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ORIGINAL ARTICLE

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Comparison between general, spinal, epidural, and combined spinal-epidural anesthesia for cesarean delivery: a network meta-analysis

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ABSTRACT

Background: This study is a network meta-analysis to compare maternal and fetal outcomes associated with four different anesthetic techniques for cesarean delivery.

Methods: An arm-based, random-effects frequentist network meta-analysis was performed. A random effect model was selected considering deviance information criteria. Randomized trials reporting the following outcomes were included: Apgar score at 1- or 5-min; umbilical arterial and venous pH; umbilical arterial pH <7.2; and neonatal score at 2–4 hours. Loop-specific heterogeneity was evaluated by risk of odds ratio and τ^2. Quality of evidence was assessed using the GRADE approach.

Results: Data from 46 randomized trials including 3689 women contributed to the study. There were significant differences in Apgar score ≤6 at 1 min between spinal versus general anesthesia (odds ratio 0.27, 95% confidence interval [CI] 0.13 to 0.55: moderate quality evidence) and Apgar scores at 1- and 5-min, favoring spinal anesthesia. Umbilical venous pH associated with epidural anesthesia was significantly higher than that with general anesthesia (mean difference 0.010, 95% CI 0.001 to 0.020: moderate quality evidence) or spinal anesthesia. Spinal anesthesia was ranked best for Apgar score ≤6 at 1-min (SUCRA=89.8), Apgar score at 1-min (SUCRA=80.4) and 5-min (SUCRA=90.5). Epidural anesthesia was ranked highest for umbilical venous pH (SUCRA=87.4) and neonatal score (SUCRA=79.3).

Conclusions: Spinal and epidural anesthesia were ranked high regarding Apgar scores and epidural anesthesia was ranked high regarding umbilical venous pH, but the results were based on small heterogeneous studies with high or unclear risks of bias.

Keywords: Cesarean delivery; Anesthesia; Apgar score; Network meta-analysis

Introduction

The cesarean delivery rate has been reported to be as high as 65% in the United States.[1] The choice of anesthesia for cesarean delivery has long been a topic of discussion, and neuraxial anesthesia is considered the safest and preferred technique.[2] Spinal anesthesia has been regarded as the first choice for uncomplicated elective cesarean delivery, because it is easy to perform and avoids the risks of difficult intubation and aspiration.[3,4] Disadvantages of neuraxial anesthesia include a relatively longer induction time, systemic toxicity of local anesthetic, inadequate analgesia, post-dural puncture headache and hypotension.[5] However, general anesthesia is still used when time constraints preclude neuraxial anesthesia, or when neuraxial anesthesia has failed or is contraindicated. Advantages include less cardiovascular depression, a secure airway and controlled respiration,[6] while disadvantages include the risk of failed intubation and pulmonary aspiration.

The aim of anesthesia for cesarean delivery is to deliver the fetus safely, with minimal risk to mother and baby, and therefore comparing fetal outcomes associated with different anesthetic techniques is an important issue. Several randomized controlled trials have compared neonatal outcomes with different anesthetic techniques for cesarean delivery, focusing on Apgar scores at 1- and 5-min after delivery.[7,8] A low Apgar score has been commonly defined as ≤6; this is associated with adverse clinical outcomes.[9,10] A Cochrane review that pooled the results of 22 studies and was updated in 2012 reported no difference in Apgar scores at 5-min and concluded that there was still insufficient evidence to demonstrate superiority of neuraxial over

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general anesthesia.[5] Studies since 2012 have reported that spinal anesthesia is superior to general anesthesia with respect to fetal acid-base status and Apgar score.[11–14] Although epidural and combined spinal-epidural anesthesia have some unique advantages,[15] few studies have compared them with general or spinal anesthesia. Therefore, the optimal anesthetic technique with respect to neonatal Apgar score at cesarean delivery is still unclear, and comparison of all four anesthetic techniques is required.

A network meta-analysis is a statistical technique for comparing different drugs or treatments that have not been directly compared through adequately powered head-to-head randomized controlled trials. The comparisons of different modalities that have never been compared are possible through a third common comparator.[16,17] It is possible to identify the superior modalities and to estimate a relative ranking, through indirect comparison based on statistical inference.

The aim of this network meta-analysis was to determine which anesthetic technique for cesarean delivery provides best maternal and neonatal outcomes. The primary outcome variables were Apgar score $\leq$6 at 1- and 5-min. The secondary aim, in a subgroup analysis, was to explore whether a particular anesthetic technique was associated with improved neonatal outcomes in an uncomplicated elective cesarean delivery.

Methods

To compare the effect on the neonatal and maternal outcomes of general, epidural, spinal, and combined spinal-epidural anesthesia for cesarean delivery, a systematic review and network meta-analysis was performed according to the recommendations of the Cochrane Handbook for Systemic Reviews of Interventions,[18] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statements for network meta-analysis (Supplemental Table S1).[19] This study was registered at the PROSPERO International Prospective Register of Systematic Reviews (CRD 42018081475). Our review protocol is available at https://doi.org/10.6084/m9.figshare.5691115.

The research question was formulated according to the Participants, Interventions, Comparisons and Outcome (PICO) model: P – parturients undergoing cesarean delivery surgery; I – neuraxial anesthesia techniques including epidural, spinal, and combined spinal-epidural anesthesia; C – general anesthesia; O – Apgar score at 1- and 5-min.

Eligibility criteria, information sources and search strategy

Randomized controlled trials comparing the effects of two or more anesthetic techniques (epidural, spinal, combined spinal-epidural, and general anesthesia) on at least one of the following eight fetal or maternal outcomes of cesarean delivery, regardless of its urgency, were included: Apgar score $\leq$6 at 1- and 5-min; Apgar score at 1- and 5-min; umbilical arterial and venous pH; maternal estimated blood loss; and neonatal neurologic and adaptive capacity score at 2–4 hours.[20]

Two authors (MH, WHK) independently searched Medline via the PubMed interface, Embase databases, and the Cochrane Central Register of Controlled Trials [Central, Issue 10 of 2016] from inception to October 2017. There was no language restriction. We did not limit risk of bias, inclusion criteria for blinding of participants, personnel and outcome assessor, because blinding in the setting of general versus neuraxial anesthesia could not be achieved. The same authors independently reviewed the titles and abstracts of all searched studies to identify eligible trials. The search strategy is presented in Supplemental Text S1.

A bibliographic search of all the included trials using the "related articles" function in PubMed was used to identify additional eligible trials which were not found by the main search queries. Conference abstracts and a clinical trial registry website (www.clinicaltrials.gov) were also searched. Non-English language literature was translated.[21–24]

Data extraction and management

Data were independently extracted from included studies by two authors (MH, WHK), using a uniform data extraction form developed by the authors. Any discrepancies were resolved through a consensus discussion. We contacted primary investigators for further details of the trial results. Extracted data were independently entered by two authors (MH, WHK) into an Excel spreadsheet and the STATA version 13.0. The following information was extracted from each trial: study first author, location, year of publication, the number of enrolled patients (general, epidural, spinal, and combined spinal-epidural anesthesia group, respectively), characteristics of study population, study design, and outcome data.

Outcome definitions

The pre-specified primary endpoints were the incidence of Apgar score $\leq$6 at 1- and 5-min after delivery. Because the low Apgar score defined as <7 is associated with adverse fetal outcomes,[9–10] categorized Apgar score was selected as the primary outcome. The secondary outcomes included umbilical arterial and venous pH, umbilical arterial pH <7.2, Apgar score at 1- and 5-min after delivery, estimated maternal blood loss, and neonatal neurologic and adaptive capacity score at 2–4 hours.[20] Umbilical blood pH data with an unknown origin (arterial or venous blood), no reported standard deviation or with a standard deviation of zero; and

Apgar scores without their measured time-point, were not included in the final analysis.

Assessment of risk of bias

The risk of bias of individual studies was assessed using the bias domains described in the Cochrane Handbook for Systemic Reviews of Interventions, version 5.1.0.[18] Two authors (MH, WHK) subjectively and independently reviewed all included studies and assigned a judgment of "high", "low", or "unclear" risk of bias across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Disagreements were resolved by discussion between the two assessors and a third outside assessor, who provided arbitration.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates derived from network meta-analysis.[25] In this approach, the rating of direct evidence from randomized controlled trials begins at a high quality, and can be evaluated down in view of the risk of bias, indirectness, imprecision, inconsistency, and/or publication bias, to levels of moderate, low and very low quality. Secondly, the evaluation of indirect estimates begins at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate; however they can be evaluated down further for imprecision or intransitivity. Thirdly, assuming direct and indirect estimates were similar, the higher rating can be assigned to the network meta-analysis estimates.

Statistical analysis

Data were analyzed using Stata/SE version 13.0 (StataCorp, College Station, Texas, USA) and Review Manager 5.3 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). Model fit was evaluated by R version 3.4.1. (R Foundation for Statistical Computing) using gemtc package (https://github.com/gertvv/gemtc). A two-sided P-value ≤ 0.05 was considered statistically significant. Odds ratios (OR) and mean differences (MD) were considered statistically significant when their 95% confidence interval (CI) did not include 1 and 0, respectively.

An arm-based, random-effect frequentist network meta-analysis was performed to compare the different anesthesia modalities by STATA (www.stata.com).[26] Our analysis included four anesthesia techniques as separate treatment nodes: general, epidural, spinal, and combined spinal-epidural. Along with analyzing the direct within-trial comparisons between two anesthetic techniques, the mixed technique comparison framework enabled incorporation of an indirect comparison of anesthesia modalities. Model fit was measured by assessment of the posterior residual deviance, and goodness of model fit was evaluated by comparing Dbar, leverage, and deviance information criterion (DIC) between a random and fixed effect model.[27] We selected a random effect Bayesian model according to the residual variance as well as DIC (Supplemental Table S1).

Pairwise associations between each modality were delineated by a graphical representation of the network. Estimates from all outcome variables were presented as OR and MD with 95% CIs. We calculated the indirect estimate as the differences from the direct estimates and obtained the corresponding 95% predictive intervals (PrI) by normal approximation. Ninety-five percent PrIs were reported, to assess their uncertainty and the magnitude of the heterogeneity in the network analysis.[28] Predictive intervals provide an interval in which future observations will fall.[29]

Consistency within each closed triangle or quadratic loop was investigated using a loop-specific approach in the network meta-analysis. In all triangular and quadratic loops, the inconsistency factor of the ratio of two odds ratios (ROR) from direct and indirect evidence in the loop and its 95% confidence interval, was estimated as the absolute difference between direct and indirect estimates for each comparison in the loop.[30] A ROR value of one means that the two sources are in-agreement, and a ROR value of two means that the difference between the two estimates is double. We also evaluated heterogeneity for the indirect comparison analyses using τ^2, which examines between-study heterogeneity (where a smaller value indicates a better model).

To rank the treatments for an outcome, the comparative influence of all anesthesia techniques for cesarean delivery with the unique dimension was estimated from a multidimensional scaling approach.[28] In addition, clustered ranking plots of the anesthesia techniques network were depicted based on the clustered analysis of surface under the cumulative ranking (SUCRA) probabilities for two different outcomes.[28]

A "comparison-adjusted" funnel plot was used to evaluate the presence of small-study effects within the network meta-analysis. Subgroup analysis of umbilical arterial pH according to the vasopressor used to treat hypotension was performed to evaluate whether the umbilical arterial pH was affected by the choice of vasopressor.[31,32] Subgroup analysis of healthy women without gestational hypertension, placental insufficiency, or fetal growth restriction and undergoing uncomplicated elective cesarean delivery was conducted to overcome the heterogeneity of inclusion criteria of the enrolled studies. Subgroup analysis in studies published before and after the year 2010 was conducted to exclude bias from the date of publication.

Results

Study selection

Fig. 1 shows the search results and reasons for exclusion from the current study. We initially screened 4944 titles and abstracts from Medline, Embase, Cochrane library, and the additional search from conference abstracts or clinical trial registration websites or reference lists of articles included. Duplicate studies (2298) and articles not meeting the inclusion criteria (2577) were excluded. After reviewing the full text of the remaining 69 studies, 23 were excluded due to the reasons shown in Fig. 1. Finally, 46 randomized controlled trials comparing general, epidural, spinal, and combined spinal-epidural anesthesia were included. There was 100% agreement on inclusion and exclusion of studies between the two reviewers (Supplemental Texts S2 and S3).

Study characteristics

Supplemental Table S3 shows characteristics of studies included in the analysis. The trials were published between 1978 and 2016 and included a total number of 3689 patients. Thirty studies, comprising 2488 women, compared different anesthetic techniques for elective cesarean delivery in healthy women. Thirty-two studies directly compared general and spinal anesthesia, and 20 studies compared general and epidural anesthesia. Eleven studies compared general, spinal and epidural anesthesia altogether, and eight studies compared combined spinal-epidural with other anesthetic techniques.

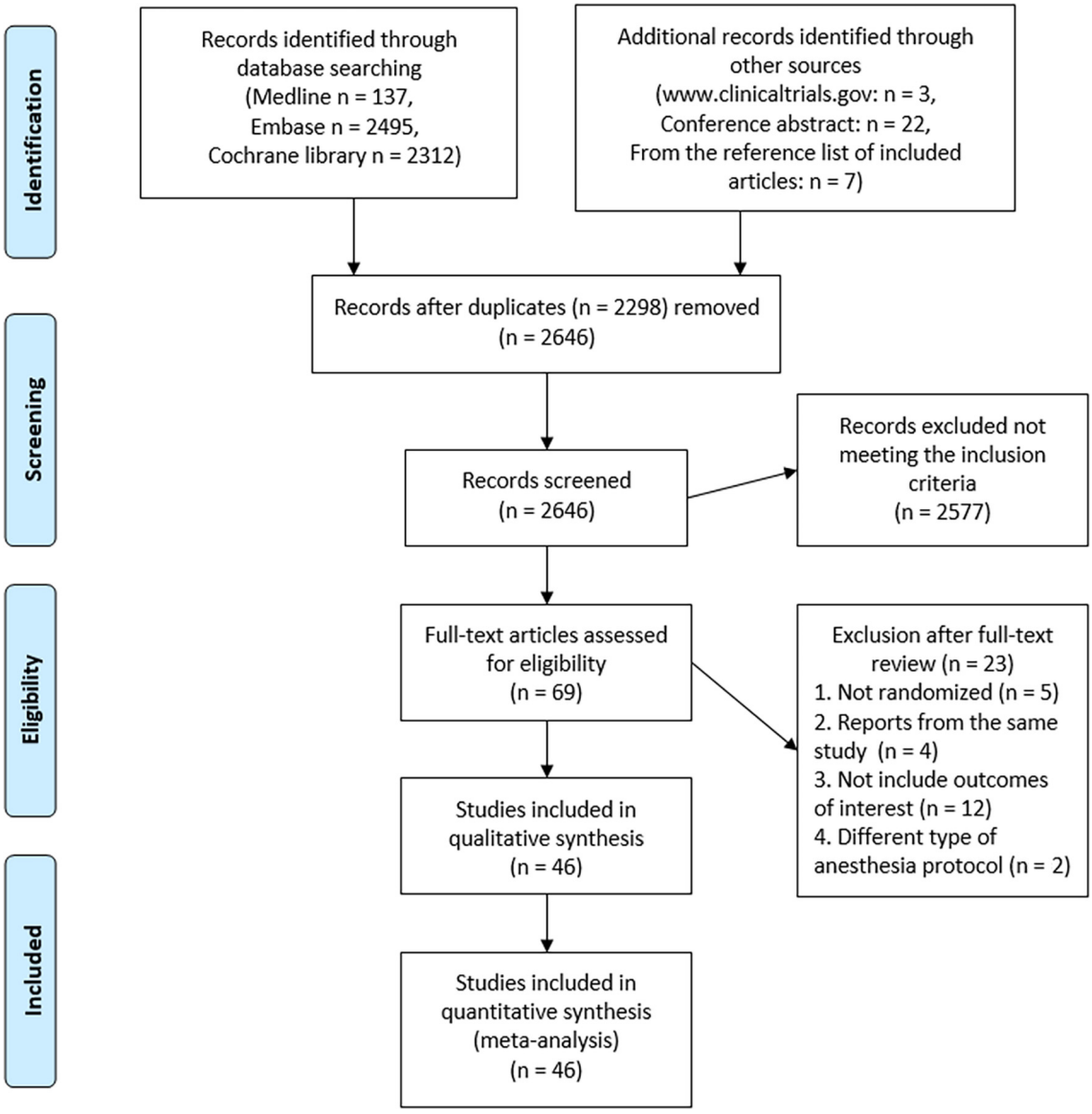

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Risk of bias and quality of evidence

Details of the assessment of risk of bias are depicted in Supplemental Fig. S1. All trials were judged to be at unclear or high risk of bias. Overall, the quality of evidence by outcomes ranged from very low to moderate.

Publication bias

The comparison-adjusted funnel plots for assessing the publication bias of small-study effects, within a network of interventions, are depicted in Supplemental Fig. S2. Most funnel plots seem symmetric, but plots for 1-min Apgar score ≤6 and neonatal neurologic and adaptive capacity score at 2–4 hours showed an outlier, suggesting the source of publication bias.

Quality of evidence

Supplemental Table S4 shows the GRADE quality of evidence. In most comparisons, there was serious imprecision in the pooled estimate, since the 95% CI was wide and crossed unity. In addition, most estimates were down-rated due to an unclear or high risk of bias. Four comparisons among comparisons of all outcomes were rated as moderate quality.

Primary outcomes: Apgar score ≤6 at 1- and 5-min after delivery

A total of 1120 patients from 11 studies and 1378 patients from nine studies were available for analysis of Apgar score ≤6 at 1- and 5-min, respectively (Table 1). Eligible comparisons in the network meta-analysis are shown in Fig. 2, demonstrating predominantly pairwise comparisons of general anesthesia with other techniques.

The ORs for Apgar score ≤6 at 1- and 5-min are depicted in predictive interval plots (Fig. 3). The incidence of 1-min Apgar score ≤6 was significantly lower in spinal anesthesia compared to general anesthesia (OR 0.27, 95% CI 0.13 to 0.55; P <0.001, moderate quality of evidence).

Secondary outcomes

The number of enrolled studies and patients are listed in Table 1. Network plots for secondary variables are shown in Supplemental Fig. S3. The MDs and ORs of all secondary variables are shown in PrIs (Supplemental Fig. S4). Neither the continuous value of umbilical arterial pH nor a categorized variable of umbilical arterial pH <7.2 were significantly different between techniques. Umbilical venous pH with epidural anesthesia was significantly higher than that with general anesthesia (MD 0.010, 95% CI 0.001 to 0.020; P=0.039, moderate quality of evidence) or with spinal anesthesia (spinal vs. epidural -0.010, 95% CI −0.020 to −0.001; P=0.031, moderate quality of evidence). With spinal anesthesia, Apgar scores at 1- and 5- min were significantly higher than that with general anesthesia, with a moderate quality of evidence (1-min Apgar score MD 0.35, 95% CI 0.15 to 0.55; P <0.001: 5-min Apgar score MD 0.24, 95% CI 0.07 to 0.41; P=0.005).

The inconsistency plot (Supplemental Fig. S5) shows the loop-specific heterogeneity estimate, and the ROR from direct and indirect comparison shows no significant inconsistency in the network meta-analysis (1-min Apgar score: general-epidural-spinal loop ROR=1.050, 95% CI 1.00 to 1.96, τ^2=0.147, P=0.880). However, 95% PrIs were mostly very wide, suggesting heterogeneity between the studies included.

Subgroup analyses and sensitivity analyses

Subgroup analysis of umbilical arterial pH according to the vasopressor used to treat hypotension was performed. While there were only four studies which reported that they used phenylephrine, 12 studies reported using ephedrine. Therefore, we performed a

Table 1 Number of enrolled studies and patients according to outcomes in the network analysis

	Overall	1-min Apgar score ≤6	5-min Apgar score ≤6	1-min Apgar score	5-min Apgar score	Umbilical arterial pH	Umbilical venous pH	Maternal EBL	Neonatal score
Overall									
Studies (n)	46	11	9	27	20	24	12	6	4
Women (n)	3689	1120	1378	2029	1652	2076	1257	566	488
Elective cesarean delivery with healthy women									
Studies (n)	30	7	7	17	13	17	10	1*	3*
Women (n)	2488	880	1238	1225	1024	1660	1257	30*	147*
Recent studies (later than 2010)									
Studies (n)	20	5	5	13	9	10	3*	3	2*
Women (n)	1783	518	918	972	749	1102	460*	130	117*

EBL: estimated blood loss. Neonatal score: neonatal neurologic and adaptive capacity score at 2–4 hours. All studies that reported the outcomes of interest were counted. However, when studies did not report standard deviations or when standard deviation equalled zero, the studies were excluded from this table.

*Could not be included in the network analysis due to limited data.

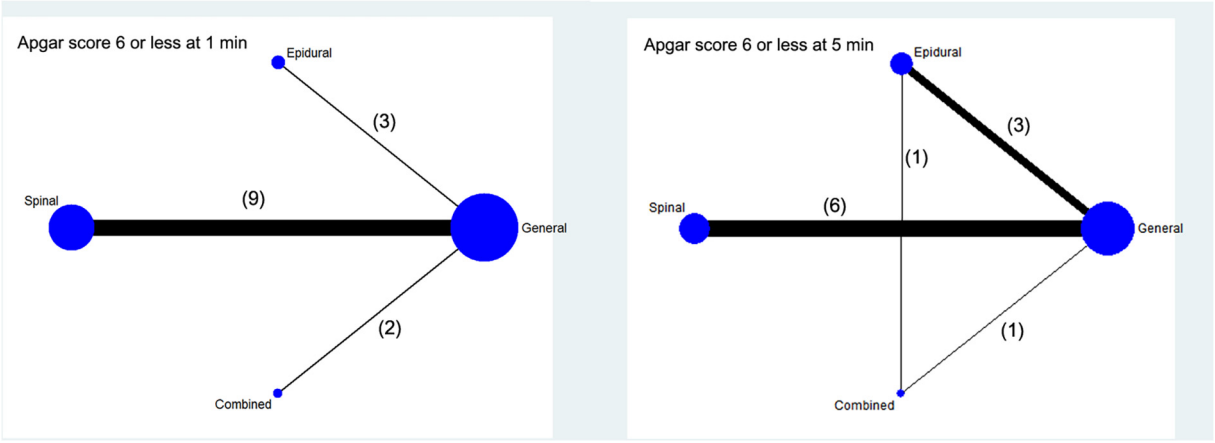

Fig. 2 Network plot of possible anesthesia techniques for Apgar score ≤6 at 1- and 5-min; and umbilical arterial and venous pH. Nodes are weighted according to the number of patients with the respective interventions. Edges are weighted according to the number of patients included in the comparison between the two connected modalities. No connection between any pair of the comparison means that the comparison was made from the indirect comparison. For example, three among six comparisons were made from network analysis regarding Apgar score ≤6 at 1-min. The number in parenthesis means the number of studies included in each pair of comparisons

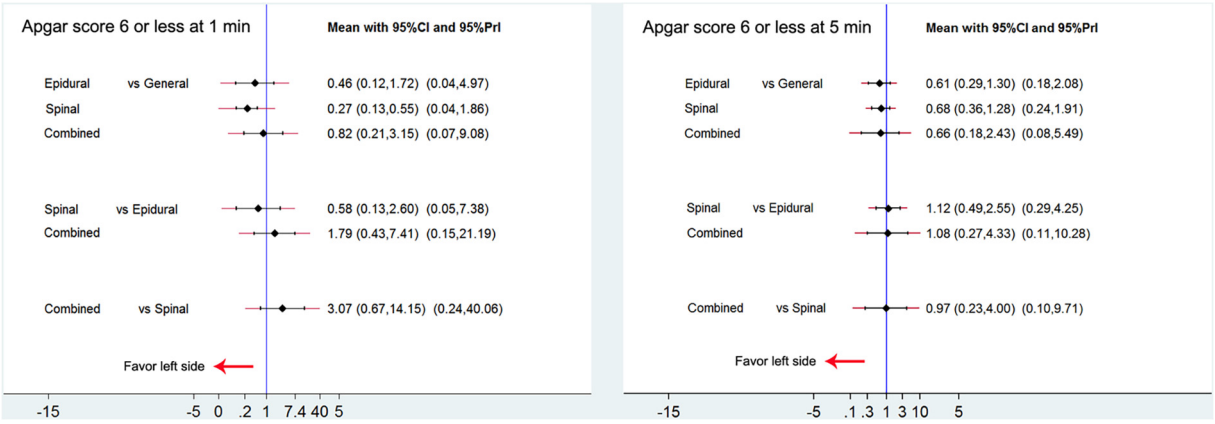

Fig. 3 Predictive interval plots of the anesthesia techniques network in terms of Apgar score ≤6 at 1- and 5-min and umbilical arterial and venous pH. The solid black lines represent the confidence intervals for summary odds ratio or mean difference for each comparison and the red lines the respective predictive intervals. The blue line corresponds to the line of no difference (odds ratio equal to 1 or mean difference to 0). The arrow with "favor right/left side" means that if the confidence interval is significant in the direction of the arrow, the anesthetic technique in the designated direction (right/left) is more favorable than the anesthetic technique in the opposite direction

subgroup analysis only for ephedrine. Umbilical arterial pH with all three neuraxial anesthetic techniques was significantly lower than that with general anesthesia (Supplemental Fig. S6), which suggests that umbilical arterial pH is adversely affected by the choice of ephedrine.

Subgroup analysis of parturients who underwent an uncomplicated elective cesarean delivery was performed and network estimates of outcome variables are shown in Supplemental Table S5. Spinal anesthesia was associated with a lower incidence of 1-min Apgar score ≤6 and higher Apgar scores at 1- and 5-min compared to general anesthesia. Epidural anesthesia was associated with higher umbilical venous pH compared to general anesthesia.

A sensitivity analysis of studies published before and after 2010 addressed the potential more recent confounder of the use of general anesthesia only for compromised pregnancies. The subgroup analysis of the more recent studies showed that spinal anesthesia was associated with a significantly lower incidence of 1-min Apgar score ≤6 and higher 1- and 5-min Apgar scores compared to general anesthesia (Supplemental Table S6). The subgroup analysis of past studies also

showed that spinal anesthesia was associated with a significantly higher 1-min Apgar score compared to general anesthesia (Supplemental Table S7).

Relative ranking of anesthesia techniques

We ranked the comparative influence of all anesthesia techniques for cesarean delivery with the unique dimension estimated from multidimensional scaling approach (Supplemental Fig. S7). Spinal anesthesia was ranked as the best modality with regard to 1-min Apgar score ≤6 (SUCRA=89.8), 1-min Apgar score (SUCRA=80.4), 5-min Apgar score (SUCRA=90.5), and estimated maternal blood loss (SUCRA=69). Epidural anesthesia was optimal for 5-min Apgar score ≤6 (SUCRA=69.3), umbilical venous pH (SUCRA=87.4), and neonatal score at 2–4 hours (SUCRA=79.3). Although general anesthesia had the highest probability of being optimal in terms of umbilical arterial pH (SUCRA=69.7), this was not based on a significant difference in the individual pair comparison. A clustered ranking plot was depicted according to the paired comparison of all six outcomes (Fig. 4). Estimated probabilities for best and worst, and SUCRA values for each anesthetic technique, are shown according to different outcome variables in Supplemental Table S8. The probabilities are also shown in elective cesarean delivery (Supplemental Table S9), and in recent and old studies (Supplemental Tables S10 and S11).

Discussion

We undertook a network meta-analysis comparing four different anesthetic techniques in women undergoing cesarean delivery. The network pooled estimates of outcomes revealed significant differences in the incidence of 1-min Apgar score ≤6 and Apgar scores at 1- and 5-min, favoring spinal anesthesia compared with general anesthesia. The mean difference in umbilical venous pH

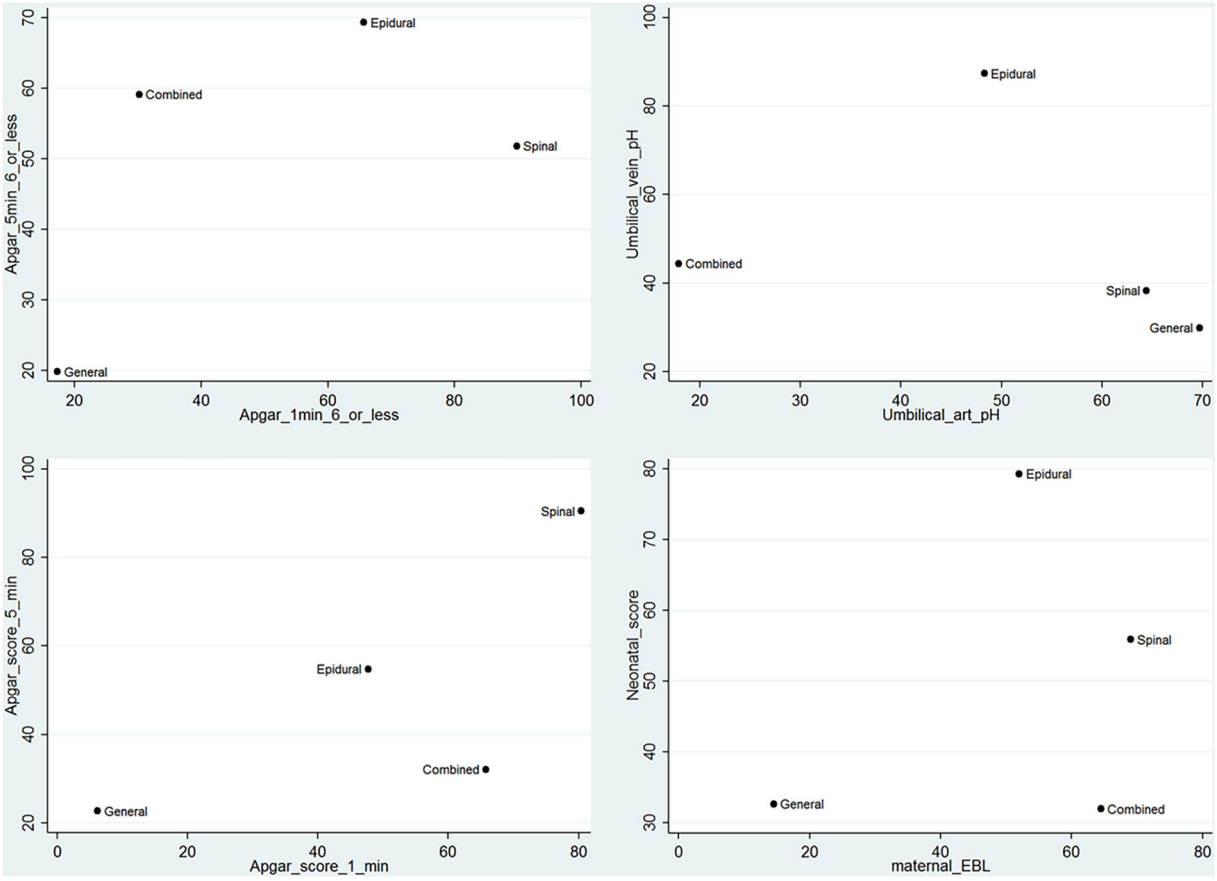

Fig. 4 Clustered ranking plots of the anesthesia techniques network based on clustered analysis of SUCRA values for paired two different outcomes: 1- and 5-min Apgar scores, the incidence of 1- and 5-min Apgar score ≤6, umbilical arterial and venous pH, maternal estimated blood loss and neonatal neurologic and adaptive capacity score at 2–4 hours. Each dot was located according to the two SUCRA values of each anesthetic technique for the two outcomes. The larger SUCRA values mean a better ranking of the technique. The anesthetic technique located in the right upper corner has higher SUCRA values for both variables of the X and Y axes and is regarded as the most preferred, compared in terms of both outcomes of the X and Y axes. EBL: estimated blood loss; Combined: combined spinal-epidural anesthesia; SUCRA: surface under cumulative ranking

was significant, favoring epidural anesthesia compared to general or spinal anesthesia. The umbilical arterial pH, assessed as either a continuous or categorized variable, was not significantly different between different techniques of anesthesia. The relative ranking showed that spinal and epidural anesthesia had the highest probabilities of being the best for all fetal outcomes investigated, except umbilical arterial pH. These findings were consistent in the subgroup and sensitivity analyses.

Spinal anesthesia is generally preferred for cesarean delivery.[24,11–14,33–35] Spinal anesthesia is superior to general anesthesia for neonatal acid-base status and Apgar score,[24,33,35,11–14] and possibly also for neurobehavioral status and need for assisted ventilation.[35,36] Nonetheless, the results of our randomized controlled trials were not consistent, with some studies reporting no differences between general and neuraxial anesthesia.[37–39] General anesthesia in term neonates was associated with a higher incidence of lower 1- and 5-min Apgar scores.[35,11–14]

In contrast, spinal anesthesia was associated with significantly lower umbilical arterial pH than general anesthesia in parturients with or without preeclampsia,[34,38] such that general anesthesia had the highest ranking with respect to umbilical arterial pH. This may be because of hypotension following spinal anesthesia that can decrease uteroplacental perfusion and produce fetal acidosis.[40] However, maternal hemodynamics were acceptable and similar to general anesthesia in one previous study.[34] Staikou et al.[41] randomized 380 parturients to general, epidural, or spinal anesthesia and found that neonatal acid-base balance was better preserved during general anesthesia compared to neuraxial anesthesia, but there were no differences in Apgar scores and neonatal outcomes. Kavak et al.[39] compared spinal versus general anesthesia in terms of short-term neonatal outcomes, including biochemistry of neonatal blood and clinical outcomes such as Apgar score, hospital length of stay and incidence of intensive care unit admission, but found no differences. Maternal hypotension associated with spinal anesthesia does not necessarily result in poor neonatal outcomes, provided that maternal arterial pressure is monitored and hypotension immediately corrected.

Previous classic meta-analyses have compared anesthetic techniques for cesarean delivery. Although there have been many studies reporting advantages from neuraxial anesthesia, these meta-analyses did not demonstrate any advantages over general anesthesia in terms of fetal outcomes.[5,42] A Cochrane review that included 22 studies found that epidural or spinal anesthesia was associated with lower EBL, but found no differences in neonatal 5-min Apgar score or the need for neonatal resuscitation,[5] and concluded that there was no evidence that neuraxial anesthesia was superior. Our results differ. Another meta-analysis of 27 studies concluded that spinal anesthesia could not be considered safer for the fetus than epidural or general anesthesia.[42] Similarly, in our network estimates, umbilical arterial and venous blood pH were not significantly different between general and spinal anesthesia, but Apgar scores were consistently higher with spinal anesthesia for three of our four Apgar score-related study outcomes. Heesen et al.[43] performed a meta-analysis assessing postpartum hemorrhage (volume and the need for transfusion) with neuraxial and general anesthesia. General anesthesia was associated with greater blood loss, but not requirement for transfusion. Our ranking plot for maternal hemorrhage also showed that general anesthesia was ranked lower than neuraxial anesthesia.

Umbilical venous blood pH associated with epidural anesthesia was significantly higher than that of general or spinal anesthesia in our network analysis. In contrast to spinal anesthesia, epidural anesthesia allows titration of the extent and duration of anesthesia,[15] and may limit the sudden deterioration of hemodynamics induced by spinal or general anesthesia. However, statistical significance for umbilical venous pH as a continuous variable does not imply a clinically relevant difference. Furthermore, umbilical arterial blood pH showed no significant difference and network analysis of base deficit was not performed. We did analyze umbilical arterial pH <7.2, because the incidence of umbilical arterial acidosis may be more clinically relevant,[44] but few studies have reported this outcome and there was no significant network estimate.

Unlike other study outcomes, we could find no evidence that neuraxial anesthesia was superior to general anesthesia regarding umbilical arterial pH. Variations in maternal ventilation will alter umbilical venous pH and subsequently umbilical arterial pH, so umbilical arterial pH may be considered a secondary variable. If specifically corrected for umbilical venous pH, the arterial pH will improve, limiting its value in assessing fetal blood acid-base balance. The umbilical arterial base deficit is a more specific and more valid index of neonatal welfare.[45] A study comparing umbilical arterial pH and base deficit found that umbilical arterial pH was significantly lower during spinal anesthesia than during general anesthesia, but with no difference in base deficit.[38]

We chose Apgar score as our primary outcome variable because most previous studies reported this outcome. However, Apgar score has received criticism and its prognostic value questioned.[46] Low Apgar score cannot be considered as evidence of asphyxia and does not predict individual neonatal mortality or neurologic outcome. We analyzed an Apgar score of >6 as our primary outcome because it is associated with adverse fetal outcomes.[9,10] However, in this study the frequency of Apgar score ≤ 6 was as low as 1–2%,[47] which limits the clinical significance due to lack of appropriate power. The overall incidence of Apgar score ≤ 6 among patients included in our network was 12.5% and 5.2%

for 1-min and 5-min score respectively, which is higher than the previous report.

Other fetal clinical outcomes could be considered for comparison between anesthetic techniques in further studies or meta-analyses. The incidence of newborn admission to an intensive care unit and breastfeeding outcomes are worth comparing.[48] In addition, the incidence of maternal hypotension, post-dural puncture headache, conversion to general anesthesia, and intraoperative supplementation of opioid or epidural anesthetic and airway problems could be compared among spinal, epidural, combined spinal-epidural and general anesthetic techniques.

Although not analyzed in our study, other clinical variables known to influence fetal and maternal outcomes during cesarean delivery should also be considered. These factors may be more important than the type of anesthesia and are likely confounders of our results. Birth weight and gestational age could be important.[49] Surgery-related parameters such as the urgency of delivery, the duration of surgery, and the interval from uterine incision to delivery, are known to influence neonatal outcomes.[50]

Maternal inhaled oxygen concentration, minute ventilation, intravenous fluid volume, blood pressure, vasopressor administration and extent of sympathetic block may be more important than the nature of the anesthetic agents.[42] The dose of local anesthetic used for spinal anesthesia and the extent of the spinal block influence maternal hemodynamics. Small incremental doses using an intrathecal catheter rather than a single-shot spinal anesthesia may decrease the cardiac output changes and an adverse effect on umbilical arterial pH.[51]

The authors acknowledge that our meta-analysis has some limitations. Firstly, the study populations included in our analysis were heterogenous, including preeclampsia, fetal growth-restriction and placenta previa. Differences in outcomes between anesthetic techniques may not be consistent among these different groups of patients. To address heterogeneity, we performed a subgroup analysis for uncomplicated elective cesarean delivery. Secondly, most of the studies included were at unclear or high risk of bias. Allocation concealment and blinding of the study group were not achieved in most studies, so the quality of our network analysis is limited by the low quality of primary data. Thirdly, various maternal and fetal outcomes could not be analyzed due to the limitations of the studies. Other important fetal outcomes include arterial oxygen and carbon dioxide pressure, laboratory evidence of fetal stress and asphyxia (serum cardiac or liver enzyme and cortisol levels), duration of hospital stay, and the incidence of respiratory depression or admission to an intensive care unit. Fourthly, because our study included all published randomized controlled trials over a long period, changes across time may act as a bias. In recent years, neuraxial anesthesia has been widely recommended for cesarean delivery and general anesthesia is most frequently performed in an emergency for compromised pregnancies.[2] We attempted to exclude the effect of publication time and urgency of cesarean delivery by subgroup analyses of more recent studies and of elective cesarean delivery only. Fifthly, as shown in network plots, studies comparing combined spinal-epidural anesthesia with other modalities were few. It could be justified to analyze combined spinal-epidural anesthesia as a separate group, but as the results associated with this technique were mostly from indirect estimates because of sparse data, our results should consider this limitation. Further studies directly comparing combined spinal-epidural anesthesia with other techniques are required.

In conclusion, we performed a network comparison of four different anesthesia techniques for cesarean delivery. There were significant estimates for network comparisons of fetal and maternal outcomes of Apgar scores at 1- and 5-min, Apgar score $\leq$6 at 1-min and umbilical venous pH, favoring spinal and epidural anesthesia over general anesthesia. Spinal and epidural anesthesia had the highest probability of being best for all outcomes except umbilical arterial pH. Our subgroup analysis of uncomplicated elective cesarean delivery revealed similar differences. We conclude that neuraxial anesthesia may be better than general anesthesia in terms of Apgar scores and umbilical venous pH, with the reservation that most studies included in the analysis had an uncertain risk of bias and had a heterogeneous population. We could not rule out a 'small-study' effect on some variables analyzed. Well-designed studies on this topic, with sufficient power and with low risk of bias, are still required.

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Conflict of interest statement

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Appendix A. Supplementary data

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