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Metaraminol use during spinal anaesthesia for caesarean section: a meta-analysis of randomised controlled trials

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ABSTRACT

Introduction: During caesarean section, the use of a vasopressor is often required to achieve haemodynamic stability of the parturient. Metaraminol is a vasopressor used in this context in some countries. However, the differences between metaraminol and other vasopressors remain unclear.

Methods: A search of the PubMed, Cochrane Library, and Embase databases was performed to identify randomised controlled trials comparing the use of metaraminol with other vasopressors during spinal anaesthesia at caesarean section. The selected studies were subjected to meta-analysis and risk-of-bias assessment.

Results: Four randomised, controlled trials met the selection criteria and 409 parturients who underwent an elective caesarean section were included in this meta-analysis. The quality of these trials was good. Metaraminol was associated with higher umbilical arterial pH (standardised mean difference [SMD] 0.82, 95% CI 0.01 to 1.62, P=0.05); a lower incidence of fetal acidosis (RR 0.08, 95% CI 0.01 to 0.63, P=0.02); and a lower incidence of nausea or vomiting (RR 0.16, 95% CI 0.04 to 0.57, P=0.0005) than was ephedrine. Metaraminol resulted in higher umbilical arterial pH (SMD 0.42, 95% CI 0.15 to 0.68, P=0.002) but a higher incidence of reactive hypertension (RR 1.80, 95% CI 1.32 to 2.46, P=0.0002) than did phenylephrine.

Conclusion: The results of this study showed that for spinal anaesthesia at elective caesarean section, metaraminol may be a more suitable vasopressor than ephedrine and its effects are at least not inferior to those of phenylephrine.

Keywords: Metaraminol; Ephedrine; Phenylephrine; Spinal anaesthesia; Caesarean section; Meta-analysis; Systematic review

Introduction

Metaraminol, also known as metaradrine, is a sympathomimetic amine that has been used for many years to treat hypotension during anaesthesia. Metaraminol is often used in some countries during obstetric anaesthesia. Metaraminol acts both directly and indirectly, mainly stimulating alpha-1-adrenergic receptors, with a weak effect on beta-receptors.[1]

Metaraminol has been suggested to be a safer alternative than ephedrine in obstetric patients, as demonstrated by studies that have reported that metaraminol maintains a more suitable umbilical arterial pH than does ephedrine.[2,3] It may also be more effective than ephedrine in preventing blood pressure fluctuations during surgery.[4] Other uses of metaraminol in medicine include the treatment of shock in emergency settings,[5,6] treatment of paroxysmal supraventricular tachycardia,[7] maintenance of mean perfusion pressure during cardiopulmonary bypass,[8] and the treatment of priapism.[9,10]

Studies over past decades have extensively compared phenylephrine and ephedrine.[11–13] Phenylephrine, an α-1-adrenergic agonist with no β-activity, is currently regarded as the preferred vasopressor for obstetric anaesthesia. In contrast, there have been few studies using metaraminol. In this study we comprehensively searched the literature and conducted a meta-analysis

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of randomised controlled trials (RCTs) to compare the outcomes after metaraminol use with those after other vasopressors, during spinal anaesthesia at the time of caesarean section.

Methods

Eligibility criteria

Randomised controlled trials reporting comparisons between metaraminol and placebo or another vasopressor, during caesarean section under spinal anaesthesia, were included. Series or duplicate publications in the same or different journals were counted only once. No restrictions were applied with respect to the language or the journal type.

Search strategy

Relevant articles were identified through an online search of the PubMed Cochrane Library, and Embase databases. To ensure a comprehensive search, all articles related to metaraminol were regarded as potentially relevant. The keywords 'metaraminol' and 'metaradrine' were used. The trade names (Aramine, Metaramin, and Pressonex) and synonyms (metaraminolum, metaraminol bitartrate, m-hydroxypropadrine, m-hydroxyphenylpropanolamine, m-hydroxy norephedrine, L-metaraminol, and hydroxynorephedrine) of metaraminol were also included in the search. The RCTs were identified through the refine search function in the databases, if available. Articles were also identified by manually searching the reference lists of the relevant articles. The literature was searched from the date of database inception to 11 March, 2018.

Two reviewers independently reviewed the full texts of all potentially relevant articles to identify articles meeting the eligibility criteria. The individually recorded decisions of the two reviewers were then compared and dissimilarities in the decisions were resolved by a third reviewer.

Data items

For each RCT identified, information regarding the characteristics of the eligibility criteria, mean age, comparator groups, numbers of participants, protocols of the vasopressor regimens, and outcome measurements, was obtained.

Risk-of-bias assessment

Risk-of-bias assessment was performed using the Cochrane Collaboration's tool for assessing risk of bias, which is a widely used quality assessment tool for evaluating RCTs.[14] The assessed domains were: (1) random sequence generation, (2) allocation concealment, (3) blinding of participant and personnel, (4) blinding of outcome assessor, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.

Outcome selection

The included studies considered various parameters for umbilical blood gas analysis. The primary outcomes were mean umbilical arterial pH and incidence of umbilical arterial pH < 7.2. Any other comparable outcomes with sufficient analytical data in two or more RCTs were regarded as secondary outcomes. These included the incidence of Apgar score below < 7 at one minute, the incidence of hypotension, the incidence of hypertension, and the incidence of nausea or vomiting. Based on the data available, the incidence of hypotension was defined as a systolic blood pressure $< 80\%$ of the intra-operative baseline value, and the incidence of hypertension was defined as a systolic blood pressure $> 120\%$ of the baseline value. The umbilical arterial pH was presented as median and interquartile range in one RCT; hence, raw data were obtained by contacting the corresponding author.[3]

Statistical analysis

The meta-analysis was performed using RevMan 5.3 software. For parameters with dichotomous data, risk ratios (RRs) were calculated, these being the ratio of the risk of an event in the two groups. For parameters with continuous data, standardised mean differences (SMDs) were calculated: an SMD is considered to be a large difference when the value is > 0.7, a moderate difference when the value is between 0.4 and 0.7, and a small difference when the value is < 0.4.[14] The 95% confidence intervals (CIs) of the above parameters were calculated. Data were pooled using the random effects model because of the expectation of the various study methods in each trial. Statistical heterogeneity, calculated using the I^2 test, was considered high if it exceeded 50%. In the case of high heterogeneity, a sensitivity analysis was conducted to confirm its effect after adjustment of the included data.

Data extraction and analysis

Two reviewers independently extracted relevant data, conducted meta-analysis, and assessed the quality of the selected articles. The individual decisions of the two reviewers were compared and dissimilarities in the decisions were resolved by a third reviewer.

Results

Study selection

After searching the databases for keywords and excluding duplicate results, 79 potentially relevant articles were identified. By reviewing the full text of these articles, four RCTs that used metaraminol during caesarean section under spinal anaesthesia were determined to meet the eligibility criteria. Among these RCTs, prophylactic administration of metaraminol was compared with ephedrine in three studies[3,15,16] and with phenylephrine

in three studies.[15–17] Three RCTs used a bolus plus infusion regimen[3,15,16] and one RCT used an infusion only regimen.[17] In total, 409 women undergoing elective caesarean section were included in this meta-analysis. Fig. 1 depicts a flow chart for the selection of trials. Table 1 lists the characteristics of the selected trials.

Risk-of-bias assessment

Random sequence generation, allocation concealment, and blinding of the participants and the medical personnel involved in anaesthesia or outcome assessment were adequately performed in all studies. A potential risk of bias was observed in one study that lost up to 18.8% of umbilical arterial data because of inadequate arterial gas sampling.[17] No notable risk of bias in regard to selective reporting or other biases was noted in these studies (Table 2). According to the risk-of-bias assessment, the overall quality of the included studies is good.

Meta-analysis

The four RCTs selected measured various outcomes (Table 1). In the comparison between metaraminol and ephedrine, the metaraminol-treated group exhibited a higher mean umbilical arterial pH (SMD 0.82, 95% CI 0.01 to 1.62, P=0.05, n=159), a lower incidence of umbilical arterial pH below 7.2 (RR 0.08, 95% CI 0.01 to 0.63, P=0.02, n=159), and a lower incidence of nausea or vomiting (RR 0.16, 95% CI 0.04 to 0.57, P=0.005, n=162) than did the ephedrine-treated group. There was no significant difference in the incidence of Apgar score <7 at one minute (RR 0.62, 95% CI 0.08 to 4.85, P=0.65, n=162), incidence of hypotension (RR 0.56, 95% CI 0.26 to 1.17, P=0.12, n=158) or incidence of hypertension (RR 1.44, 95% CI 0.82 to 2.54, P=0.20, n=112) between the metaraminol- and ephedrine-treated groups. The forest plots of these outcomes are shown in Fig. 2.

In the comparison between metaraminol and phenylephrine, the metaraminol-treated group exhibited a higher mean umbilical arterial pH (SMD 0.42, 95% CI 0.15 to 0.68, P=0.002, n=273) but also a higher incidence of hypertension (RR 1.80, 95% CI 1.32 to 2.46, P=0.0002, n=304) than the phenylephrine-treated group. There was no significant difference in the

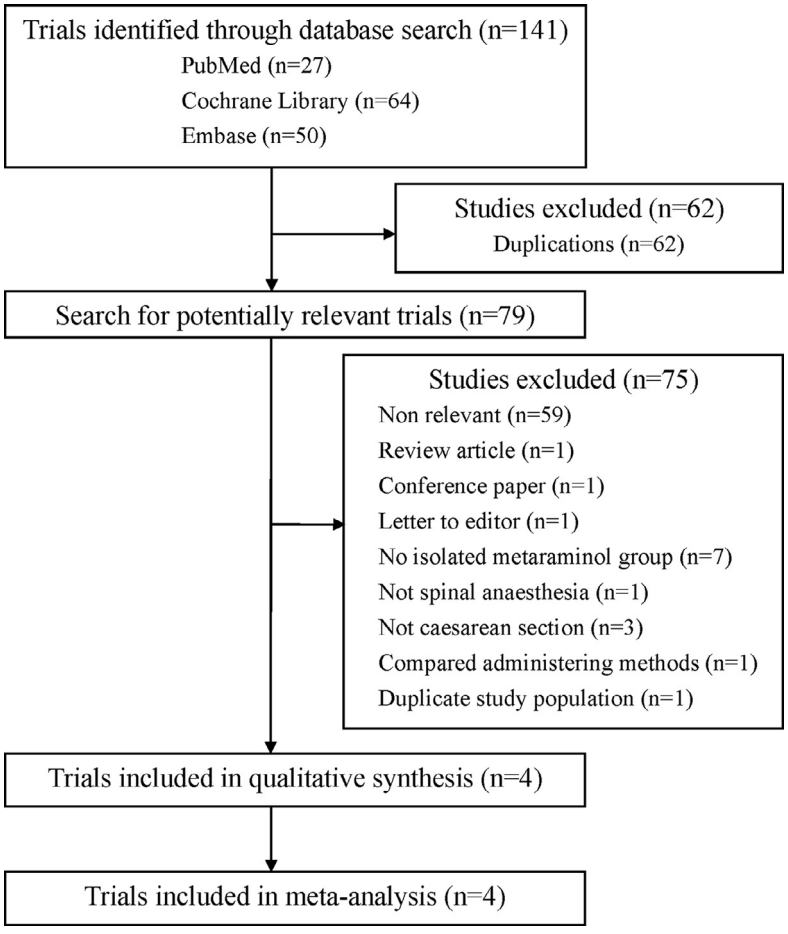

Fig. 1 Flow chart for the selection of trials

Table 1 Characteristics of the included trials

Study	Eligibility criteria	Mean age (y)	Group	Initial (bolus) + infusion dose	Adjusting dose	Outcome measurements
Ngan Kee, 2001[3]	Incl: ASA I/II parturients with singleton pregnancies undergoing elective CS Excl: Pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, fetal abnormalities	32.5	Metaraminol (n=25) Ephedrine (n=25)	0.5 mg + 0.25 mg/min 10 mg + 5 mg/min	Start infusion if SAP <90% of baseline Stop infusion if SAP >100% of baseline Double infusion rate if SAP <80% of baseline	SAP, heart rate, Apgar score, umbilical blood gas, uterine artery pulsatility index, nausea or vomiting
Bhardwaj, 2013[16]	Incl: ASA I parturients with singleton pregnancies scheduled for elective CS Excl: fetal abnormalities, pre-eclampsia, or cerebrovascular diseases	27.6	Metaraminol (n=28) Ephedrine (n=28) Phenylephrine (n=34)	0.5 mg + 0.25 mg/min 5 mg + 2.5 mg/min 30 μg + 15 μg /min	Add a bolus dose if SAP <90% of baseline Stop infusion if SAP >125% of baseline	SAP, heart rate, umbilical blood gas, Apgar score, nausea, vomiting
de Aragão, 2014[15]	Incl: ASA I parturients of age 20–34 years, singleton pregnancy, gestational age 39–40 weeks, no comorbidities, scheduled for elective CS Excl: fetal abnormalities, insufficient umbilical cord blood collection, anaesthetic block failure	20–34	Metaraminol (n=30) Ephedrine (n=30) Phenylephrine (n=30)	0.25 mg + 0.25 mg/min 4 mg + 4 mg/min 50 μg + 50 μg/min	Add a bolus dose if SAP <80% of baseline Double the infusion rate if SAP is 80%–100% of baseline Halve the infusion rate if SAP is 100%–120% of baseline Stop infusion if SAP >120% of baseline	SAP, heart rate, umbilical blood gas, Apgar score, nausea or vomiting
McDonnell, 2017[17]	Incl: ASA I/II parturients with BMI 20–35 kg/m^2, singleton pregnancy, scheduled for elective CS Excl: diabetes, pre-eclampsia, cardiovascular or cerebrovascular disease, fetal abnormality or intra-uterine growth restriction, inadequate sensory block, monitoring unreliable due to severe shivering	31.9	Metaraminol (n=91) Phenylephrine (n=95)	30 mL/h (0.5 mg/mL) 30 mL/h (100 μg/mL)	Add a 1 mL bolus if SAP <80% of baseline Increase by 5 mL/h if SAP <90% of baseline Reduce by 5 mL/h if SAP >100% of baseline Stop infusion if SAP >120% of baseline	SAP, heart rate, umbilical blood gas, Apgar score, nausea, vomiting

ASA: American Society of Anesthesiology physical status classification; BMI: body mass index; CS: caesarean section; Inc.: inclusion criteria; Excl.: exclusion criteria; SAP: systolic arterial pressure.

Table 2 Risk-of-bias assessment of the included trials

Study	Random sequence generation	Allocation concealment	Participant and personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective reporting	Other bias
Ngan Kee, 2001[3]	LRB	LRB	LRB	LRB	LRB	LRB	LRB
Bhardwaj, 2013[16]	LRB	LRB	LRB	LRB	LRB	LRB	LRB
de Aragão, 2014[15]	LRB	LRB	LRB	LRB	LRB	LRB	LRB
McDonnell, 2017[17]	LRB	LRB	LRB	LRB	HRB	LRB	LRB

HRB: high risk of bias, LRB: low risk of bias.

incidence of umbilical arterial pH <7.2 (RR 0.18, 95% CI 0.02 to 1.48, P=0.11, n=273), incidence of Apgar score <7 at one minute (RR 0.40, 95% CI 0.11 to 1.45, P=0.16, n=304), incidence of hypotension (RR 0.80, 95% CI 0.53 to 1.22, P=0.30, n=304), or incidence of nausea or vomiting (RR 0.53, 95% CI 0.16 to 1.73, P=0.29, n=304) between the metaraminol- and phenylephrine-treated groups. The forest plots of these outcomes are shown in Fig. 3.

Statistical heterogeneity

Within 12 forest plots in this meta-analysis, high statistical heterogeneity (I^2=83%) was found only in the mean umbilical arterial pH values in the comparison between metaraminol and ephedrine use (Fig. 2.1). Within the three RCTs included in this latter comparison, one was regarded as an outlier because there were no episodes of umbilical arterial pH <7.2 in either study group.[16] After excluding this study, the metaraminol-treated group still exhibited a higher mean umbilical arterial pH than the ephedrine-treated group (SMD 1.19, 95% CI 0.62 to 1.76, n=109, P< 0.0001, I^2=47%). Therefore, the initial result of this comparison was regarded as reliable. Statistical heterogeneity was low (I^2=0–34%) in the remaining comparisons.

Outcomes not included in the meta-analysis

One RCT evaluated the uterine artery pulsatility index by means of Doppler ultrasound. Changes in uterine artery pulsatility index were similar between the metaraminol- and ephedrine-treated groups. This outcome was not included in the meta-analysis because it was examined in only a single RCT.[3]

Heart rate as an outcome was also excluded. Across the four RCTs, the metaraminol- and phenylephrine-treated groups exhibited heart rates lower than the baseline rates, whereas the ephedrine-treated groups exhibited heart rates higher than the baseline rates. Because neither a higher nor a lower heart rate is a favourable effect direction, meta-analysis of the heart rate was not considered appropriate.

Three RCTs investigated reflex bradycardia.[15–17] The data were not pooled in the meta-analysis because these RCTs used different definitions for bradycardia. Within these RCTs, one reported no maternal bradycardia in any patient treated with metaraminol, phenylephrine or ephedrine.[16] One showed equal rates of bradycardia between phenylephrine and metaraminol (10% and 10%; n=3 and n=3), and no bradycardia in the ephedrine-treated group.[15] The remaining trial demonstrated a non-significantly higher incidence of bradycardia in the phenylephrine group (46.3%, n=44) compared to the metaraminol group (37.8%, n=34).[17]

Figure 2.1 Mean umbilical arterial PH

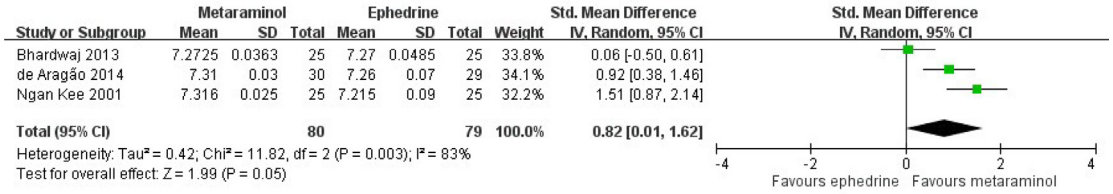

Figure 2.2 Incidence of umbilical arterial PH below 7.2

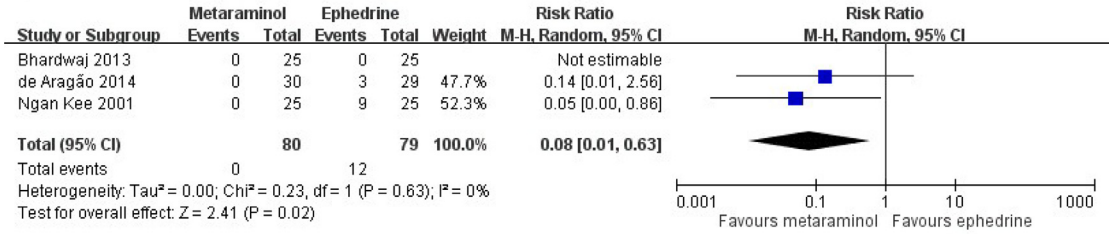

Figure 2.3 Incidence of Apgar score below 7 at one minute

Figure 2.4 Incidence of hypotension

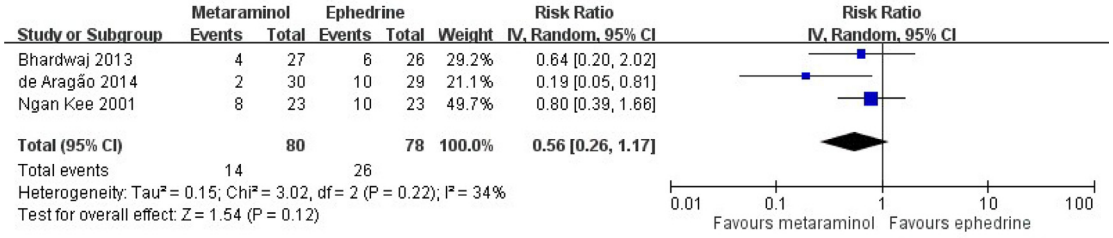

Figure 2.5 Incidence of hypertension

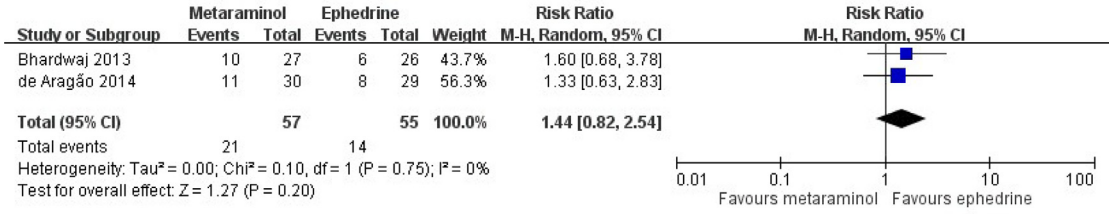

Figure 2.6 Incidence of nausea or vomiting

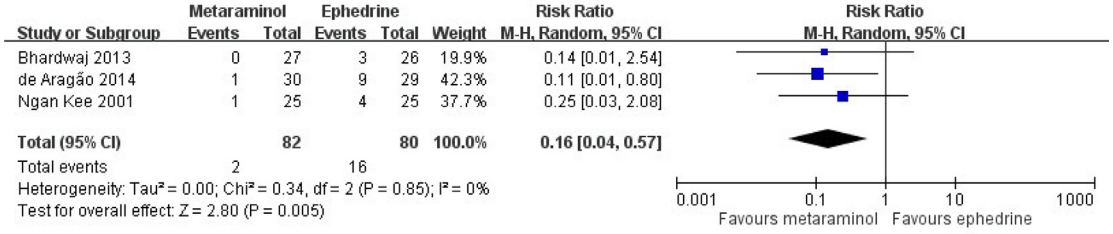

Fig. 2 Comparison of metaraminol and ephedrine use

Figure 3.1 Mean umbilical arterial PH

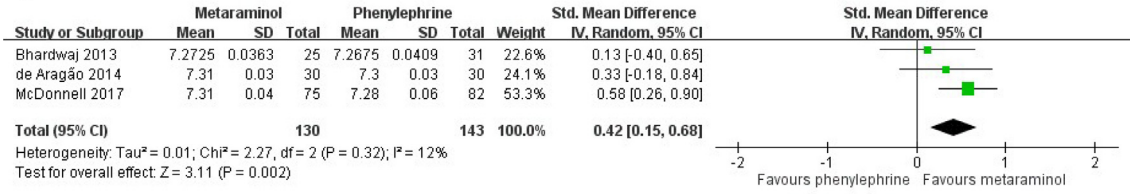

Figure 3.2 Incidence of umbilical arterial PH below 7.2

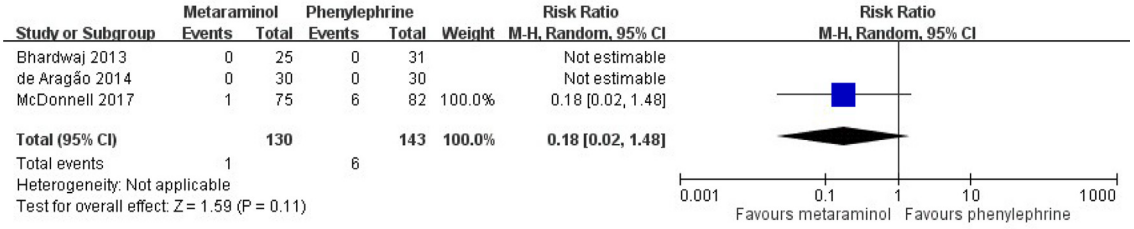

Figure 3.3 Incidence of Apgar score below 7 at one minute

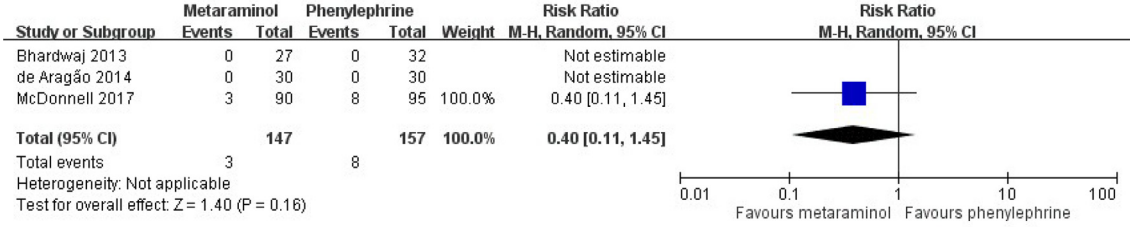

Figure 3.4 Incidence of hypotension

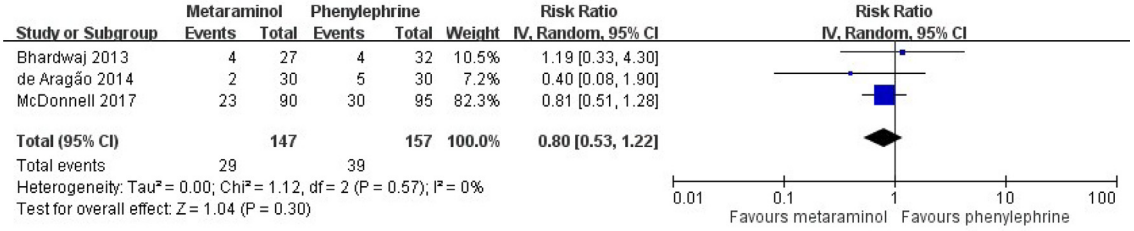

Figure 3.5 Incidence of hypertension

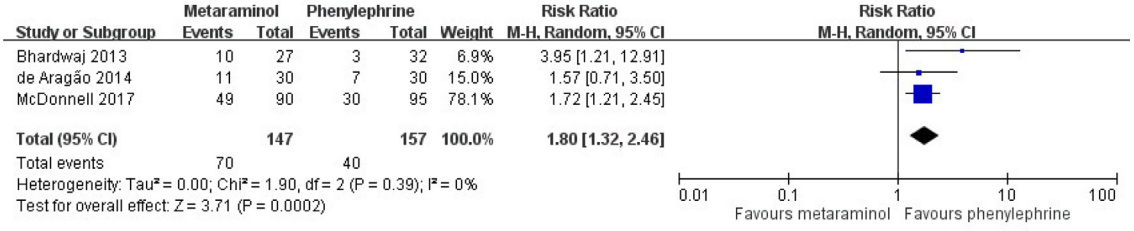

Figure 3.6 Incidence of nausea or vomiting

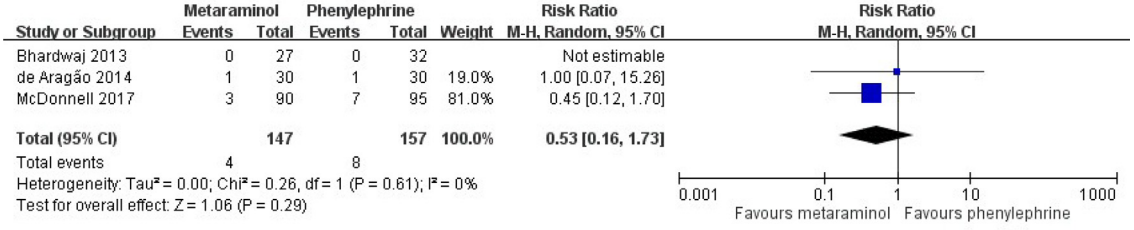

Fig. 3 Comparison of metaraminol and phenylephrine use

Discussion

We identified four RCTs that compared the effects of metaraminol, ephedrine and phenylephrine during spinal anaesthesia for caesarean section.[3,15–17] Our primary outcomes suggested that metaraminol is associated with higher umbilical arterial pH and a lower incidence of neonatal acidosis than ephedrine. Metaraminol also resulted in higher umbilical arterial pH level than did phenylephrine. Our secondary outcomes suggested that metaraminol might result in a lower incidence of maternal nausea or vomiting than ephedrine but a higher incidence of reactive hypertension than phenylephrine. Other differences were not statistically significant.

Ephedrine exerts indirect effects by releasing norepinephrine from sympathetic neurons, thus producing a slower onset of action.[18] Because the effect of ephedrine has a delayed onset, it is usually administered in small boluses as infusions may cause the blood pressure to overshoot the target range.[18] It cannot be said for certain that equivalent doses of ephedrine were used compared with metaraminol, as ephedrine is less suitable for continuous infusion. The RCTs in this meta-analysis used a metaraminol to ephedrine potency ratio of 20:1, 16:1 and 10:1, respectively.

Metaraminol and phenylephrine are both suitable for administration as an infusion. Pharmacologically, metaraminol has a longer duration of action than does phenylephrine. After intravenous administration, the duration of action of phenylephrine is 5 to 10 minutes, whereas that of metaraminol is 20 to 60 minutes.[18,19] An international consensus statement has recommended that phenylephrine infusions be started soon after spinal anaesthesia, at a rate of 25–50 μg/min, for the maintenance of stable maternal pressure.[1] The ideal metaraminol to phenylephrine potency ratio has yet to be established, though two of the studies used a ratio of 5:1[15,17]. This 5:1 ratio of metaraminol and phenylephrine may be close to the comparative potency of these vasopressors but further studies are needed.

We observed that the use of metaraminol produced higher umbilical arterial pH values than those associated with the other two vasopressors. Although early animal studies suggested that ephedrine is more effective than the other vasopressors in the preservation of uteroplacental blood flow,[20,21] this has not been observed clinically in humans.[3,22] Ngan Kee et al. showed that ephedrine crosses the placenta more easily than phenylephrine, which could result in fetal tachycardia and greater beat-to-beat variability.[23,24] There have been claims that the placental transfer of ephedrine and phenylephrine has no major effect on neonatal outcomes.[25,26] However, a systematic review and meta-analysis by Malin et al. confirmed the association between low umbilical cord values and clinical fetal outcomes.[27] Therefore, ephedrine may be associated with more risk of fetal acidosis and worse fetal outcomes, especially when used in high doses.[2]

The prevention of maternal bradycardia is recommended when managing caesarean section.[28,29] A pure α-agonist, such as phenylephrine, has the potential to cause dose-related reflex bradycardia and a reduction in cardiac output.[30] The RCT by Bhardwaj et al. used a very low dose of phenylephrine (15 μg/min after a loading dose of 30 μg) in an effort to prevent reflex bradycardia. They reported no single incidence of a maternal bradycardia among their study patients.[16] The RCT by McDonnell et al. did not demonstrate a significantly higher incidence of bradycardia in the phenylephrine group compared to a metaraminol group at a potency ratio of 5:1, with phenylephrine infused at 50 μg/min, but the study was not powered for this outcome.[17] This RCT used an infusion-only regimen, with no pre-selected loading dose of vasopressor as the idea of a loading bolus has been challenged.[27] Since metaraminol has both α- and β-agonist properties, it may be superior to phenylephrine in preserving cardiac output when bradycardia occurs.[17]

This meta-analysis has several strengths. A comprehensive search in several major databases was performed using rigorous criteria. In addition, quantitative analyses were performed to explore the potential problems. Moreover, the methodological quality of the RCTs was evaluated using the Cochrane Collaboration tool for assessing the risk of bias and was generally acceptable.

The major limitation of this study is that few relevant RCTs have been published, so incorporating future RCTs into the analysis is likely to strengthen the conclusions. Furthermore, the included RCTs varied in their dosing regimens, which increased the risk of bias in this study. Lastly, the time-frame of the studies ranged from 2001 to 2017. With the introduction of automated closed-loop feedback systems and smaller spinal needles, anaesthetic practice is likely to also have changed over the years.

Our meta-analysis revealed that prophylactic administration of metaraminol during spinal anaesthesia for caesarean section appears to result in higher umbilical arterial pH levels than does phenylephrine. Metaraminol also resulted in a higher umbilical arterial pH, a lower incidence of fetal acidosis, and a lower incidence of nausea or vomiting than did ephedrine. However, metaraminol was associated with a higher incidence of reactive hypertension than was phenylephrine. On the basis of the results, during spinal anaesthesia for elective caesarean section, prophylactic administration of metaraminol appears to be more suitable than ephedrine and at least not inferior to phenylephrine. Given the paucity of comparative RCTs in the literature, additional studies are required to guide the optimal selection of a vasopressor in obstetric anaesthesia.

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