peak sensory block, motor block, catheter manipulation/replacement, fetal bradycardia, hypotension, PDPH and incidence of CS.
Gupta et al. 2013[14]	112	ASA 1-3 patients requesting labour epidural analgesia	ASA 4-5 patients, patients with history of back surgery or central nervous system disease and patients who refused dural puncture	Initial 2h after procedure incidence of failure of epidural analgesia	Dural puncture with a 25G Pencan needle	L2-3 or L3-4; 17G Tuohy needle. 19G catheter, advanced 5cm. Initial bolus: 2 x5ml Bupivacaine 0,125% - Fentanyl 102µg/ml. Infusion: 10ml/h Bupivacaine 0,125% - Fentanyl 2,5µg/ml	DPE: lower failure rate within first 2h but higher incidence of paresthesia. No intergroup differences in terms of intravascular placement of epidural catheter, LA consumption, ephedrine use for hypotension and patient satisfaction.
Wilson et al. 2018[11]	80	Parturient admitted to the labour and delivery unit planning to request neuraxial labour analgesia	Contraindication to neuraxial Anesthesia, non-English speaking, BMI> 50kg/m2, patient refusal and VAS score <50mm during an active contraction at the time of request for neuraxial analgesia	Percentage of patients with adequate analgesia (VAS ≤10) 10min after the block	Dural puncture with 26G Whitacre spinal needle	L3-4 or L4-5: 17G Tuohy needle; 19G catheter advanced 4-5cm. Initial bolus: 3x4ml Bupivacaine 0,125%- Fentanyl 50µg. PCEA: Bupivacaine 0,1%-Fentanyl 2µg/ml: 10ml/h + 5ml q 10 min PRN	No intergroup differences in percentages of patients with adequate analgesia in 10 min. No intergroup differences in degree of sensorimotor block, patient satisfaction, adverse events, rate of instrument-assisted vaginal delivery and incidence of CS. DPE shorter median times to adequate analgesia.

Yadav et al. 2018[20]	60	ASA 1-2 primigravida with uncomplicated pregnancy in vertex presentation. Active labour and requesting labour analgesia.	Hypersensitivity to study drugs, bleeding disorders, decreased platelet counts, local or systemic sepsis, blood/CSF in epidural catheter during procedure, history of drug abuse and refusal	VAS score at 5 min	Dural puncture with 27G Whitacre spinal needle	L3-4; 16G Tuohy needle; 18G multi-orifice catheter advanced 5cm. Initial bolus: 4x2,5ml Ropivacaine 0,2%-Fentanyl 2µg/ml. Additional 10ml top ups Ropivacaine 0,2%- Fentanyl 2µg/ml as requested by patient q 15min	DPE: lower VAS scores a 5 and 10min, quicker onset and better quality of analgesia. No intergroup differences in duration of LA bolus, duration of labour, time to first top up request, LA consumption and incidence of CS.
Song et al. 2020[13]	116	nulliparous women with singleton vertex presentation at 37-42 weeks' gestation and in active labour with cervical dilation <5cm, baseline pain score >50mm on a 100mm VAS at the time of epidural request.	age <20 or >40years, morbid obesity, pregnancy-related diseases, history of drug abuse, contraindications to neuraxial blocks, conditions associate with increased risk of caesarean delivery and know fetal abnormalities.	Time to adequate analgesia (VAS <30mm during 2 consecutive contractions within 30min)	Dural puncture with a 25G Whitacre needle. DPE + CEI and DPE + PIEB	L3-4 or L2-3. 17G Tuohy needle. 19G multi-orifice stainless steel impregnated epidural catheter. Initial bolus: 10ml 0,1% ropivacaine with 0,3µg/ml of sufentanil. PCEA: 5ml 0,1%ropivacaine with 0,3µg/ml sufentanil. CEI: 0,1% ropivacaine with 0,3µg/ml sufentanil at a constant rate of 8ml/h. PIEB: ropivacaine 0,1% witch 0,3µg/ml sufentanil, first bolus of 8ml q 60min	DPE +CEI and DPE + PIEB: VAS score significantly faster than those in EP + CEI. The median time until adequate analgesia was 6 min (DPE + PEIB), 8min (DPE + CEI) and 10min (EP+CEI). S2 sensory block at 30min more frequently observed in DPE patients. DPE + PIEB significantly lower PCEA count and fewer provider boluses. The hourly and total consumption of ropivacaine lowest in DPE + PIEB. Duration of labour, mode of delivery, Bromage score, Apgar scores, adverse effects and patient satisfaction did not significantly differ. No postpartum complications in any group.
Chau et al. 2017[12]	120	Healthy pregnant women with singleton, vertex presentation foetuses at 38-42 weeks' gestation in active labour with cervical dilatation <5cm and desiring epidural labour analgesia	diseases of pregnancy, contraindications to neuraxial analgesia techniques, known fetal anomalies or conditions associated with an increased risk of caesarean delivery.	Time to NPRS ≤1 on a 0-10 scale.	Dural puncture with a 25G Whitacre needle.	L2-3 or L3-4; 17G Weiss needle; 19G Flextip plus single open end catheter, advanced 5cm. Initial bolus: 4x5ml bolus of bupivacaine 0,125% - Fentanyl 2µg/ml. PCEA: Bupivacaine 0,125%-Fentanyl 2µg/ml: 6ml/h + 6ml q 15min PRN. CSE: bupivacaine 1,7mg-17µg Fentanyl in 1ml.	DPE vs EP: No intergroup differences in time to NPRS ≤1. No differences between peak sensory block, motor block, nausea, pruritus, hypotension, PDPH, rate of instrument assisted vaginal delivery and incidence of CSE. DPE had higher incidence of bilateral S2 block at 10min, 20 and 30min, lower incidence asymmetric block at 30min and fewer physician top-up bolus interventions. CSE vs DPE: DPE achieves NPRS≤1 significantly slower than CSE. DPE had significantly lower incidence of physician top-up bolus, hypotension, pruritus, post neuraxial placement combined uterine tachysystole and hypertonus and NICHD category I to II conversion in FHR tracing. No differences between peak sensory block, motor block or nausea.

CS= Caesarean section ; DPE=Dural Puncture Epidural, LA =Local Anesthetic, G=Gauge ; PCEA=Patient controlled epidural analgesia ; CEI= Continuous epidural infusion; PIEB=Programmed intermittent epidural bolus; NPRS=Numerical pain rating scale; VAS=Visual analog scale, PRN=Pro rate necessita; PDPH=post dural puncture headache.

Table 2

Outcomes

Outcome	Studies	DPE Group: Events/ Participants; Mean(±SD)	Control Group: Events/Participants; Mean(±SD)	RR (95%CI); Mean Difference (95%CI)
Patients' Satisfaction	Gupta[14] Intra procedure	8.08(±2.57)	8.10(±2.86)	0.02(-1.01 to 1.05)
	Gupta[14] Delayed	8.95(±1.96)	8.68(±2.74)	-0.27(-1.18 to 0.65)
	Yadav[20]	3.0(±0.00)	2.87(±0.35)	-0.13(-0.25 to -0.01)
	Song[13] ; DPE + CEI	92.5(±5)	90(±3.12)	-2.5(-4.39 to -0.61)
	Song[13] ; DPE + PIEB	97.5(±2)	90(±3.12)	-7.5(-8.7 to -6.30)
	Song[13] ; Combined CEI + PIEB	94.94(±4.57)	90(±3.12)	-4.94(-6.57 to -3.31)
Catheter Replacement Rate	Thomas[9]	10/107	10/123	1.15(0.50 to 2.66)
	Cappiello[19]	1/39	5/40	0.21(0.03 to 1.68)
	Chau[12] ; EA	0/40	0/40	Not estimable
	Chau[12] ; CSE	0/40	0/40	Not estimable
	Wilson[11]	0/40	0/40	Not estimable
Catheter Manipulation Rate	Thomas[9]	40/107	34/123	1,35(0,93 to 1,97)
	Cappiello[19]	5/39	11/40	0,47(0,18 to 1,22)
	Chau[12] ; Epidural	2/40	4/40	0,50(0,10 to 2,58)
	Chau[12] ; CSE	2/40	3/40	0,67(0,12 to 3,78)
Unilaterblock Rate	Thomas[9]	27/107	28/123	1.10(0.70 to 1.76)
	Cappiello[19]	3/39	10/40	0.31(0.09 to 1.03)
	Chau[12] ; EA	4/40	21/40	0.19(0.08 to 0.50)
	Chau[12] ; CSE	4/40	4/40	1(0.27 to 3.72)
Intravascular Placement Rate	Thomas[9]	11/107	7/123	1.81(0.73 to 4.49)
	Cappiello[19]	0/39	0/40	Not estimable
	Gupta[14]	5/49	2/63	3.21(0.65 to 15.87)
	Chau[12] ; EA	0/40	0/40	Not estimable
	Chau[12] ; CSE	0/40	0/40	Not estimable
Post-Dural Punctur Headache	Cappiello[19]	0/39	0/40	Not estimable
	Gupta[14] Early	0/49	1/63	0.43(0.02 to 10.25)
	Gupta[14] Delayed	4/49	2/63	2.57(0.49 tot 13.47)
	Chau[12] ; EA	0/40	0/40	Not estimable
	Chau[12] ; CSE	0/40	0/40	Not estimable
	Wilson[11]	0/40	1/40	0.33(0.01 to 7.95)
	Song[13] ; DPE + CEI	0/40	0/38	Not estimable
	Song[13] ; DPE + PIEB	0/38	0/38	Not estimable
	Song[13] ; Combined CEI + PIEB	0/78	0/38	Not estimable
Pruritus	Cappiello[19]	1/39	0/40	3.08(0.13 to 73.27)
	Chau[12] ; EA	4/40	4/40	1.00(0.27 to 3.72)
	Chau[12] ; CSE	4/40	27/40	0.15(0.06 to 0.38)
	Wilson[11] (48h)	1/40	5/40	0.20(0.02 to 1.64)
	Song[13] ; DPE + CEI	1/40	0/38	2.85(0.12 to 67.97)
	Song[13] ; DPE + PIEB	0/38	0/38	Not estimable
	Song[13] ; Combined CEI + PIEB	1/78	0/38	1.46(0.06 to 35.09)
Nausea	Cappiello[19]	0/39	2/40	4.88(0.24 to 98.47)
	Chau[12] ; EA	1/40	4/40	0.25(0.03 to 2.14)
	Chau[12] ; CSE	1/40	1/40	1.00(0.7 to 15.44)
	Song[13] ; DPE + CEI	1/40	2/38	0.47(0.04 to 5.03)
	Song[13] ; DPE + PIEB	0/38	2/38	Not estimable
	Song[13] ; Combined CEI + PIEB	1/78	2/38	0.24(0.02 to 2.60)
Presence of motor block	Chau[12] ; EA	6/40	15/40	0.40(0015 to 1.03)
	Chau[12] ; CSE	6/40	3/40	1.57(0.38 to 6.52)
	Wilson[11]	37/40	39/40	0.95(0.86 to 1.05)
	Song[13] ; DPE + CEI	0/40	1/38	0.32(0.01 to 7.55)
	Song[13] ; DPE + PIEB	0/38	1/38	0.33(0.01 to 7.93)
	Song[13] ; Combined CEI + PIEB	0/78	1/38	0.16(0.01 to 3.95)

Outcome	Studies	DPE Group: Events/ Participants; Mean(±SD)	Control Group: Events/Participants; Mean(±SD)	RR (95%CI); Mean Difference (95%CI)
Fetal Heart Rate Tracings	Cappiello[19]	0/39	0/40	Not estimable
	Chau[12] ; EA	18/40	17/40	1.06(0.64 to 1.74)
	Chau[12] ; CSE	18/40	21/40	0.86(0.55 to 1.35)
	Wilson[11]	0/40	3/40	0.14(0.01 to 2.68
	Song[13] ; DPE + CEI	0/40	0/38	Not estimable
	Song[13] ; DPE + PIEB	0/38	0/38	Not estimable
	Song[13] ; Combined CEI + PIEB	0/78	038	Not estimable

DPE=Dural Puncture Epidural, CSE=Combined Spinal and Epidural; EA: Epidural analgesia CEI= Continuous epidural infusion; PIEB=Programmed intermittent epidural bolus

comparable local anesthetic boluses and infusion, had a RR respectively of 1.07 (95% CI 0.84 to 1.36) and 1.31(95% CI 1.00 to 1.69) for achieving a NPRS≤1 at 20 min or VAS <10mm at 20min in the DPE group compared to EA. However, Wilson et al. (11), showed no difference in the number of women having a VAS <10mm at 10min (P=0.256, RR 1.31, 95%CI 1.00 to 1.69). In the study by Yadav et al. (20) lower VAS score were seen at 5 and 10 min with DPE compared to an EA group (P≤0008). Song et al. (13) showed lower VAS scores at 20min and at 120min in the pooled results (P=0.01, P=0.03) and in the DPE with PIEB at 120min (P= 0.03). Six trials reported data on the number of epidural top-ups (9, 11-14, 19): the RR was 0.76 (95%CI 0.51 to 1.14) compared with EA and showed a reduced number of epidural top-ups in the DPE group. However, the data were highly heterogenic (I^2 67%, P= 0.009). Only 3 studies (13, 14, 20) looked at satisfaction score of analgesia. Gupta et al. (14) and Song et al. (13) found no significant difference in patient satisfaction between the DPE and EA groups, while Yadav et al. (20) did observe improved patient satisfaction in the DPE compared to the EA group. Similarly, when comparing the DPE groups individually with the EA group, Song et al. (13) did find a difference in patient satisfaction in favour of DPE.

Four studies (9, 11, 12, 19) investigated catheter replacement rate. In two studies by Thomas et al. (9) and Cappiello et al. (19) events of replacement were reported. However, no statistically significant differences were noted. Similarly, four studies (9, 12, 14, 19) assessed intravascular placement rate of the epidural catheter. Gupta et al. (14) and Thomas et al. (9) reported unintended intravascular catheters but the difference was not statistically significant. Unilateral block and catheter manipulation rates, were assessed by three studies (9, 12, 19), and no significant difference was identified.

Data on hypotension were provided by six studies (9, 11-14, 19). The RR for hypotension after DPE vs. EA was 1.03 (95%CI 0.73 to 1.44). For data on PDPH, 5 studies (11-14, 19) reported data but only two (11, 14) described events of PDPH. The 95%CI were wide and no significant difference was found. Similar results were found for nausea and pruritus with the reported number of events being low when comparing DPE with EA (11-13, 19).The presence of motor block was assessed by three trials (11-13). None showed any significant difference between the groups.

Spontaneous and instrumental vaginal delivery as well as caesarean section did not differ between DPE and EA. Respectively, the RR were 1.00 (95%CI 0.91 to 1.10), 1.56 (95%CI 0.90 to 2.73) and 0.91 (95% CI 0.62 to 1.34). Fetal heart rate tracings were studied in four studies (11-13, 19). Adverse tracings were very low or absent in these trial with no significant difference between interventions.

Chau et al. (12) was the only RCT to compare DPE with CSE. They observed that the onset of analgesia in DPE was significantly slower compared to CSE (hazard ratio 0.36, 95% CI 0.22 to 0.59, P=0.0001). However, DPE showed a significantly lower rate of epidural top-ups (RR 0.45;95%CI 0.23 to 0.86), hypotension (RR 0.38; 95%CI 0.15 to 0.98), pruritis (RR 0.15;95%CI 0.08 to 0.60) and post neuraxial placement combined uterine tachysystole and hypertonus (RR 0.22;95%CI 0.08 to 0.60) without any significant difference in fetal heart rate tracings or labour outcome.

Discussion

Our study identified seven studies investigating DPE as compared to EA in women in labour of which, one study compared DPE, EA and CSE. The collective results of these trials on labour analgesia remain inconclusive. We did find a trend for faster

onset of analgesia and a lower need for epidural top-ups when compared to EA. However, both results were not statistically different and showed great between-study heterogeneity. All other investigated outcomes were similar between the groups.

A faster onset of analgesia and less need for epidural top-ups were reported in DPE in some but not all studies when comparing DPE and EA (9, 11-14, 19, 20). An important element to explain this heterogeneity is spinal needle size. In trials that used smaller spinal needle size (i.e. 26- or 27- gauge), Yadav et al. (20) showed an improved analgesic quality and lower VAS scores during the first ten minutes in the DPE group. In contrast, Wilson et al. (11) and Thomas et al. (9) found no additional benefit for the use of DPE except for a slightly faster onset time compared to EA. Trials investigating DPE with *larger* size (25-gauge) show the same range of conflicting results. While Cappiello et al. (19), Chau et al. (12) and Song et al. (13) all agreed that DPE results in improved sacral blockade and lower rates of unilateral blocks in comparison to EA, Gupta et al. (14) reported a lower incidence of labour analgesia failure when compared to EA. Contreras et al. (21) compared 25-gauge needles to 27-gauge needle when using DPE and found a statistically significant difference in onset time of analgesia, favouring the 25-gauge needle. However, the absolute difference was rather small and the authors themselves question the clinical relevance of this finding. When looking at studies in non-obstetric patients that used *smaller* needle sizes (i.e. 26- or 27-gauge), Suzuki et al. (10) showed an improved caudal spread of analgesia when using a 27-gauge needle to perform dural puncture in patients undergoing lower abdominal surgery compared to a control group without dural puncture. However, Beaubien et al. (22) showed no difference in postoperative PCEA requirements in patients undergoing major abdominal surgery under general anesthesia with a preoperative dural puncture with a 25-gauge needle compared to EA without dural puncture.

To understand the importance of needle size in the DPE technique, the mechanism of trans-meningeal drug diffusion needs to be explained. Firstly, the flux of drugs from the epidural to the subarachnoid space depends on the diameter of the needle (23). This was demonstrated by Bernards et al. (23) in an in vitro study in monkey meninges. They showed that needle puncture results in a significant increase in flux through the meninges and this increase was related to the diameter of the needle (23). However, intrathecal drug migration is exceptionally complex and depends on more than the diameter of the dural puncture. Other variables include diffusion capacity of the drug, total drug mass, pressure gradient between the epidural and subarachnoid space, the pressure of the epidural bolus and the distance between the puncture site and epidural drug administration (23, 24). Swenson et al. (24) showed that the epidural administration of morphine after dural puncture resulted in greater concentrations of morphine in the cisterna magna of sheep. They used a 25-gauge needle and a 18-gauge needle to perform dural puncture in two groups and compared these to a control group without dural puncture. The mean morphine concentrations for intact dura, 25-gauge and 18-gauge puncture 22.2±12(3.4-53.0), 154±32 (81-217.0) and 405±53(309.0-527.0)ng/ml respectively(P=0.0005) (24). Similarly, Bernards et al. (23) showed an increased flux of morphine in the presence of a dural hole. However, in contrast to morphine, the flux of lidocaine was not greater through tissue with a dural hole compared to intact tissue when using a 27-gauge needle. Thus, the flux of drugs is dependent on the ratio between diffusion through intact tissue and the translocation through the dural hole. Simply explained, a dural puncture hole will have a negligible impact on the transfer of a drug that already readily crosses the meninges without a hole. Conversely, a drug that does not readily cross the spinal meninges, will have an increased flux to the subarachnoid space in the presence of the dural hole. These findings can be used to explain why no difference was observed in the study by Thomas et al. (9) who used a 10ml bolus of 2% lidocaine with a 27-gauge Whitacre needle and why a quicker onset time in the DPE-group was observed in the study by Wilson et al. (11) who performed a similar puncture with a 26-gauge needle, while administrating lidocaine *and* bupivacaine. The difference in outcome could potentially be explained by the use of a 26-gauge needle. However, another explanation can be found when looking at a study on rabbit models that showed that the transmeningeal flux of bupivacaine is slower than that of lidocaine due to different epidural disposition (25). Conversely, the dural hole may favour the flux of bupivacaine through the dural hole in the DPE-group. Hence this explains why Wilson et al. (11) found a difference in onset time in the DPE group compared to the epidural group. Equal to the previous trial, Yadav et al. (20) showed a quicker onset and improved analgesia by using DPE with repeated top-ups of ropivacaine. Again, these results could be attributed to the fact that bupivacaine and ropivacaine have a similar

transmeningeal flux (25, 26). The same could be said for the study by Song et al. (13) since they too used ropivacaine. Additionally, total drug mass embodies another vital factor of transmeningeal diffusion (23). An increased number of drug molecules inside the epidural space will support sufficient natural transmeningeal diffusion for dural holes to become negligible. This is seen in trials using a large bolus of local anesthetic which have not been able to show a difference between DPE and epidural analgesia in terms of time to peak sensory block and motor block (12, 14, 19). Alternatively, a small drug mass may fail to produce the required pressure to push drug molecules across the meninges or dural hole, but DPE might be helpful to improve onset of analgesia (19, 23). This could clarify why, in the context of dilute concentrations of local anesthetics (and thus low difference in molecules across the meninges), very little differences are seen between DPE and epidural with regard to drug consumption (20). However, this is not the case when using PIEB as shown by Song et al. (13). Needle size, however, does not explain why we see a trend towards fewer physician top-ups in the DPE group. Even when compared to CSE Chau et al. (12) reported a lower number of epidural top-ups with DPE as compared to CSE. Moreover, they observed an earlier request for top-up interventions in the CSE group in comparison with DPE. A meta-analysis by Heesen et al. (7) showed no difference in top-up interventions between CSE and epidural analgesia. Chau et al. (12) hypothesized that the transition from initial spinal analgesia to epidural analgesia elicits an intervention by a physician. Excellent quality analgesia with the spinal component is quite abruptly halted and hence with progressing labour relatively suddenly breakthrough pain occurs and additional analgesia is requested. However, this remains speculative and this hypothesis warrants further investigation.

Finally, the stage and intensity of labour might explain why results are different between studies since not all studies corrected for this confounding factor (12, 19, 20), whilst some studies did (11, 13).

This review also found no significant difference for catheter replacement, manipulation, intravascular placement or unilateral block. How-ever, small number of events and studies make it hard to assess if the quality of the block achieved by DPE is better than the conventional technique. Furthermore, most of the RCT's elected to exclude patients when no CSF was seen after dural punc-ture (11-14, 19). A meta-analysis (7) comparing CSE with epidural found a significant lower rate of unilateral block. This study was not able to show any difference between CSE and epidural technique when looking at catheter replacement. Chau et al. (12) also reported a considerably greater rate of bilateral block with DPE as compared to epidural. A possible mechanism that might explain these findings, could be that CSF return provides an indirect confirmation that the epidural needle is correctly positioned in the epidural space, namely centrally within the vertebral canal (7, 27). In other words, DPE can offer an alternative potential benefit due to the fact that the dural puncture offers confirmation of the loss of resistance and the midline position (27). This is interesting since Thomas et al. (9) found 14.8% of patients exposed to DPE did not have return of CSF after dural puncture. This group showed a higher rate of catheter replacement and intravascular placement compared to those with CSF return. Even though, this difference was not statistically significant. Even so, many of the studies (9, 12, 14, 19) implied that DPE could be utilized to verify the correct midline position of the epidural needle.

In addition, comparing DPE with epidural analgesia no significant difference in adverse events such as hypotension, PDPH, pruritus, nausea, motor blockade or fetal heart rate changes was observed. However, Chau et al (12) did show a significant reduction in pruritus, hypotension and adverse foetal events with DPE when comparing it with CSE. Furthermore, this study found no impact of DPE technique on the mode of delivery.

This study has several limitations. Although we performed a meta-analysis for some outcomes, the difference in needle size, variable study methodology and limited number of studies should be taken into account when the results are interpreted. This, together with a high failure rate of puncturing the dura, make quantitative pooling of data difficult. Moreover, RCT's were not excluded on basis of sample size justifications, blinding, statistical power, definition of intervention allocation or clinical outcome. This may lead to evidence being derived from weaker RCT and could pose a potential methodological limitation. Additionally, there is a lack of universally accepted definitions of some of our outcome measures and consequently the definitions used could have been discordant between studies. Even so, as the same definitions and reporting would have been used for each treatment arm within any one study, it is not expected that these between-study differences were to introduce a systematic bias. Lastly, there are a few possible confounders that may hamper with the correct interpretation of these RCT's. Not much is known

about the duration of patency of the dural hole so duration of labour could possibly be a confounding variable (14). Likewise, the same could be said about stage of labour since DPE improves sacral root block (12, 19). Further research is warranted to elucidate on how these factors interact with DPE.

Conclusion

This systematic review showed no significant difference when comparing DPE with conventional EA. Due to substantial heterogeneity between studies and a low number of certain events, the benefits of DPE for labour analgesia continue to be unclear. There is a trend for better analgesic outcome and evidence that DPE has a favourable risk-benefit profile in labouring patients. However, the need for more studies comparing DPE with epidural as well as CSE remains high. Future trials should focus on investigating the optimal needle size along with researching the different factors and confounders controlling the transmeningeal flux of drugs to the subarachnoid space. Likewise, further studies are needed to explain the specificity, sensitivity and predictive value of CSF return through the spinal needle as confirmation of the correct position of the epidural needle. Furthermore, attempts should be made to standardize the type and administration of the drugs used and create universal definitions of outcome parameters. Lastly, more studies are warranted to elucidate on the mode of delivery of drugs, dosing schemes and interval settings. Whenever possible, future trials should make the effort to register satisfaction scores, duration of labour and consumption of local anaesthetic agents and reflect present day obstetric anesthesia practice.

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