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Review Article

Choice of local anaesthetic for epidural caesarean section: a Bayesian network meta-analysis

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Summary

Rapid-onset epidural local anaesthesia can avoid general anaesthesia for caesarean delivery. We performed a Bayesian network meta-analysis of direct and indirect comparisons to rank speed of onset of the six local anaesthetics most often used epidurally for surgical anaesthesia for caesarean delivery. We searched Google Scholar, PubMed, EMBASE, Ovid, CINAHL and CENTRAL to June 2019. We analysed 24 randomised controlled trials with 1280 women. The mean (95%CrI) onset after bupivacaine 0.5% was 19.8 (17.3–22.4) min, compared with which the mean (95%CrI) speed of onset after lidocaine 2% with bicarbonate, 2-chloroprocaine 3% and lidocaine 2% was 6.4 (3.3–9.6) min faster, 5.7 (3.0–8.3) min faster and 3.9 (1.8–6.0) min faster, respectively. Speed of onset was similar to bupivacaine 0.5% after ropivacaine 0.75% and l-bupivacaine 0.5%: 1.6 (−1.4 to 4.8) min faster and 0.4 (−2.2 to 3.0) min faster, respectively. The rate (95%CrI) of intra-operative hypotension was least after l-bupivacaine 0.5%, 315 (236–407) per 1000, and highest after 2-chloroprocaine 3%, 516 (438–594) per 1000. The rate (CrI) of intra-operative supplementation of analgesia was least after ropivacaine 0.75% 48 (19–118) per 1000 and highest after 2-chloroprocaine 3%, 250 (112–569) per 1000.

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Introduction

Approximately 3–15% of women who have epidural analgesia for labour receive supplemental local anaesthetic drugs intended to achieve surgical anaesthesia for unscheduled caesarean delivery [1]. The choice of local anaesthetic drug may not be determined by evidence and can be influenced by the immediate availability of the local anaesthetic and institutional convention. Variation in practice is further compounded by drug shortages [2].

A recent meta-analysis of epidural local anaesthetics suggested that the onset of surgical anaesthesia for caesarean delivery was fastest after lidocaine 2% [3]. However, the meta-analysis was limited to three groups of local anaesthetic due to no direct comparisons with other local anaesthetics. As a consequence, 2-chloroprocaine 3%, a drug commonly used in the USA and widely considered to have the fastest onset of action, was not reviewed [4].

We have performed a Bayesian network meta-analysis to synthesise as much data as possible from both direct and indirect comparisons of the most commonly available local anaesthetic drugs. Our aim was to provide pooled estimates and a ranked order for the onset times for the different local anaesthetics used to provide epidural anaesthesia for caesarean delivery.

Methods

We followed standard procedures for this prospectively registered systematic review and network meta-analysis [5,

6]. Two authors (MR and SV) searched Google Scholar, PubMed, EMBASE, Ovid, CINAHL and CENTRAL to June 2019 without language or date limits (see also Supporting Information, Appendix S1). We searched for randomised controlled trials that compared the onset of surgical anaesthesia for scheduled or unscheduled caesarean section after epidural injection of local anaesthetics through a catheter, using 'epidural local anaesthetic', 'emergency epidural for caesarean section', 'epidural anaesthesia caesarean section' and 'time to onset epidural local anaesthetic'. We did not include trials that used 'combined spinal epidural'. The catheter could be sited after the decision to deliver by caesarean section or could be one already in use, for instance for labour analgesia. We analysed separately different concentrations or chiral isomers of the same anaesthetic. We did not separately analyse anaesthetics to which fentanyl or adrenaline had been added. We limited this systematic review to the six local anaesthetics used most often: lidocaine 2%; bupivacaine 0.5%; l-bupivacaine 0.5%; 2-chloroprocaine 3%; lidocaine 2% plus bicarbonate; and ropivacaine 0.75%. We did not analyse abstracts that were not subsequently published in full. Bicarbonate is added to lidocaine to enhance the speed of onset of lidocaine. As time to onset of surgical anaesthesia was our primary outcome, we considered lidocaine and lidocaine with bicarbonate as separate groups.

Two authors (MR and PS) extracted year of publication; country; the number, age and weight of participants; whether the epidural catheter was sited before the decision to deliver by caesarean section; whether the caesarean section was scheduled; the trial's definition of adequate surgical anaesthesia, for instance method used to test which dermatome; the epidural local anaesthetic and additives; the onset time; intra-operative supplementation for loss of surgical anaesthesia; maternal adverse events, including the rate of hypotension (as defined by trial authors), nausea or vomiting; and neonatal Apgar scores and umbilical artery pH.

We categorised as present, absent or unclear the risk of biases for generation and concealment of allocation sequence, blinding of personnel and participants, blinding of outcome assessment, participant attrition, selective reporting and other biases [7]. We judged the overall risk of bias for each trial as low, moderate or high. We inspected the funnel plot of the primary outcome for asymmetry (see also Supporting Information, Fig. S1). We evaluated evidence with the GRADE framework [8]. We produced network graphs with nodes representing the competing local anaesthetics, sized by sample size, linked by an edge, the thickness of which was proportionate to the number of trials. We estimated mean (SD) from median values and ranges [9, 10]. We used Markov Chain Monte Carlo algorithm to derive inferences from the random-effects Bayesian network constructed with the R statistical package 'gemtc'. We also used the 'netmeta' package to evaluate the assumptions of transitivity (distribution of treatment effects is similar across the trials) and consistency (of direct and indirect estimates) [11]. We used the Brooks–Gelman–Rubin diagnostics to determine the number of iterations to reduce the 'potential scale reduction factor' below 1.05 (see also Supporting information, Fig. S2) [12]. We used meta-regression to assess the interactions of two covariates with the onset of surgical anaesthesia: epidural fentanyl; and placement of the epidural catheter before the decision to deliver by caesarean section. The statistician handling the data was blinded to the treatment groups. We assessed the network for disparities between direct and indirect comparisons [13].

Results

We included 24 trials with 1280 women (Fig. 1; Table 1) [14–37]. Fourteen trials studied lidocaine 2%; 14 studied bupivacaine 0.5%; 6 studied l-bupivacaine 0.5%; 5 studied 2-chloroprocaine 3%; 5 studied lidocaine 2% plus bicarbonate; and 4 studied ropivacaine 0.75% (Fig. 2). We categorised risks of bias as low for most domains in most trials (see also Supporting Information, Fig. S3). The direct and indirect assessment of effects were consistent (see also Supporting Information, Figs. S4 and S5).

The speeds of onset of surgical anaesthesia, from fastest to slowest, were: lidocaine 2% with bicarbonate; 2-chloroprocaine 3%; lidocaine 2%; ropivacaine 0.75%; l-bupivacaine 0.5%; bupivacaine 0.5% (Fig. 3). The mean (95%CrI) onset after bupivacaine 0.5% was 19.8 (17.3–22.4) min, compared with which the mean (95%CrI) speeds of onset after lidocaine 2% with bicarbonate, 2-chloroprocaine 3% and lidocaine 2% were 6.4 (3.3–9.6) min faster, 5.7 (3.0–8.3) min faster and 3.9 (1.8–6.0) min faster, respectively (see also Supporting Information, Table S1). Surgical anaesthesia onset time was similar to bupivacaine 0.5% after ropivacaine 0.75% and l-bupivacaine 0.5%: 1.6 (−1.4 to 4.8) min faster and 0.4 (−2.2 to 3.0) min faster, respectively (Table 2). The ordering of local anaesthetics did not interact with epidural fentanyl or when the catheter was placed (see also Supporting Information, Tables S2–S4).

The rate of intra-operative hypotension was reported by 14 trials with 807 women (Fig. 2). l-bupivacaine 0.5% was least likely to cause hypotension and bupivacaine

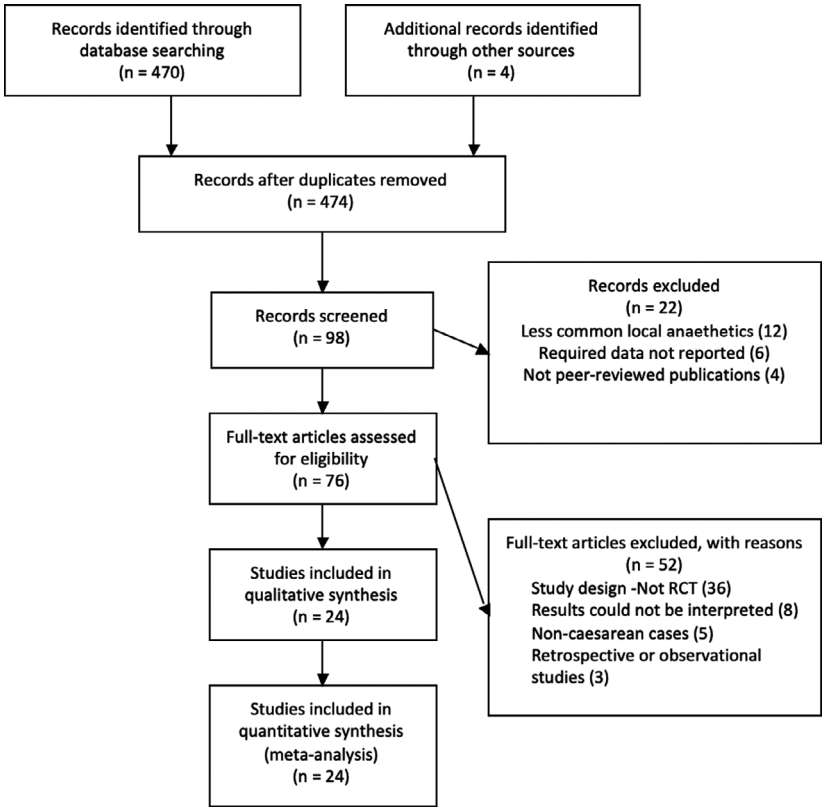

Figure 1 PRISMA flow chart of 24 randomised controlled trials included in the network meta-analysis.

0.5% was most likely to cause hypotension (Fig. 2 and see also Supporting Information, Fig. S6 and Table S5). Loss of surgical anaesthesia requiring intra-operative supplementation was reported by 15 trials with 886 women (Fig. 2). Intra-operative supplementation of anaesthesia was most likely after 2-chloroprocaine 3% and least likely after ropivacaine 0.75% (see also Supporting Information, Fig. S7 and Table S5). We were unable to pool rates of nausea and vomiting as it was inconsistently documented across trials. No trial reported neonatal outcome.

Discussion

We found that lidocaine 2% with bicarbonate caused the fastest onset of surgical anaesthesia for caesarean delivery. Surgical anaesthesia was also fast after 2-chloroprocaine 3%, but anaesthesia became inadequate more often than other anaesthetics, requiring intra-operative supplementation. Ropivacaine 0.75%, l-bupivacaine 0.5% and bupivacaine 0.5% were relatively slow in onset and may be inappropriate for emergency delivery.

Better understanding of speed of surgical anaesthesia after injection of epidural local anaesthetics may improve decision making for unscheduled caesarean delivery. For instance, general anaesthesia with its associated risk of failure to ventilate might be avoided if the credible onsets of different anaesthetics through a functioning epidural are known [38]. Standard meta-analysis is limited to direct comparisons, which has restricted previous syntheses to fewer trials of fewer drugs [3]. Network meta-analysis incorporates direct and indirect sources of uncertainty and often precludes clear ordering of alternatives [39]. Nevertheless, we established faster onset of surgical anaesthesia with lidocaine 2% (with or without bicarbonate) or 2-chloroprocaine 3% than with bupivacaine 0.5%: any of these three drugs should be considered preferable to bupivacaine 0.5% for emergency caesarean delivery under epidural anaesthesia. The two drugs with the fastest epidural onset of surgical anaesthesia, lidocaine 2% with bicarbonate and 2-chloroprocaine 3% have not been directly compared: it would be useful to compare their onsets directly in the future.

This review – like any – was limited by the heterogeneity of the included studies. The sensory endpoints used to establish surgical anaesthesia varied across included studies. Dermatomal levels T4–T7 were used to indicate adequate surgical anaesthesia, tested with cold, touch and

Table 1 Characteristics of 24 randomised controlled trials included in the Bayesian network analysis.

Trial	Country	Group 1	Group 2	Group 3	Group 4	Sensory test	Other outcomes	New or old	Scheduled or not
James et al. [14]	USA	20 ml bupivacaine 0.5% (n = 15)	20 ml 2-chloro' 3% (n = 15)	–	–	T4-6	Hypotension, maternal arterial blood gas, Apgar 1 & 5 min, time to breathe	New	Scheduled
Abboud et al. [15]	USA	15 ml bupivacaine 0.75% (n = 16)	15 ml 2-chloro' 3% (n = 18)	15 ml lidocaine 2% (n = 11)	15 ml of 2% Lidocaine with 1:200,000 adrenaline (n = 9)[a,b]	T6	Hypotension, time to delivery, Apgar 1 and 5 min, foetal acid–base, neonatal neurobehavioural score, maternal and foetal plasma local anaesthetic	New	Scheduled
Norton et al. [16]	Scotland	20 ml lidocaine 2% 1:200,000 adrenaline (n = 30)[c]	20 ml bupivacaine 0.5% (n = 30)[c]	–	–	T6	Block duration, intra-operative supplementation, hypotension, sensory and motor block, urinary retention, Apgar 1 and 3 min	New	Scheduled
Reid et al. [17]	Scotland	10–17 ml bupivacaine 0.5% (n = 16) sitting[a,d]	10–17 ml bupivacaine 0.5% (n = 14) lateral[d]	10–17 ml lidocaine 2% 1:200,000 adrenaline (n = 18) sitting[d]	10–17 ml lidocaine 2%, 1:200,000 adrenaline (n = 16) lateral[a,d]	Pinprick T5-S5	Intra-operative supplementation, hypotension.	New	Scheduled
Howell et al. [18]	UK	20 ml bupivacaine 0.5% (n = 20)	20 ml bupivacaine 0.5% 1:200,000 adrenaline (n = 20)[a]	20 ml lidocaine 2% 1:200,000 adrenaline (n = 19)	10 ml bupivacaine 0.5% & 10 ml lidocaine 2% 1:200,000 adrenaline (n = 20)[a]	Cold T4	Intra-operative supplementation, sensory and motor block quality and duration, Apgar 1 and 5 min, neonatal resuscitation	New	Scheduled
Liepert et al. [19]	Canada	19.2 ± 3.1 ml lidocaine hydrochloride 2% (n = 20)[e]	17.5 ± 3.2 ml lidocaine carbonate 2% (n = 20)[a,e]	18 ± 2.6 ml lidocaine 2% & HCO_3 (n = 20)[e]	–	T4 cold & pinprick	Intra-operative supplementation, onset anaesthesia S2, time to delivery, block duration	New	Scheduled
Son et al. [20]	Korea	20 ml lidocaine 2% (n = 15)	20 ml bupivacaine 0.5% (n = 15)				Hypotension, Apgar	New	Scheduled
Johnson et al. [21]	USA	15–20 ml bupivacaine 0.5% (n = 7)[f]	15–20 ml bupivacaine 0.5% and fentanyl 75 mcg (n = 7)[a,f]	15–20 ml 2-chloro' 3% (n = 7)[f]	15–20 ml 2-chloro' 3%, fentanyl 75 mcg (n = 7)[a,f]	T4 pinprick	Hypotension, Apgar 1 and 5 min	New	Scheduled
Capogna et al. [22]	Italy	19.0 ± 2.8 ml lidocaine 2% 1:200,000 adrenaline and fentanyl 100 mcg (n = 50)[g]	20.1 ± 4.1 ml lidocaine 2% 1:200,000 adrenaline & HCO_3 & fentanyl 100 mcg (n = 62)[g]	–	–	T4 pinprick	Intra-operative supplementation, hypotension, nausea, vomiting, pruritus, sedation, motor block, block onset S1, times to delivery, Apgar 1 and 5 min, neonatal neurology and function, maternal satisfaction	New	Scheduled
Kim et al. [23]	Korea	20 ml lidocaine 2% and HCO_3 (n = 30)	20 ml lidocaine 2% (n = 30)			T5 cold	Intra-operative supplementation, motor block onset, hypotension	New	Scheduled
Lucas et al. [24]	UK	20 ml bupivacaine 0.5% (n = 30)	10 ml bupivacaine 0.5% & 10 ml lidocaine 2% 1:200,000 adrenaline (n = 30)[a]	20 ml lidocaine 2% 1:200,000 adrenaline (n = 30)	–	T4 cold	Intra-operative supplementation, quality and duration motor block, Apgar 1 and 5 min	Old	Unscheduled
Lam et al. [25]	China	15 ml lidocaine 2% 1:200,000 adrenaline and fentanyl 75 mcg (n = 20)	3 ml lidocaine 2% 1:200,000 adrenaline and 12 ml lidocaine 2% and fentanyl 75 mcg (n = 20)	–	–	T6 pinprick	Hypotension, nausea and vomiting, motor block, shivering, Apgar 1 and 5 min, umbilical cord blood gases	Old	Unscheduled
Faccenda et al. [26]	Scotland	25 ml bupivacaine 0.5% (n = 31)	25 ml l-bupivacaine 0.5% (n = 31)	–	–	T5 pinprick	Hypotension, nausea, motor block, intra-operative supplementation, Apgar 1 and 5 min, neonatal neurology and function	New	Scheduled
Sanders et al. [27]	UK	20 ml bupivacaine 0.5% (n = 22)	3 ml lidocaine 2% and 20 ml ropivacaine 0.75% (n = 23)	–	–	T4 cold	Intra-operative supplementation, VAS for analgesia	Old	Unscheduled
Christelis et al. [28]	UK	3 ml lidocaine 2% and 20 ml bupivacaine 0.5% & fentanyl100 mcg (n = 36)	3 ml lidocaine 2% and 20 ml ropivacaine 0.75% (n = 31)	–	–	T4 cold	Hypotension, intra-operative pain and supplementation, Apgar 1 min umbilical artery pH	New	Scheduled

(continued)

Table 1 (*continued*)

Trial	Country	Group 1	Group 2	Group 3	Group 4	Sensory test	Other outcomes	New or old	Scheduled or not
Ngamprasertwong et al. [29]	Thailand	3 ml lidocaine 2% 1:200,000 adrenaline & 15 ml bupivacaine 0.5% (n = 30)	3 ml lidocaine 2% 1:200,000 adrenaline & 15 ml l-bupivacaine 0.5% (n = 31)	–	–	T6 pinprick	Hypotension, nausea, vomiting, pruritus, shivering, sedation, motor block, intra-operative pain and supplementation, Apgar 1 & 5 min	New	Scheduled
Goring-Morris et al. [30]	UK	Unspecified test dose + 20 ml bupivacaine 0.5% (n = 36)	Unspecified test dose & 22.1 ml lidocaine 2% 1:200,000 adrenaline and fentanyl 100 mcg (n = 30)	–	–	T7 sharp	Intra-operative supplementation, hypotension, nausea, vomiting	Old	Unscheduled
Bjornestad et al. [31]	Norway	16 ml lidocaine 2% (n = 20)	16 ml 2-chloro' 3% (n = 20)	–	–	T5 cold	Intra-operative supplementation, hypotension, nausea, bradycardia, Apgar 1 and 5 min	New	Scheduled
Piatkowski et al. [32]	Poland	Uncertain volume of bupivacaine 0.5% and fentanyl (n = 30) [h]	Uncertain volume of ropivacaine 0.75% and fentanyl (n = 30) [h]	–	–		Motor and sensory block duration. maternal HR, analgesic requirements	New	Scheduled
Sng et al. [33]	Singapore	15 ml l-bupivacaine 0.5% (n = 30)	15 ml ropivacaine 0.75% (n = 30)	15 ml lidocaine 2% 1:200,000 adrenaline and fentanyl 50 mcg (n = 30)	–	T4 cold	Intra-operative supplementation, hypotension, Apgar, vomiting, shivering, pruritus	Old	Unscheduled
Allam et al. [34]	UK	20 ml l-bupivacaine 0.5% (n = 19)	20 ml lidocaine 1.8%, 1:200,000 adrenaline and HCO_3 (n = 16)	–	–	T5 light touch	Intra-operative supplementation, nausea and vomiting, sedation, pain, Apgar 1 and 5 min, umbilical cord gases	Old	Unscheduled
Balaji et al. [35]	UK	20 ml l-bupivacaine 0.5% (n = 50)	22.1 ml lidocaine 2% & fentanyl 100 mcg and adrenaline 100 mcg (n = 50)			T7 touch	Intra-operative pain and supplementation, hypotension, nausea, vomiting, motor block, postop' nausea, vomiting, itching and satisfaction	Old	Unscheduled
Feng et al. [36]	China	15 ml 2-chloro' 3% (n = 20)	15 ml 2-chloro' 3%, 1:200,000 adrenaline (n = 20 [a]	15 ml lidocaine 2% 1:200,000 adrenaline (n = 20)		T7 cold	Duration and quality block, hypotension, pain VAS, nausea, Apgar, umbilical acid-base, neonatal neurology and function	New	Scheduled
Pahuja et al. [37]	India	15–20 ml bupivacaine 0.5% and fentanyl 25 mcg (n = 30)	15–20 ml l-bupivacaine 0.5% and fentanyl 25 mcg (n = 30)			T6 sharp	Intra-operative supplementation, hypotension, postop' analgesia, Apgar 1 and 5 min, analgesic duration	New	Scheduled

Apgar, Apgar score; 2-chloro' 3%, 2-chloroprocaine 3%; New or old, placement after or before the decision to deliver by caesarean section.

[a] Local anaesthetics that were not six of the most commonly used and therefore were not in the meta-analysis.

[b] Added post-hoc: 'because 2% lidocaine was associated with unsatisfactory anaesthesia and discomfort'.

[c] Administered in two aliquots of 8–10 ml separated by 5 min in the left and right lateral positions; onset timed from the first injection.

[d] The woman's height determined the volume of first injectate: < 1.52 m, 10 ml; 1.52–1.71 m, 13 ml; > 1.71 m, 17 ml.

[e] Administered in 3-ml aliquots every 1–2 min until sensory block to T4 was achieved. Volumes provided are mean ± SD.

[f] The woman's height determined the volume of the second injectate (after a test dose of 3 ml lidocaine 1% + adrenaline 1:200,000): 150–160 cm, 15 ml; 160–170 cm, 20 ml.

[g] After 3 ml lidocaine 2% with adrenaline 1:200,000 as a test dose, patients received 5 ml increments (every 2–3 min) to until a block to T4 was achieved. Volumes provided are mean ± SD.

[h] Volumes for each patient calculated based on patient characteristics. Unable to retrieve raw data from authors.

Table 2 Summary of evidence for epidural local anaesthetic injections for caesarean section. Values are mean (credible interval), odds ratio (credible interval) or number.

Outcomes	Value with worst agent	Value with best agent	Relative effect (95%CrI)	Women (trials)	Certainty (GRADE)	Comments
Onset of surgical anaesthesia	Bupivacaine 0.5% 19.8 (17.3–22.4) mins	Lidocaine 2% + HCO_3 10.7 (8.8–12.6) mins	6.4 (3.3–9.7) min	1280 (24)	⊕⊕◯ low	2-chloroprocaine 3% was 6 (3–8) min faster than bupivacaine 0.5%
Intra-operative hypotension	Bupivacaine 0.5% 516 (438–594) per 1000	l-bupivacaine 0.5% 315 (236–407) per 1000	0.52 (0.20–1.26)	807 (14)	⊕◯◯ Very low	2-chloroprocaine 3% OR (CrI) was 0.61 (0.20–1.96) vs. bupivacaine 0.5%
Intra-operative supplementation	2-chloroprocaine 3% 250 (112–469) per 1000	Ropivacaine 0.75% 48 (19–118) per 1000	0.05 (0.00–0.76)	886 (15)	⊕◯◯ Very low	Lidocaine 2% + HCO_3 OR (CrI) was 0.22 (0.06–0.83) vs. 2-chloroprocaine 3%

CrI, credible interval.

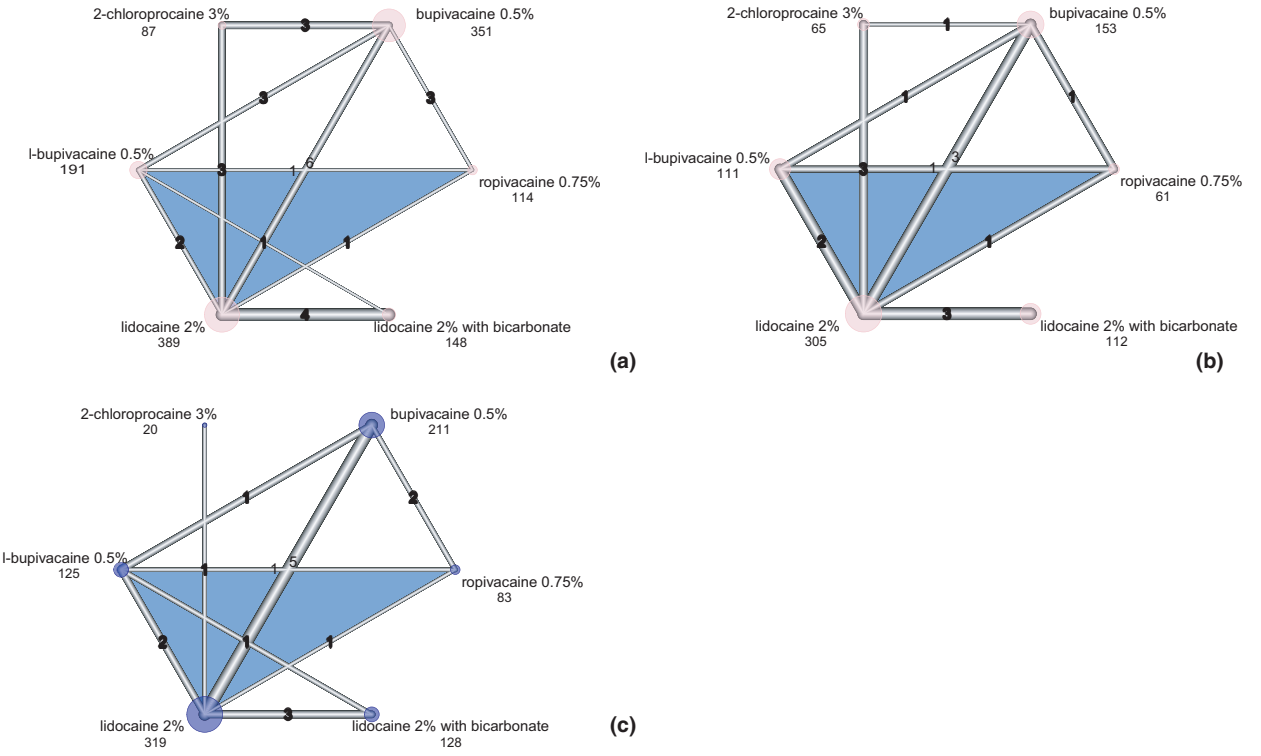

Figure 2 Network plots of geometries for: (a) onset of surgical anaesthesia; (b) rate of intra-operative hypotension; (c) intra-operative supplementation of epidural anaesthesia. The size of the nodes is proportional to the number of women, the thickness of the line is proportional to the number of trials. Numbers are participants in each group.

'pinprick'. We considered that direct comparisons of drugs within trials would be unaffected by these varying definitions, although the heterogeneity related to the methodological variations could have contributed significantly to the inconsistency of the network meta-analysis. There was also variable use of test doses and volumes and speeds of injection. It is possible that the onset of surgical anaesthesia is accelerated by the addition of fentanyl [21]. We were unable to identify any effect of fentanyl on the time to onset. Networks include indirect evidence that needs a covariate to have a strong effect to be identified. Our decision to pool trials of injection through established epidurals with trials of new epidurals may have reduced the precision of our estimates but increased the

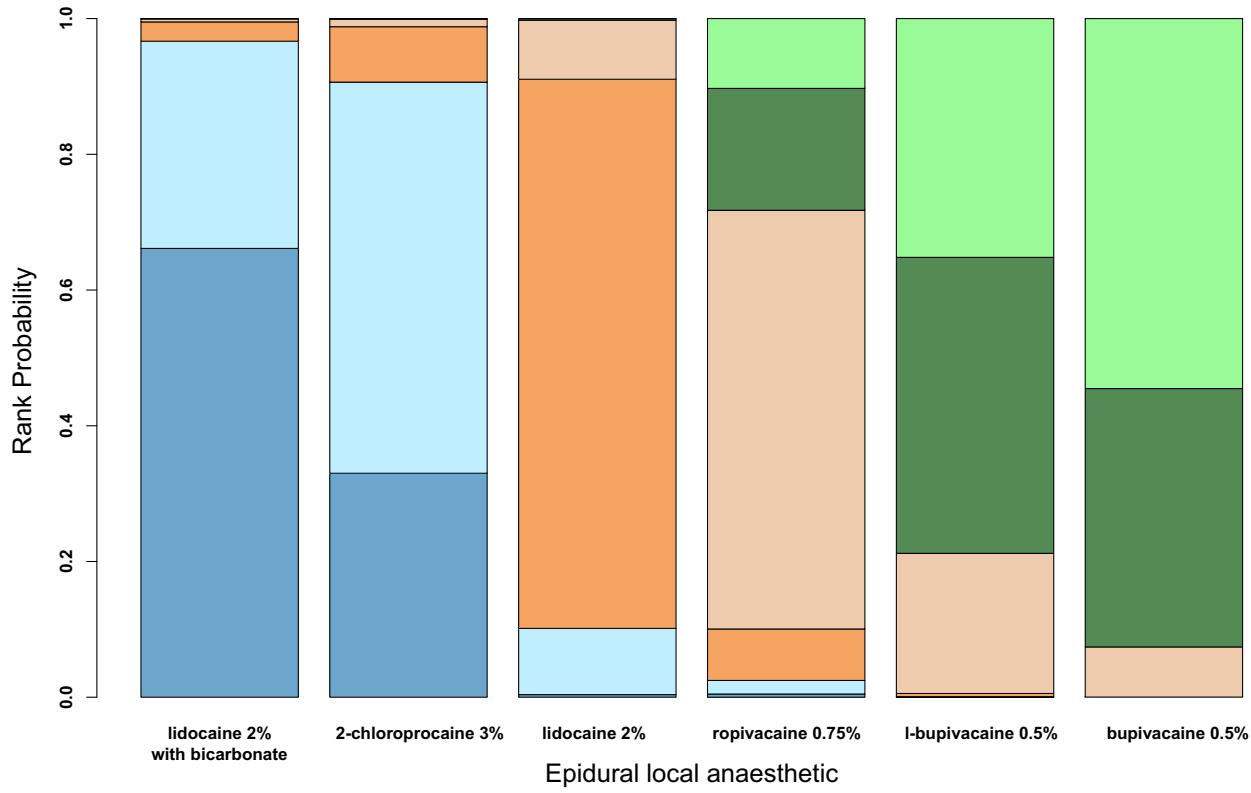

Figure 3 A rankogram of the probabilities that the speed of onset for six local anaesthetics was rank: first (■); second (■); third (■); fourth (■); fifth (■); and sixth (■).

generalisability of our results. Partial pre-existing anaesthesia, for labour analgesia, may have influenced the measured effect.

In conclusion, we found the onset of surgical anaesthesia was fastest after epidural lidocaine 2% with bicarbonate, followed by 2-chloroprocaine 3% and lidocaine 2%. Ropivacaine 0.75%, l-bupivacaine 0.5% and bupivacaine 0.5% were slower in onset times and may be less appropriate for emergency caesarean delivery. Future research should test lidocaine 2% with bicarbonate vs. 2-chloroprocaine 3%.

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Supporting Information

Additional supporting information may be found online via the journal website.

Figure S1 Forest plot evaluating publication bias.

Figure S2 Gellman Rubin convergence diagnostics.

Figure S3 Risk of bias for 24 included trials.

Figure S4 Net-heat graph of inconsistency across the network.

Figure S5 A node-split model exploring variations in pairwise comparisons.

Figure S6 Incidence of hypotension rankogram.

Figure S7 Need for supplementation rankogram.

Table S1 A league table of difference in onset of surgical anaesthesia.

Table S2 Rank probabilities of relative speeds of onset of surgical anaesthesia.

Table S3 The same as Table S1, adjusted for the use of fentanyl.

Table S4 The same as Table S1, adjusted for whether the epidural catheter was inserted before or after the decision to proceed to caesarean section.

Table S5 Odds ratios for intra-operative hypotension.

Appendix S1 Search strategy.