Systematic Review and Meta-Analysis

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Colloid preloading versus crystalloid preloading to prevent hypotension after spinal anesthesia for cesarean delivery

A protocol for systematic review and meta-analysis

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Abstract

Background: Maternal hypotension is the most frequent complication of spinal anesthesia for cesarean delivery, and intravenous fluid preloading is a preventive measure. We aimed to assess the efficacy of colloids versus crystalloids for preloading to reduce the incidence of spinal anesthesia-induced hypotension and vasopressor requirement in healthy parturients during elective cesarean delivery.

Methods: We searched the Cochrane Library, MEDLINE and EMBASE to identify all studies published to June, 2019, through OVID and PubMed. We included randomized controlled trials, comparing colloid preloading with crystalloid preloading in women having spinal anesthesia for cesarean delivery. Primary outcomes were the incidence of hypotension and vasopressor requirement. Secondary outcomes included nausea and/or vomiting, neonatal Apgar score, neonatal umbilical blood pH. We used standardized mean differences for expressing continuous outcomes and risk ratios for dichotomous outcomes. Random-effect model was performed to estimate the pooled risk ratios and standardized mean differences.

Results: Thirty-three randomized controlled trials contributed data for this meta-analysis. Fewer women experienced hypotension in the colloid group compared with the crystalloid group (risk ratio: 0.72, 95% confidence interval: 0.63–0.82; 2566 women, 32 studies; $P < .00001$). The total ephedrine dose required was significantly lower with colloid preloading (standardized mean difference: −0.37, 95% CI: −0.64 to −0.09; 1472 women, 19 studies; $P = .009$). Colloid preloading was also associated with fewer phenylephrine requirement compared with crystalloid preloading (standardized mean difference: -0.54, 95% CI: -0.82 to -0.25; 169 women; $P = .0002$). The incidence of nausea and/or vomiting was significantly reduced with colloid preloading (risk ratio: 0.72, 95% CI: 0.55–0.95; 1601 women, 20 studies; $P = .02$). However, the incidence of 1-minute Apgar score < 7, umbilical artery pH < 7.2 and umbilical vein pH < 7.2 were not statistically different between groups.

Conclusions: Colloid preloading is superior to crystalloid preloading in reducing the incidence of hypotension induced by spinal anesthesia and vasopressor requirement in the healthy parturients undergoing elective cesarean delivery.

The PROSPERO registration number: CRD42018096402.

Abbreviations: CI = confidence interval, GRADE = the grading of recommendations assessment, development and evaluation, HES = hydroxyethyl starch, I-V = Inverse Variance, MD = mean difference, MeSH = medical subject heading, M-H = Mantel-Haenszel, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, RR = risk ratio, SE = standard error, SMD = standardized mean difference.

Keywords: cesarean delivery, colloid, crystalloid, hypotension, preload, spinal anesthesia

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YS and HL contributed equally to this study.

The authors declare no conflicts of interest.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Spinal anesthesia is a very popular technique for cesarean delivery in healthy pregnant women.[1] However, hypotension secondary to the sympathetic vasomotor block associated with spinal anesthesia remains a common complication.[2] In severe cases, hypotension has adverse effects on both mother (altered consciousness and cardiovascular collapse or arrest) and neonate (hypoxia, acidosis and neurological injury).[3,4] To reduce these adverse effects, preventing hypotension is better than treating established hypotension.

A range of strategies can be used by clinicians to minimize or prevent hypotension currently, such as intravenous fluids, pharmacological treatments, left uterine displacement and others.[5] Nowadays, intravenous fluid loading prior to spinal anesthesia is accepted standard practice for cesarean delivery.[2,6] American Society of Anesthesiologists Practice guideline from 2016 declared that intravenous fluid preloading can be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery.[7] Intravenous crystalloids or colloids can be administered by anesthetists to increase maternal blood volume, resulting in an increase in venous return, stroke volume and blood pressure.[5] The previous meta-analyses[5,8] demonstrated that colloids were better than crystalloids to prevent hypotension, however, these studies didn't mention whether colloids are better than crystalloids in the condition of preloading alone, or not. Furthermore, the vasoactive drugs requirement of two fluids preloading are still unclear. In this study, we aimed to explore whether the incidence of hypotension and total required vasopressor dose are different when using preloaded colloids compared with preloaded crystalloids to prevent the spinal anesthesia-induced hypotension in healthy parturients undergoing elective cesarean delivery.

2. Methods

We performed a systematic review and meta-analysis in accordance with the PRISMA statement.[9] We defined the research question, search strategy and inclusion criteria, and performed the data extraction and statistical analyses in accordance with a predefined protocol which was registered in the PROSPERO database. The registration number was CRD42018096402. Unlike clinical trials, this meta-analysis was a secondary analysis based on the original study. So, ethical approval and patient consent in this study were not necessary.

2.1. Search strategy

We identified randomized controlled trials (RCTs) comparing colloid preloading with crystalloid preloading to prevent hypotension induced by spinal anesthesia in healthy parturients undergoing elective cesarean delivery from several sources, starting with a database search. A systematic search of Ovid Cochrane Library, Ovid MEDLINE, Ovid Embase and PubMed was performed by two investigators (PL, SL) on October, 2018 to identify relevant studies, without language restriction. The authors then performed additional literature searches of the clinical trials registry (www.clinicaltrials.gov). The database searches were repeated on June, 2019. Search terms were crystalloid, colloid, spinal anesthesia and cesarean delivery, and the detailed search information was presented in Supplemental Content 1(see text, Supplemental Content 1, which demonstrates the detail of the search strategy, http://links.lww.com/MD/F625). The resultant search including this text words and Medical Subject Headings (MeSH) terms, were subjected to the Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials. We imported the reference lists for all of the identified studies into EndNote X9 (Clarivate Analytics, Boston, MA, USA) and checked them manually.

2.2. Study selection

Two authors (JM, RW) independently screened all of the titles and abstracts of the retrieved references for eligibility. Any disagreement was resolved by consensus. For inclusion, studies had to have the following characteristics:

(1) patients: healthy women with full term, singleton pregnancy undergoing elective cesarean delivery performed with spinal anesthesia;
(2) intervention: colloid preloading;
(3) comparator: crystalloid preloading;
(4) outcome: intraoperative incidence of hypotension or total vasopressor requirement and
(5) type of study: randomized controlled trial.

We also included any dose or type of fluid for preload, as well as its combination with any other method to prevent hypotension. We excluded preterm, multiple pregnancies and studies investigating prevention of hypotension without fluid preloading. Abstracts published from international meetings, comments and reviews were also excluded as well as trials that were nonrandomized controlled studies, retrospective studies, case reports, cohort studies and studies having no comparator group.

2.3. Outcome measures

The primary outcomes were the incidence of hypotension and vasopressor requirement after spinal anesthesia combined with colloid preloading or crystalloid preloading. We did not stipulate the definition of hypotension, we classified patients according to the criteria in the original studies. Secondary outcomes included the incidence of nausea and/or vomiting, 1- and 5-minute Apgar scores <7 and neonatal acidosis.

2.4. Data extraction

Using standard forms, one author (YS) extracted information on outcomes; authors; year of publication; total number of patients; country of origin; spinal anesthesia details; volume and type of fluid for preloading; other techniques to prevent hypotension; the definition of hypotension and treatment. A second author (HL) crosschecked the original extracted data. Discrepancies were resolved by consensus or, if necessary, by discussion with a third author (BS).

2.5. Risk of bias assessment

Two authors (SL and RW) independently assessed the methodological quality of each study using the Cochrane Collaboration Risk of Bias tool for RCTs.[10] This tool includes assessment of the risks of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias),

selective reporting (reporting bias) and other bias. The risk of bias was classified as high, low, or unclear. Disagreement between the two reviewers regarding the overall risk of bias assessment were resolved through discussion and consensus. We aimed to evaluate potential publication bias using a funnel plot if the outcomes included more than 10 studies.[11] In addition, we performed Egger's regression test to evaluate publication bias using the Stata software (StataCorp LP, College Station, TX).

2.6. Statistical analysis

We performed the statistical analyses using Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). For dichotomous data, we calculated the risk ratio (RR) and 95% CIs for the outcomes using the Mantel–Haenszel method. For continuous data, we determined the mean differences (MD) or standardized mean differences (SMD) with 95% CIs for the outcomes using the inverse variance method.

$$SMD = \frac{Difference\ in\ mean\ outcome\ between\ groups}{Standard\ deviation\ of\ outcome\ among\ participants}$$

We performed all analyses using the random-effects model, and we considered $P < .05$ for all outcomes as statistically significant. We used the I^2 statistic to assess statistical heterogeneity: I^2 values $> 50\%$ suggested significant heterogeneity between studies,[12] and the heterogeneity should be explored by appropriate subgroup analyses, or by meta-regression utilizing the Stata software.

Grading of Recommendation Assessment, Development, and Evaluation(GRADE) assessment

We judged the quality of the evidence for the outcomes according to the GRADE methodology,[13,14] which includes four levels of quality (high, moderate, low, and very low).

3. Results

The systematic database search identified 923 reports: 722 from OVID; 196 from PubMed and 5 from www.clinicaltrials.gov. After removing duplicate studies, two authors screened 587 records. 125 full-text publications were assessed for eligibility after title and abstract reviewing. We excluded 92 studies because the participants, interventions or outcomes did not meet our inclusion criteria or because the study was not an RCT. We selected and included a final 33 RCTs for the final analysis.[15–47]Figure 1 shows the flow chart of the study selection process.

3.1. Characteristics of the studies

Trials were performed in a diverse array of countries and reported in different languages: English, Japanese, Korean, Turkish and French. Most of the studies used 9 to 15 mg bupivacaine with or without opioid for spinal anesthesia, one study used 0.75% hyperbaric bupivacaine and the dose was unclear, one study used $\leq$ 15 mg ropivacaine with 20 μg fentanyl, one study used 8 mg tetracaine and one study used dibucaine dosed according to each patient's height. Eighteen studies administered 500 ml or 7 to 10 ml/kg of 6% hydroxyethyl starch in the colloid group, three studies administered 1 L of 6% hydroxyethyl starch, one study administered 500 ml of 10% hydroxyethyl starch, one study administered 500 ml of 6% hydroxyethyl starch plus 500 ml lactated Ringer's solution and the others administered dextrans, pentastarches or gelatins. For crystalloid preloading, nine studies used 1 L of lactated Ringer's solution, three studies used 1.5 L of lactated Ringer's solution, one study used 0.5 L of lactated Ringer's solution, 6 studies used 20 ml/kg of lactated Ringer's solution, three studies used 10 ml/kg of lactated Ringer's solution, two studies used 15 ml/kg of lactated Ringer's solution and the others used acetated Ringer's solution, Hartmann's solution or 0.9% sodium chloride solution. The studies' characteristics are shown in Supplemental Content 2 (see Table, Supplemental Content 2, which demonstrates the characteristics of the included studies, http://links.lww.com/MD/F626).

3.2. Risk of bias

The results of the risk-of-bias evaluation are shown in Figure 2. Most of the studies received an 'unclear risk' or a 'low risk' assessment with regards to random sequence generation, allocation concealment, blinding, incomplete outcomes, selective reporting and other bias. It was incidentally high in some domains, except for incomplete outcome data.

3.3. The incidence of hypotension

Thirty-two studies comprising 2566 patients reported the incidence of hypotension following prophylactic fluid for healthy parturients undergoing elective cesarean delivery under spinal anesthesia.[15–46] Fewer women experienced hypotension in the colloid group compared with the crystalloid group (risk ratio: 0.72, 95% CI: 0.63–0.82; $I^2 = 67\%$; $P < .00001$; Fig. 3). Subgroup analyses showed that 7–10 ml/kg or 500 ml of 6% hydroxyethyl starch (130/0.4) preloading resulted in a lower incidence of hypotension (risk ratio: 0.63, 95% CI: 0.54–0.74; $I^2 = 45\%$; $P < .00001$). For other types or volume of colloids, there was no significant difference in the incidence of hypotension (risk ratio: 0.84, 95%CI: 0.69–1.01; $I^2 = 73\%$; $P = .07$). Moreover, meta-regression indicated that the type and volume of colloids modified the effect of colloid preloading on the incidence of spinal anesthesia induced hypotension (test of interaction, $P = .008$).

3.4. The requirement of vasopressor

Nineteen studies including 1472 women provided usable data for the effect of fluid preloading on ephedrine requirement.[15,17,18,20–22,24,25,28,29,31–36,40,42,43,47] The requirement of ephedrine with colloid preloading was lower than that with crystalloid preloading (standardized mean difference: -0.37, 95% CI: -0.64 to -0.09; $P = .009$; Fig. 4). The I^2 statistic was 85% with $P < .00001$, indicating a statistical heterogeneity among the studies. In order to explore the source of heterogeneity, we conducted subgroup analyses based on the volume or type of colloid: 7–10 ml/kg or 500 ml 6% hydroxyethyl starch(yes/no). In 7–10 ml/kg or 500 ml of 6% hydroxyethyl starch (130/0.4) preloading subgroup, resulted in a reduction in heterogeneity (SMD: -0.47, 95% CI: -0.69 to -0.25; $I^2 = 34\%$; $P < .0001$). For another subgroup, the degree of heterogeneities was still significant (SMD: -0.32, 95% CI: -0.72 to 0.09; $P = .12$; $I^2 = 89\%$). However, from our meta-regression analyses, there was no evidence that 7–10 ml/kg or 500 ml 6% HES influenced the effect (test interaction, $P = .56$). Only two studies reported the requirement of phenylephrine following spinal anesthesia

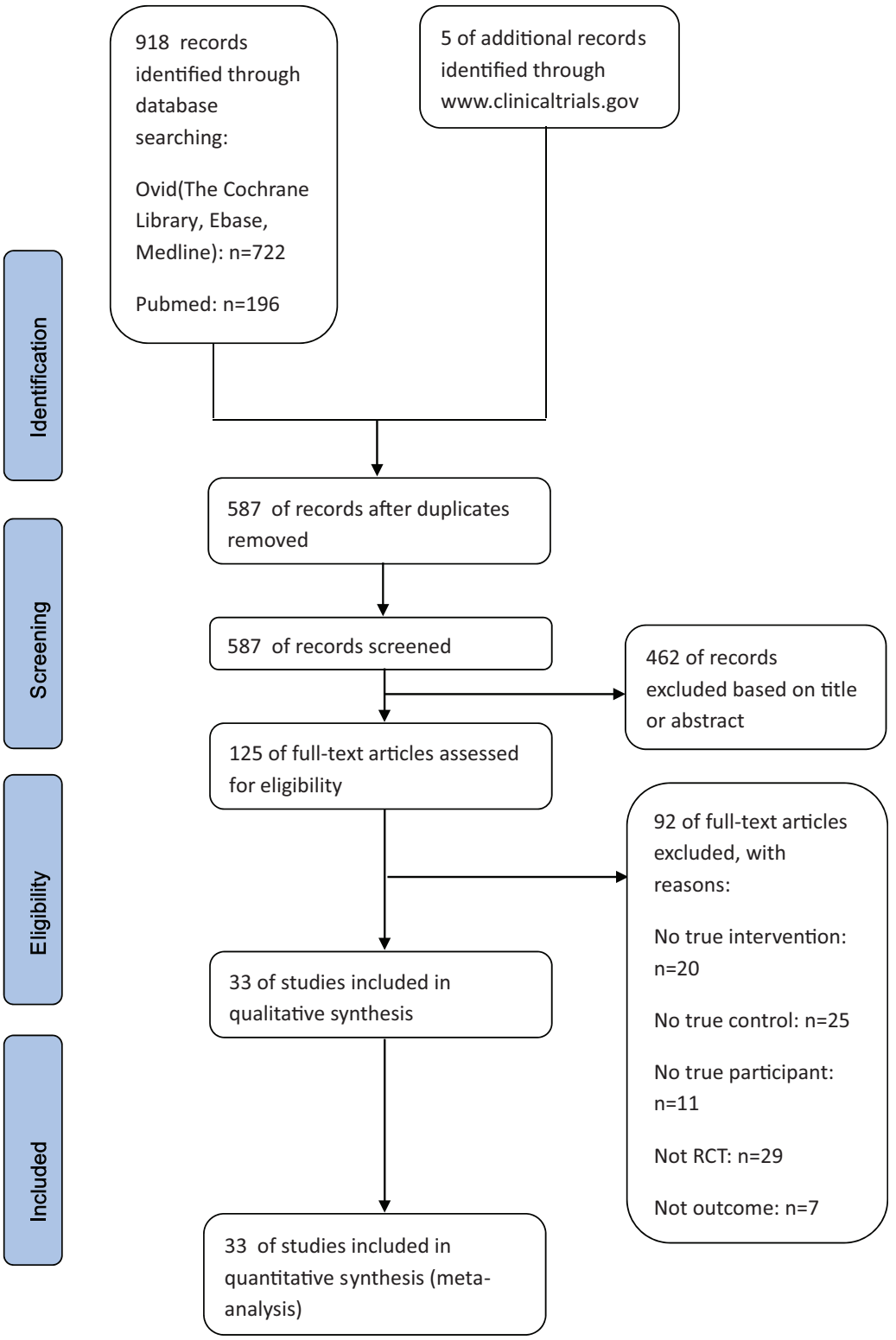

Figure 1. PRISMA flow diagram.

induced hypotension.[39,44] A statistically significant reduction in phenylephrine requirement was observed with the use of colloid preloading compared with crystalloid preloading (standardized mean difference: -0.54, 95% CI: -0.82 to -0.25; 169 women; $I^2 = 0\%$, $P = .0002$).

3.5. The incidence of nausea and/or vomiting

The incidence of intraoperative nausea and/or vomiting was reported in 20 trials.[15,17,20,23,24,26,27,29,30,32–35,37,39–42,44,47] Among these trials, a statistically significant reduction in nausea and/or vomiting was found when colloid preloading was

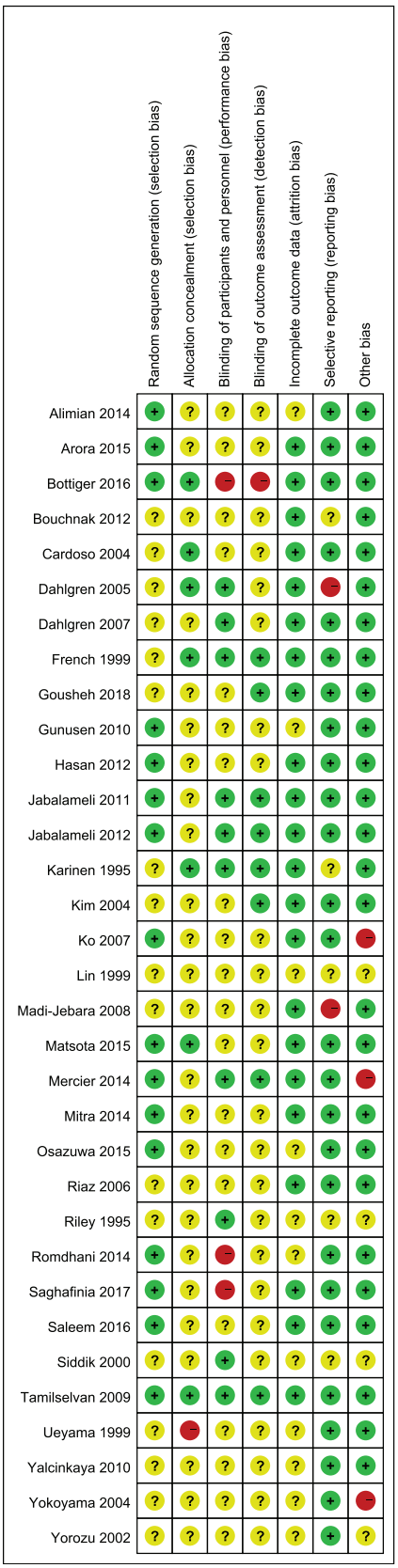

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Low risk of bias is indicated by green, high risk is indicated by red. Yellow shows that the description is unclear.

administered compared with crystalloid preloading (risk ratio: 0.72, 95% CI: 0.55–0.95; 1601 women; $P = .02$; Fig. 5) with mild heterogeneity ($I^2 = 36\%$).

3.6. Neonatal Apgar score less than 7

Six studies reported the incidence of 1-minute neonatal Apgar score < 7.[21,25,28,36,37,42] The pooled estimates did not demonstrate a significant statistical difference between colloid preloading and crystalloid preloading for the incidence of neonatal 1-minute Apgar score < 7 (risk ratio: 0.75, 95% CI: 0.41–1.38; 526 babies; $I^2 = 0\%$, $P = .35$; see Figure, Supplemental content 3, http://links.lww.com/MD/F627, which shows the forest plot for the rate of neonatal Apgar score less than 7 at one minute). Eight studies reported the data of the 5-minute Apgar score < 7, however, only one study[21] documented three newborns with a 5-minute Apgar score < 7 in the crystalloid group. No newborns scored < 7 in the other studies.

3.7. Umbilical blood pH less than 7.2

Two trials reported on the rate of neonatal umbilical artery pH $<$ 7.2.[25,37] There were no significant differences between colloid preloading and crystalloid preloading for the rate of neonatal umbilical artery pH < 7.2 (risk ratio: 0.69, 95% CI: 0.12–3.78, 276 newborns, $I^2 = 44\%$, $P = .67$). Two studies reported the rate of umbilical vein pH < 7.2 following fluid preloading.[18,41] Similarly, there was no significant difference in the rate of umbilical vein pH < 7.2 between the two groups (risk ratio: 0.26, 95% CI: 0.03–2.25, 190 newborns, $I^2 = 0\%$, $P = .22$).

3.8. Sensitivity analyses

By excluding one study at a time in repeated analyses, we found that the point estimates for all outcomes changed minimally. Secondly, we performed additional sensitivity analyses according to excluding studies with high risk of bias. Analogously, these data did not lead to any change in effect estimate or statistical significance for all outcomes.

3.9. Publication bias

Following visual inspection of the funnel plot (see Figures, Supplemental Content 4, http://links.lww.com/MD/F628 and 5, http://links.lww.com/MD/F629, which show the funnel plots of hypotension and nausea and/or vomiting) and Egger testing for the incidence of hypotension and nausea and/or vomiting, we found asymmetrical patterns and p-values following Egger testing of .00003927, .03136, respectively, which indicated statistical evidence of publication bias. In contrast, we found no evidence of publication bias for ephedrine requirement (see Figure, Supplemental Content 6, http://links.lww.com/MD/F630, which shows the funnel plot of ephedrine requirement) and 1-minute Apgar score < 7, the P value of Egger test were .08538 and .6531. There were too few studies included in the requirement of phenylephrine, the rate of neonatal umbilical artery pH < 7.2 and the rate of neonatal umbilical vein pH < 7.2 to perform a meaningful Egger test.

3.10. GRADE assessment

We used the GRADE system to assess the quality level of each outcome. Because all the included studies were RCTs, there was a

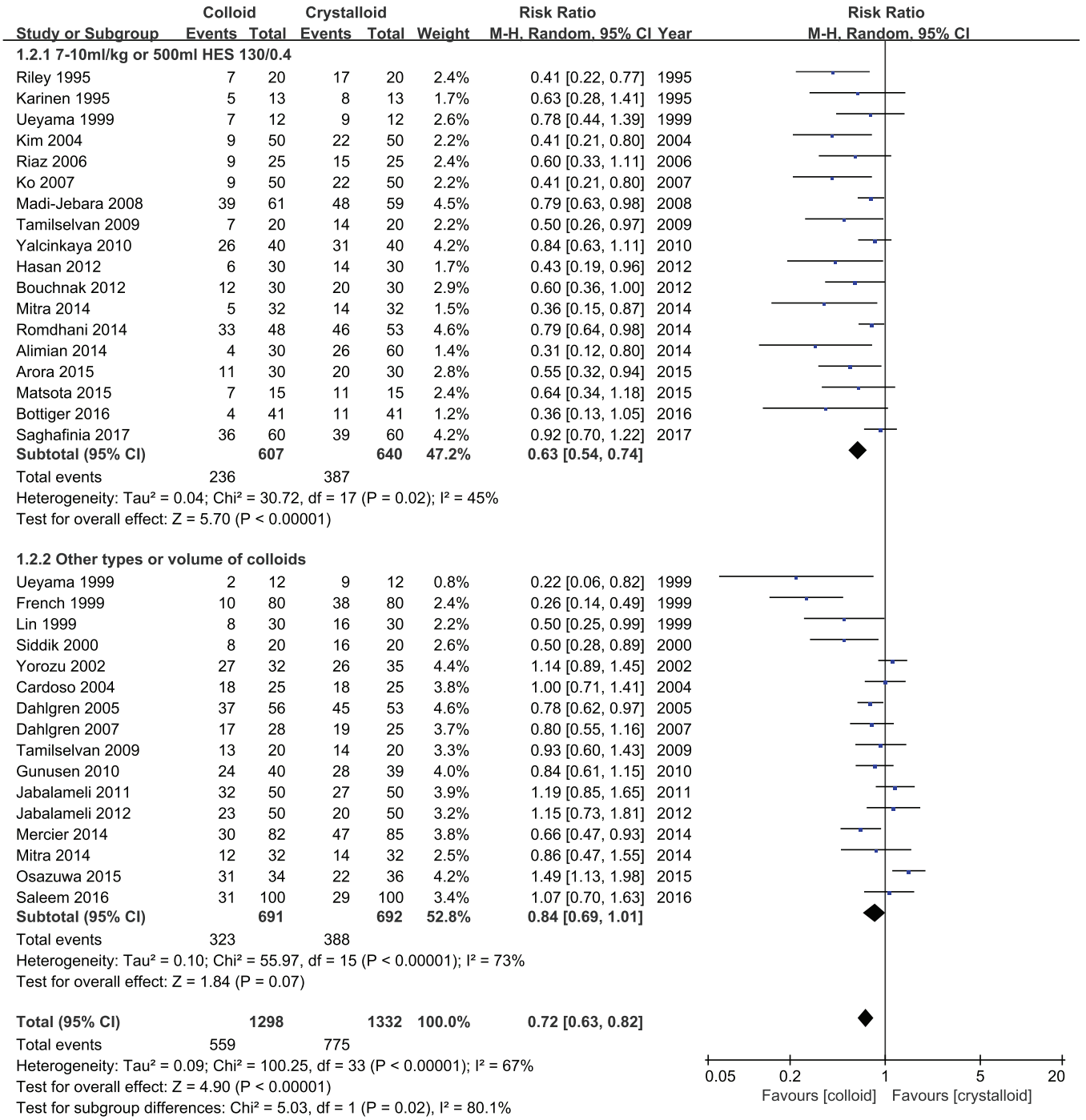

Figure 3. Forest plot for the rate of hypotension during cesarean delivery after spinal anesthesia. CI = confidence interval, M-H = Mantel-Haenszel.

high starting quality for each outcome. However, most of these studies' selection, performance, and detection bias were subject to moderate or high level risk of bias. As a result, we downgraded the evidence for each outcome by one level for methodology limitations. We assessed the incidence of hypotension and ephedrine requirement to have low-quality evidence due to the reasons of high possibility of publishing bias and unexplained heterogeneity respectively. Overall, the quality of evidence was assessed as low or very low (see Table, Supplemental Content 7, http://links.lww.com/MD/F631, which shows the quality of the evidence for the outcomes according to the GRADE methodology).

4. Discussion

This study was a comprehensive systematic review and meta-analysis evaluating the use of colloid preloading to prevent hypotension after spinal anesthesia compared with crystalloid

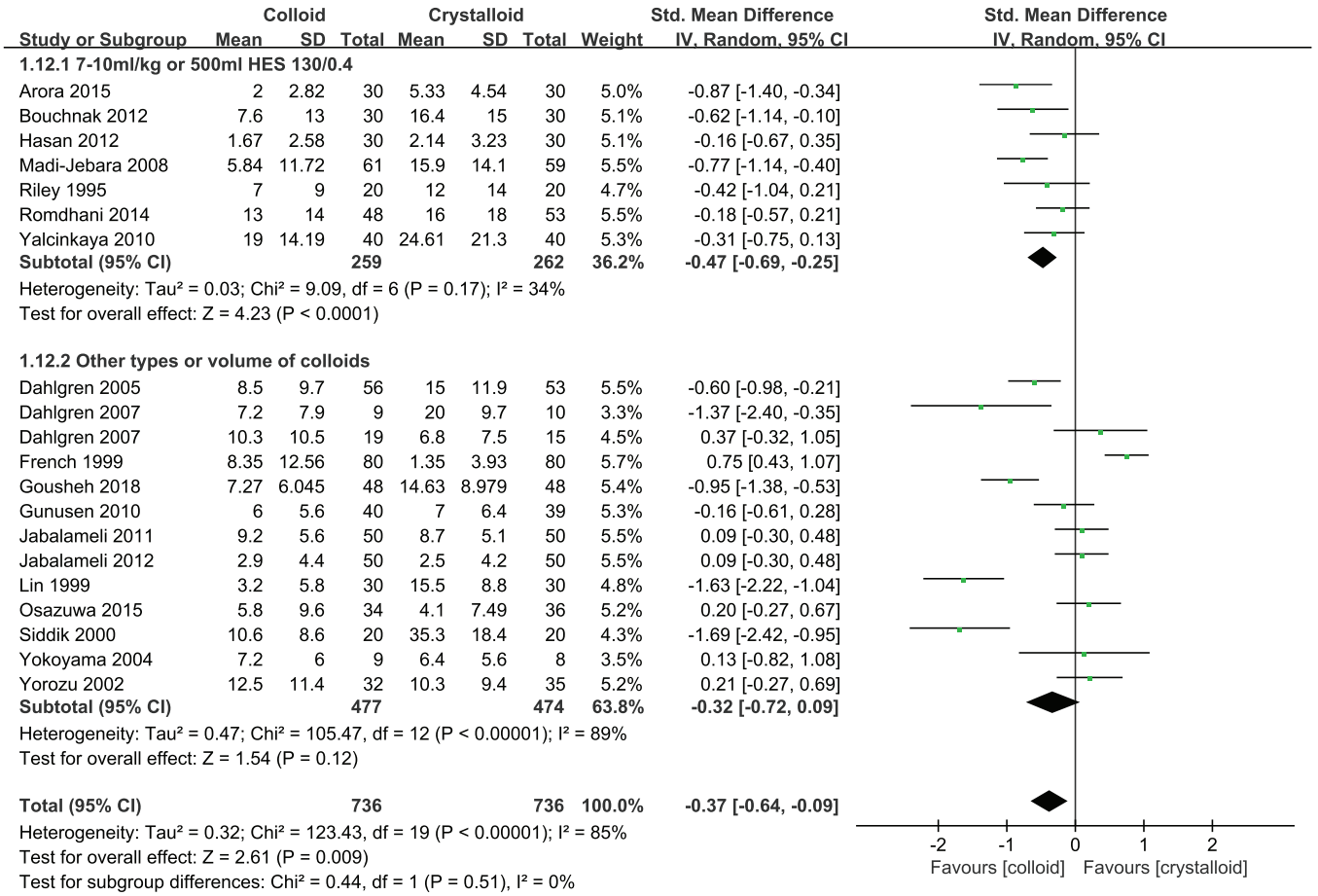

Figure 4. Forest plot for ephedrine dose required. SD = standard deviation, IV = Inverse Variance.

preloading in healthy women undergoing elective cesarean delivery. Our results showed that administering colloids before spinal anesthesia was associated with a significant reduction in the incidence of hypotension, vasopressor requirement and nausea/vomiting compared with crystalloids. In contrast, the rates of 1-minute neonatal Apgar score <7, umbilical artery pH <7.2 and umbilical vein pH <7.2 were comparable between the two groups.

Fluid-loading techniques were recommended to improve the hemodynamic stability provided by vasopressor prophylaxis in a recent international consensus statement.[2] The most recent meta-analysis by the Cochrane group determined the effects of colloids and crystalloids regarding the incidence of hypotension induced by spinal anesthesia in elective cesarean delivery and showed that colloids were more effective than crystalloids to decrease the incidence of maternal hypotension (risk ratio: 0.68, 95% CI: 0.52–0.89; 11 trials, 698 women).[5] However, it was difficult to determine the specific periods of time of the fluid administration. Our study confirmed that colloid preloading was more effective than crystalloid preloading. We found substantial heterogeneity ($I^2=67\%$) among the studies included in our analysis regarding hypotension. Our subgroup and meta-regression analyses suggested that the benefit of colloids was limited to 7–10 ml/kg or 500 ml of 6% hydroxyethyl starch (130/0.4). Therefore, we believe that the type and volume of colloids might be an important source of between-study heterogeneity. Differences in the dose of local anesthetic for spinal anesthesia might also explain the heterogeneity.

Ephedrine and phenylephrine are the most commonly used agents to treat or prevent hypotension following spinal anesthesia during cesarean delivery. Clinical work dating from the 2000s indicated that phenylephrine effectively reduced hypotension and was associated with less neonatal acidosis than ephedrine.[48] Nineteen studies in our review used ephedrine as the vasopressor to treat hypotension, four studies[37,39,44,45] used phenylephrine, one study[23] used metaraminol and one[26] used dopamine. Logically, the requirement for vasopressors is consistent with the incidence of hypotension because the drug is used to treat hypotension. Unlike other studies,[5,8] in our analysis, we reported the vasopressor requirement and found a significant difference between colloid preloading and crystalloid preloading in that the colloid group required less frequent ephedrine. We noted an extremely high level of heterogeneity when reporting ephedrine requirement. However, by meta-regression analyses, we did not find the source of heterogeneity.

Intraoperative nausea and/or vomiting is a complication for patients, which worsens conditions for the surgeon and increases medical risks such as aspiration of gastric contents. Intraoperative nausea and vomiting associated with cesarean delivery varies in incidence and presentation depending on pre-existing

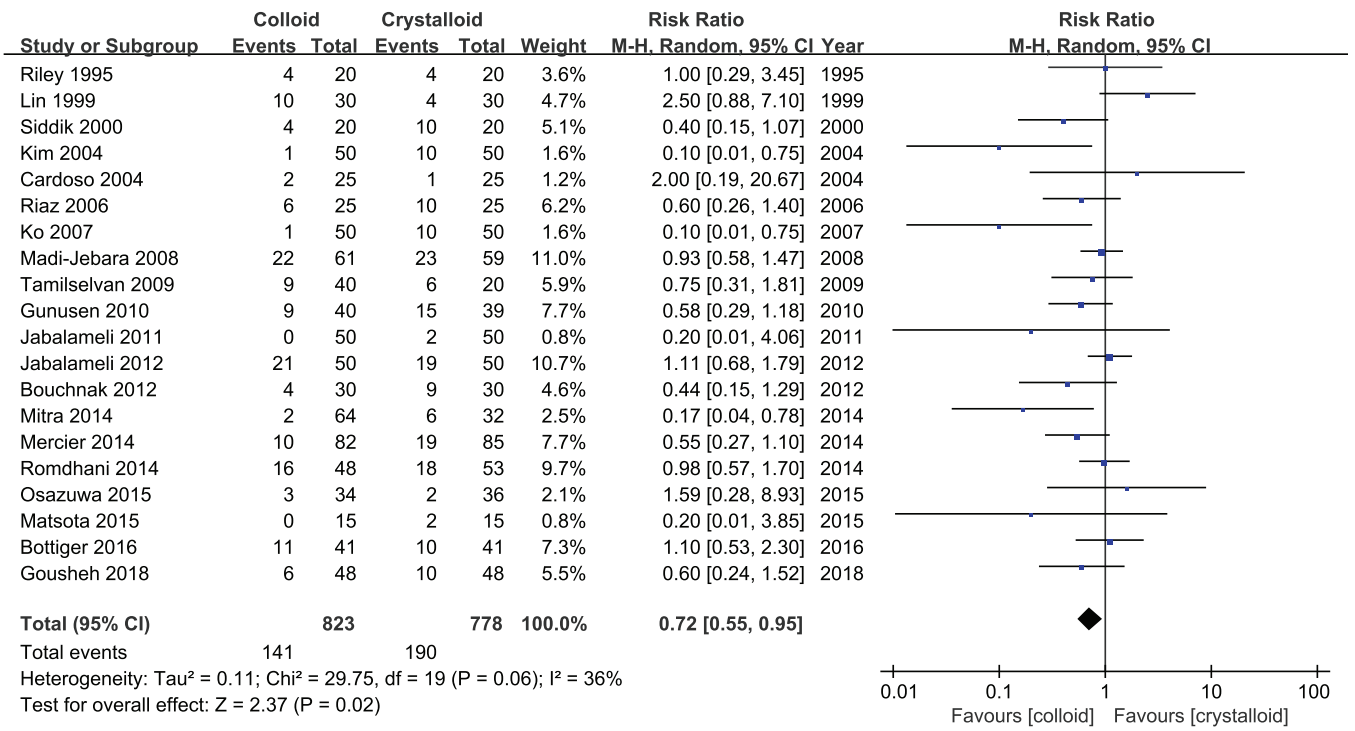

Figure 5. Forest plot for the incidence of intraoperative nausea and/or vomiting. CI = confidence interval; M-H = Mantel-Haenszel.

symptoms, anesthetic and obstetric techniques and preventive and therapeutic measures.[49] Most intraoperative nausea and/or vomiting is associated with intraoperative hypotension secondary to cerebral and brainstem hypoperfusion and gut ischaemia.[49,50] Our results showed that colloid preloading was associated with a statistically significant reduction in the incidence of intraoperative nausea and vomiting. This might be a consequence of colloid preloading reducing the incidence of hypotension after spinal anesthesia compared with crystalloid preloading. However, our results differed from a previous review that found no difference between colloids and crystalloids regarding nausea and/or vomiting.[5] This might be explained that fluid preloading alone was included in our study, and our meta-analysis covered several recent findings.[41,42,44,47]

Despite a significant difference in the incidence of hypotension between the two groups, neonatal outcome values were often within normal ranges and similar between the two groups, which were, 1-minute Apgar score <7, umbilical artery pH $<$ 7.2 and umbilical vein pH <7.2. The authors of one study stated that hypotension can lead to impaired uteroplacental perfusion, resulting in fetal hypoxia, acidosis and neonatal depression or injury, however, the normal fetal findings in our review might have resulted from the lack of persistent and severe hypotension in both groups because of treatment timely. Differing from previous meta-analyses,[5,8] our study reported the incidence of 1-minute Apgar scores <7. Despite repeated questioning of the value of the Apgar score, the 1-minute score is considered to be inversely proportional to the risk of neonatal mortality. Our results were consistent with one meta-analysis which found that there was no significant differences in the incidence of neonatal acidosis between colloid and crystalloid groups.[5]

The quality of our evidence was assessed as low or very low. There were some reasons: Firstly, most of these studies had moderate or high level selection, performance and detection bias risk. So, we downgraded the evidence for each outcome by one level for methodology limitations. Secondly, because of high possibility of publishing bias and unexplained heterogeneity, we downgraded the evidence of the incidence of hypotension, the incidence of nausea/vomiting and ephedrine requirement by one level. Lastly, for the other evidence, we downgraded one or two level as a result of the lack of adequate RCTs.

There are certain limitations in our study. First, as a design flaw, we found irregularities and unclear descriptions in the included studies' methodologies. We considered that most studies had a moderate risk of selection bias. In addition, we considered a moderate to high risk of performance and detection bias in most studies regarding outcomes. Second, despite colloids being more effective than crystalloids for reducing the incidence of maternal hypotension, cost analysis were not performed in the analyzed studies. Finally, because of limit of times, most studies in our analysis used ephedrine; however, currently, phenylephrine is the major choice to reverse the circulatory effects of spinal anesthesia and has the most evidence supporting its use.[51] Therefore, further studies evaluating phenylephrine are anticipated.

5. Conclusions

In conclusion, our meta-analysis of several important outcomes demonstrated that colloid preloading is superior to crystalloid preloading to decrease the incidence of hypotension induced by spinal anesthesia, vasopressor requirement and nausea/vomiting in healthy pregnant women undergoing elective cesarean delivery. Additionally, we found that colloid preloading was

not associated with a significant reduction in the rate of adverse neonatal outcomes compared with crystalloid preloading. Future studies should focus on the requirement of phenylephrine between colloid preloading and crystalloid preloading.

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Validation: Rurong Wang.
Visualization: Rurong Wang.
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Writing – review & editing: Bo Sheng.

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