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ORIGINAL ARTICLE

Fluid loading therapy to prevent spinal hypotension in women undergoing elective caesarean section

Network meta-analysis, trial sequential analysis and meta-regression

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BACKGROUND Fluid loading is one of the recognised measures to prevent hypotension due to spinal anaesthesia in women scheduled for a caesarean section.

OBJECTIVE We aimed to evaluate the current evidence on fluid loading in the prevention of spinal anaesthesia-induced hypotension.

DESIGN Systematic review and network meta-analysis with trial sequential analysis and meta-regression.

DATA SOURCES Medline, Epub, Embase.com (Embase and Medline), Cochrane Central, Web of Science and Google Scholar were used.

ELIGIBILITY CRITERIA Only randomised controlled trials were used. Patients included women undergoing elective caesarean section who received either crystalloid or colloid fluid therapy as a preload or coload. The comparator was a combination of either a different fluid or time of infusion.

RESULTS A total of 49 studies (4317 patients) were included. Network meta-analysis concluded that colloid coload and preload offered the highest chance of success (97 and 67%, respectively). Conventional meta-analysis showed that crystalloid preload is associated with a significantly higher incidence of maternal hypotension than colloid preload: risk ratio 1.48 (95% CI 1.29 to 1.69, $P < 0.0001$, $I^2 = 60\%$). However, this result was not supported by Trial Sequential Analysis. There was a significant dose–response effect for crystalloid volume preload (regression coefficient = −0.073), which was not present in the analysis of only double-blind studies. There was no dose–response effect for the other fluid regimes.

CONCLUSION Unlike previous meta-analyses, we found a lack of data obviating an evidence-based recommendation. In most studies, vasopressors were not given prophylactically as is recommended. Studies on the best fluid regimen in combination with prophylactic vasopressors are needed. Due to official european usage restrictions on the most studied colloid (HES), we recommend crystalloid coload as the most appropriate fluid regimen.

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Introduction

Hypotension following spinal anaesthesia for caesarean section can occur in up to 80% of women without prophylactic measures.[1] For many years, this was believed to arise primarily as a result of venous vasodilation. However, studies that have utilised cardiac output monitoring have demonstrated that arterial vasodilation is more likely to be responsible for the decrease in blood pressure following spinal anaesthesia, at least initially.[2] The focus of attention for prophylaxis and management has therefore shifted from fluid-loading strategies to the extensive investigation of the role of vasopressors. Currently, the alpha-agonist phenylephrine, which directly counteracts the sympatholysis-induced decrease in arterial resistance and is associated with a lower incidence of foetal acidosis, has become the preferred agent.[3,4] A phenylephrine infusion commencing at the time of the spinal injection

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is currently recommended as the most effective approach to prevent hypotension,[5,6] although phenylephrine boluses given prophylactically or noradrenaline infusion may be at least as effective.[7–9]

However, fluid loading strategies remain another part of an antihypotensive strategy, as they can counteract the relative hypovolaemia due to venodilation and, by increasing the venous return, help to maintain haemodynamic stability.[1] Despite the effectiveness of phenylephrine, a significantly higher frequency of hypotension has been observed when no fluid is given.[10] In addition, the CAESAR study demonstrated that a mixed hydroxyethyl starch–Ringer's lactate based preload infusion reduced maternal hypotension compared with a pure Ringer's lactate based preload when combined with intravenous (i.v.) phenylephrine boluses. In addition, the decrease in the incidence of severe and/or symptomatic hypotension is even more pronounced.[11] A survey showed that many obstetric anaesthetists still favour fluid therapy in their clinical practice.[12]

Recently, a meta-analysis was published focusing on the use of vasopressors in the prevention of hypotension after spinal anaesthesia for caesarean delivery.[13] This found that either norepinephrine or metaraminol is less likely than phenylephrine to affect foetal acid-base status adversely. Another meta-analysis addressing methods to prevent hypotension after spinal anaesthesia for caesarean section was also recently published[14]: the main focus was on vasopressor use, but also included fluid therapy. Metaraminol was found to be the most effective vasopressor, and colloid, given as a preload, was the most effective fluid for preventing maternal hypotension. However, it is unclear whether this meta-analysis is sufficiently powered to make firm conclusions. Previously, it has been shown that the conclusions of meta-analyses that do not incorporate trial sequential analysis (TSA) are often premature due to a lack of sufficient data.[15,16] The use of TSA can calculate the power of a meta-analysis and thereby provide more definite and reliable conclusions.[17]

Traditional meta-analysis only enables direct pairwise comparison of two interventions. Although most studies have two treatment arms for fluid therapy, there are variations in the combinations of time of administration and type of fluid used. We therefore chose to carry out a network meta-analysis, which allows conclusions from indirect comparisons: if regimen A is better than B and if C is better than B, then network meta-analysis allows for conclusions on the relationship between C and A, although no direct comparisons have been performed. Consequently, this statistical method is more appropriate than conventional meta-analysis. for suggesting the most promising treatment regimen. The aim of this article is to define the best fluid strategy to prevent spinal anaesthesia-induced hypotension in elective caesarean section.

Materials and methods

Protocol and registration

Our study was registered with PROSPERO (https://www.crd.york.ac.uk, registration number CRD42018099347) and was conducted in agreement with the PRISMA statement.[18]

Search strategy

We performed an electronic search on 22 October 2019, searching the databases Medline, Epub, Embase.com (Embase and Medline), Cochrane Central, Web of Science and Google Scholar, with details of the search strategy given in the appendix (S2. Details of literature search, http://links.lww.com/EJA/A404). There was no language restriction.

Eligibility criteria and study selection

We used the items of the PICOS acronym to define inclusion criteria:

Patients: Adult (as defined by the authors of the studies) women undergoing elective caesarean section.
Intervention: Two types of fluid were studied, crystalloid and colloid, given at one of two possible timepoints: A, as a preload before spinal anaesthesia and B, as a coload on injection of the spinal medication.
Comparator: Each of the above fluid/time combinations was compared with a combination that had either a different fluid (number) or time (letter) of administration.
Outcomes: Primary outcome: incidence of maternal hypotension, as defined by the individual authors. Secondary outcomes: umbilical artery pH, ephedrine use, phenylephrine use, nausea and vomiting.
Study type: Only randomised controlled trials were included.

Data collection and data extraction

Two authors (KR, MH) independently extracted data from the original papers and entered them into the RevMan file. These authors also screened the retrieved references and performed the risk of bias assessment, with discrepancies being resolved by discussion. In case this was not possible, our protocol stipulated involvement of a third author (MK). Risk ratios of dichotomous variables or mean differences of continuous variables and 95% confidence intervals were computed.

Assessment of the methodological quality

The risks of selection, performance, detection and attrition bias were assessed with the Cochrane tool[19] and entered into the RevMan file. Only double-blind studies were considered as 'low risk of bias studies'. For our primary outcome, we assessed the quality of evidence according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group approach.[20] Evidence may be downgraded due to risk of bias, inconsistency, indirectness, imprecision and publication bias.

Statistical analysis

Conventional meta-analysis

We used the random effects model because heterogeneity was expected. An aggregate effect estimate was only calculated when there were at least three studies with a combined total of 100 patients (minimum) per treatment group. To estimate heterogeneity in our analyses, the I^2 statistic was used.[21] A P value of less than 0.05 was used as an indicator of statistical significance. For further clarification of our findings, a sensitivity analysis was performed based on the blinding status of studies: only double-blind studies were analysed. We also intended to carry out a similar sensitivity analysis on vasopressor use; prophylactically or therapeutically given.

Network meta-analysis

To compare the different treatment regimens, we used network meta-analysis (NMA), a statistical approach that combines direct and indirect evidence into single treatment effects.[22,23] For the calculations, we used the frequentist method, based on the graph-theoretical method by Rücker *et al.*[24] Treatment effects were expressed as risk ratios or mean difference with corresponding 95% confidence intervals (95% CIs). The I^2 statistic was used to assess heterogeneity in the network analysis. Potential inconsistency was explored by looking at differences between estimates from direct and indirect comparisons.[25] The results of the NMA were presented in a league table. All pairwise comparisons are given in a square matrix. The treatments were ranked by P-scores. P-scores are based on the point estimate and standard errors of the network estimates. A P-score is an averaged measure of the extent of certainty that a treatment is better than others.[26] The league table is sorted by the P-scores. A sensitivity analysis was performed including only double-blind studies.

Meta-regression

To look for dose–response relationships of volume, we performed a meta-regression. A random effects model was used. Proportions of events were log transformed. All analyses were presented in bubble plots. When significant differences were found, we performed a sensitivity analysis on the double-blind studies.

Trial sequential analysis

This analysis was performed only for the 'low risk of bias' studies for our primary outcome namely, the incidence of maternal hypotension. The methodology has been described earlier.[27] In short, cumulative meta-analyses are at risk of type I errors (false positive results) and type II errors (false negative results) because of repetitive testing as data accumulates.[17,28,29] Trial sequential analysis (TSA) aims to adjust the statistical threshold to minimise these errors. Results are presented as a graph with lines representing the cumulative Z-curve (the Z test curve is updated after each study is added), a conventional line of significance (Z score $= 1.96$ for a P value threshold or alpha of 5%), the required information size (RIS), the futility boundaries and a trial sequential monitoring boundary as based on the O'Brien-Fleming alpha-spending function. RIS is calculated allowing for a type I error of 5% and a type II error of 20% and heterogeneity was set to 25%. TSA figures will only be presented when trial sequential monitoring or futility boundaries were crossed.

Publication bias

A comparison-adjusted funnel plot was made to visually inspect the possibility of publication bias. We also performed the Egger test.[30] We did the analysis for all studies and for the double-blind studies only.

Statistical programmes

Conventional meta-analysis, NMA and meta-regression were performed using RStudio (version 1.0.153; Integrated Development for R. RStudio, Inc., Boston, Massachusetts, USA) with package 'netmeta' (version 0.9–8), and 'meta' (version 4.9–7). Trial sequential analysis software (version 0.9; Copenhagen Trial Unit, Copenhagen, Denmark) was used to perform this analysis.

Results

Study selection and study characteristics

With our systematic literature search, we found 49 trials considered as eligible for our analysis (Fig. 1).[11,31–78] These included 4317 patients in total. Details of the studies are given in Table 1. Only three of the 49 studies (6%) used a prophylactic vasopressor. All 49 studies included therapeutic vasopressor use in their study protocol. Ephedrine was most often used as the vasopressor (74%), followed by phenylephrine (14%), a combination of ephedrine and phenylephrine (8%), and less often used were mephentermine (2%) and metamarinol (2%).

Risk of bias within studies

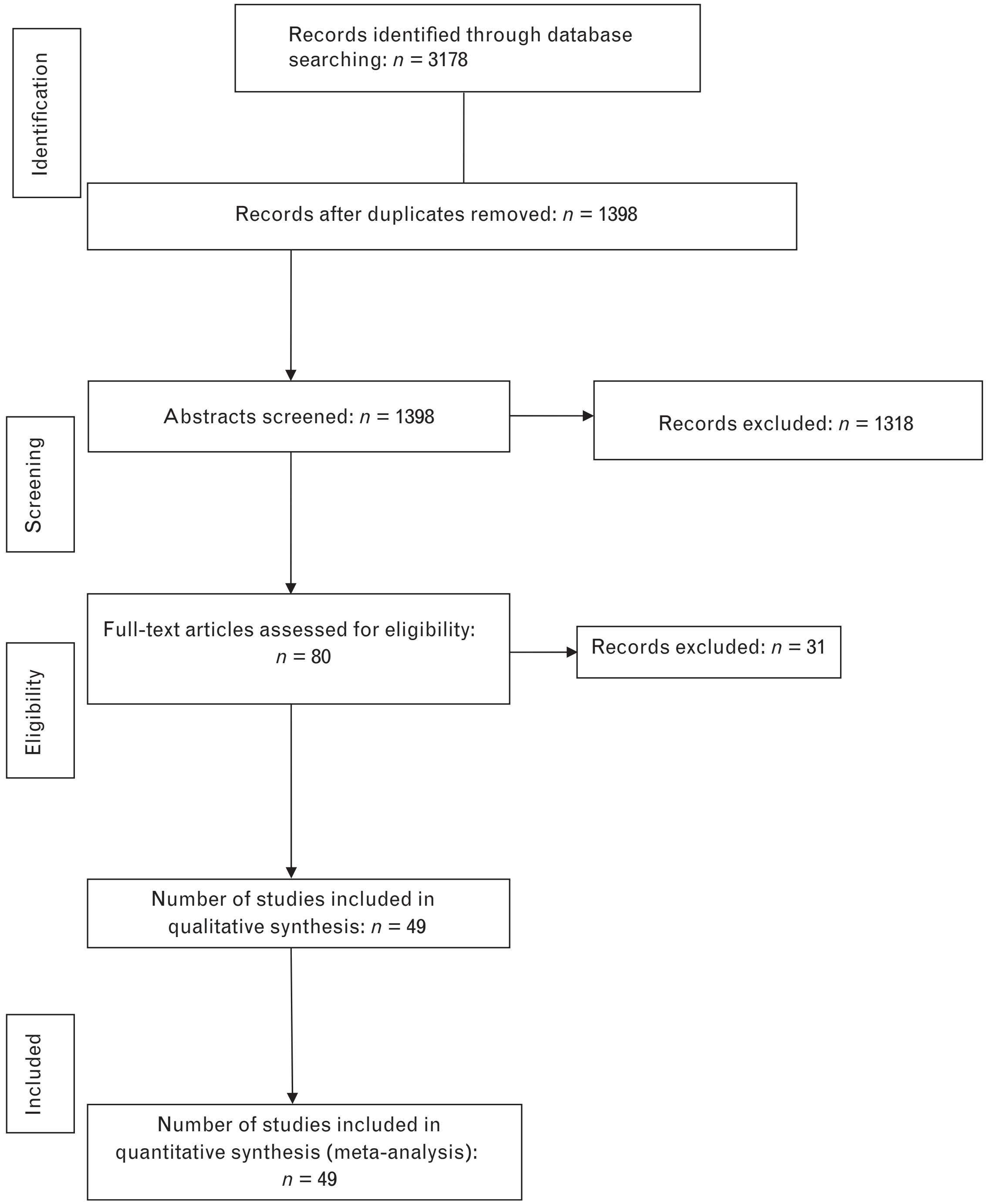
The risk of bias summary is presented in Fig. 2 and the GRADE quality of evidence can be found in Table 2. A total of 19 out of 49 studies (39%) were double-blind.

Primary outcome was incidence of hypotension

Conventional meta-analysis

Figure 3 shows the conventional meta-analysis for the incidence of hypotension. Significant results were found for the comparison of crystalloid coload with colloid coload, with a risk ratio of 1.55 (95% CI 1.25 to 1.92, $P < 0.0001$, $I^2 = 0\%$) (Fig. 3a). Crystalloid preload compared with colloid preload gave a risk ratio for incidence of hypotension of 1.48 (95% CI 1.29 to 1.69, $P < 0.0001$, $I^2 = 60\%$ (Fig. 3b). Risk ratio for crystalloid preload compared with crystalloid coload was 1.31 (95% CI 1.04 to 1.65, $P = 0.02$, $I^2 = 69\%$) (Fig. 3c). There were no significant differences

Fig. 1. Flow chart of the literature search



for the comparison colloid preload vs. colloid coload; risk ratio of 1.01 (95% CI 0.84 to 1.20, $P = 0.92$, $I^2 = 12\%$) (Fig. 3d). The other comparisons had less than three studies; hence, no effect estimate was calculated.

Trial sequential analysis

For all comparisons, the cumulative Z-curve did not cross the trial sequential monitoring or futility boundary, indicating that all these meta-analyses were insufficiently powered to answer the clinical question.

Network meta-analysis

In Figure 4a, we present the network geometry for the primary outcome. Figure 4b shows a forest plot of the network meta-analysis for the primary outcome. In Figure 4c, we present a league table sorted by rank. This shows that colloid coload had a 97% chance of being the

Table 1 Study details

Ref.	Year	Comparison	Number of patients comparison 1 vs. 2	Colloid	Crystalloid	Vasopressor and amount	Vasopressor given as	Spinal anaesthesia	Definition of hypotension	Primary outcome	Blinding
Mercier *et al.*[11]	2014	Colloid preload vs. Crystalloid preload	82/85	6% HES 0.5l	Lactated Ringers 1 l	Phenylephrine 50, 100 or 150 µg	Therapeutic	Sitting position L2/3, L3/4 or L4/5, 11 mg of 0.5% HB bupivacaine and 3 µg sufentanil and 100 µg morphine	SBP decrease of < 80% of baseline	Incidence of hypotension	Double
Alimian *et al.*[31]	2014	Colloid preload vs. Crystalloid preload	Unclear. A total of 90 patients in 3 groups, so presumably 30/30/30	HES 6% 7.5 ml kg^{-1}	Lactated Ringers 1 l; Sodium chloride 0.9% 1 l	Ephedrine 5 mg	Therapeutic	Lateral position L3/4 or L4/5, 12 mg of HB bupivacaine 0.5%. Patients immediately turned to supine position	20% decrease in SBP or SBP < 100 mmHg	Incidence of hypotension and ephedrine administration	Double
Arora *et al.*[32]	2015	Colloid preload vs. colloid coload vs. Crystalloid preload	30 / 30 / 30	6% HES 10 ml kg^{-1}	Lactated Ringers 10 ml kg^{-1}	Ephedrine 5 mg	Therapeutic	Left lateral position L3/4, 0.5% HB bupivacaine 2.2 ml	SBP < 80% of baseline	Incidence of hypotension	Not mentioned
Bennasr *et al.*[33]	2014	Colloid coload vs. Crystalloid coload	60 / 60	HES 0.5 l	0.9% Isotonic saline 0.5 l	Ephedrine 6 mg	Therapeutic and prophylactic	L4/5, 10 mg of 0.5% HB bupivacaine and 5 µg sufentanil and 100 µg morphine	SBP < 90 mmHg or decrease > 20% of baseline	Incidence of hypotension	Single
Bottiger *et al.*[34]	2016	Colloid preload vs Crystalloid preload	37 / 37	6% HES 0.5 l in 0.9% normal saline	Lactated Ringers 1.5l	Phenylephrine infusion	Therapeutic and prophylactic	Sitting position L2/3 or L3/4, 12 mg 0.75% HB bupivacaine with morphine and 200 µg intrathecally injected	SBP < 20% below baseline	Incidence of hypotension	Single
Bouchnak *et al.*[35]	2012	Colloid preload vs. Crystalloid preload	30 / 30	HES 130/0.4, 0.5 l	Isotonic saline 1 l	Ephedrine 6 mg	Therapeutic	Sitting position L4/5, 10 mg of HB bupivacaine 0.5% + sufentanil 5 µg + morphine 100 µg	SBP < 80% of baseline	Incidence of hypotension	Single
Cardoso *et al.*[36]	2004	Colloid preload vs. Crystalloid preload	25 / 25	Modified fluid gelatin 10 ml kg^{-1}	Lactated Ringers 10 ml kg^{-1}	Metamarinol 0.2 mg or 0.4 mg	Therapeutic	Sitting position at L2/3 or L3/4 interspace. Spinal injectate 0.5% HB bupivacaine with 40 µg morphine.	10% decrease in SBP and 20% decrease in SBP	Incidence of hypotension	Double
Carvalho *et al.*[37]	2009	Colloid coload vs. Colloid preload	23 / 23	6% HES 0.5 l as coload or preload	NA	Ephedrine 5 mg with phenylephrine 25 µg	Therapeutic	Sitting position L2/3 or L3/4, 12 mg of 0.75% HB bupivacaine and 10 µg fentanyl and 200 µg morphine	SBP decrease < 90% of baseline	Incidence of hypotension	Not blinded
Chumnanvej *et al.*[38]	2018	Crystalloid preload vs. Crystalloid coload	51 / 51	NA	Acetated solution 10 ml kg^{-1} as coload or preload	Ephedrine 6 mg	Therapeutic	L3/4, 2 to 2.4 ml of 0.5% HB bupivacaine and 0.2 mg morphine	SBP < 90 mmHg or decrease < 80% of baseline	Incidence of hypotension	Single
Dahlgren *et al.*[39]	2005	Colloid preload vs. Crystalloid preload	56 / 53	3% Dextran 60 1l	Lactated Ringers 1 l	Ephedrine 5 mg	Therapeutic	Sitting position L3/4. 2.5 ml of 0.5% HB bupivacaine in 8.25% glucose and 10mcg fentanyl	Overall hypotension: SBP < 100 mmHg, clinically sign hypotension: above + maternal discomfort, severe hypotension: SBP < 80 mmHg	Incidence of hypotension	Double
Dahlgren *et al.*[40]	2007	Colloid preload vs. Crystalloid preload	28 / 25	3% Dextran 60 1 l	Acetated Ringers 1 l	Ephedrine 5 mg	Therapeutic	Sitting position L3/4. 2,5 ml of 0.5% HB bupivacaine in 8.25% glucose and 10 µg fentanyl	Overall hypotension: SBP < 100 mmHg, clinically sign hypotension: above + maternal discomfort, severe hypotension: SBP < 80 mmHg	Frequency of hypotension and ephedrine consumption in patients with positive and negative supine stress test	Double
Dyer *et al.*[41]	2004	Crystalloid preload vs. Crystalloid coload	25 / 25	NA	Lactated Ringers 20 ml kg^{-1} as coload or preload	Ephedrine 5 mg	Therapeutic	L3/4, 9 mg of 0.5% HB bupivacaine and 10 µg fentanyl	MAP < 80% of baseline	Incidence of hypotension	Not blinded
Ewaldsson *et al.*[42]	2011	Colloid coload vs. Crystalloid coload	25 / 25	Dextran 2 ml kg^{-1}	Acetated Ringers 5 ml kg^{-1}	Ephedrine 5 mg	Therapeutic	Left lateral position L2/3 or L3/4, IB bupivacaine	SBP decrease > 30% from baseline	Haemodynamic outcomes	Not blinded

Table 1 (*continued*)

Ref.	Year	Comparison	Number of patients comparison 1 vs. 2	Colloid	Crystalloid	Vasopressor and amount	Vasopressor given as	Spinal anaesthesia	Definition of hypotension	Primary outcome	Blinding
Farid *et al.*[43]	2016	Crystalloid preload vs. Crystalloid coload	37 / 37	NA	Lactated Ringers $15\,ml\,kg^{-1}$ as coload or preload	Ephedrine or phenylephrine	Therapeutic	Sitting position L3/4 or L4/5, 1.6 ml of 0.75% HB bupivacaine	MAP decrease > 20% form baseline	Incidence of hypotension	Not blinded
French *et al.*[44]	1999	Colloid preload vs. Crystalloid preload	80 / 80	HES $15\,ml\,kg^{-1}$	Lactated Ringers $15\,ml\,kg^{-1}$	Ephedrine 3 to 6 mg	Therapeutic	Sitting position L2/3, 2.5 to 3 ml 0.5 HB bupivacaine	SBP < 90 mmHg or < 70% of baseline	Incidence of hypotension	Double
Golmohammadi *et al.*[45]	2013	Colloid coload vs Colloid preload	56 / 56	6% HES 0.5 l in 0.9% NaCl as preload or $15\,ml\,kg^{-1}$ as coload	NA	Ephedrine or phenylephrine	Therapeutic	Sitting position L2/3 or L3/4, 10 mg of 0.5% IB bupivacaine	SBP decrease > 20% from baseline	Incidence of hypotension	Not mentioned
Hasan *et al.*[46]	2012	Colloid preload vs. Crystalloid preload	30 / 30	6% HES $8\,ml\,kg^{-1}$	Lactated Ringers $20\,ml\,kg^{-1}$	Ephedrine 5 mg	Therapeutic	Sitting position L3/4, 10 mg of 0.5% HB bupivacaine	SBP < 100 mmHg or < 20% below baseline	Incidence of hypotension	Not mentioned
Jacob *et al.*[47]	2012	Crystalloid preload vs. Crystalloid coload	50 / 50	NA	Lactated Ringers $15\,ml\,kg^{-1}$ as coload or preload	Ephedrine 6 mg	Therapeutic	Left lateral position L3/4 or L4/5, 2.5 ml. Of HB bupivacaine	SBP < 90 mmHg or < 80% of baseline	Incidence of hypotension	Not blinded
Karinen *et al.*[48]	1995	Colloid preload vs. Crystalloid preload	13 / 13	6% HES 0.5 l	Lactated Ringers 1 l	Ephedrine 5 to 10 mg	Therapeutic	Right lateral position L3/4, 13 mg of 0.5% HB bupivacaine	SBP < 90 mmHg or < 80% of baseline	Incidence of hypotension	Single
Kaya *et al.*[49]	2007	Colloid preload vs. Crystalloid preload	30 / 60	Gelofusine 0.5l	Lactated Ringers 0.5l	Ephedrine 5 mg	Therapeutic	L2/3 or L3/4, 10 or 4 mg of 0.5% bupivacaine	SBP < 90 mmHg or 30% decrease from baseline	Incidence of hypotension	Double
Khan *et al.*[50]	2013	Crystalloid preload vs. Crystalloid coload	50 / 50	NA	Lactated Ringers $20\,ml\,kg^{-1}$ as coload or preload	Ephedrine 5 mg	Therapeutic	Left lateral position L3/4, 3 ml of 0.5% HB bupivacaine	SBP < 90 mmHg or 20% decrease from baseline	Incidence of hypotension	Not blinded
Ko *et al.*[51]	2007	Colloid preload vs. Crystalloid preload	50 / 50	6% HES 500 ml	Lactated Ringers $20\,ml\,kg^{-1}$	Ephedrine 5 mg	Therapeutic	Right lateral position L3/4, 9 mg of 0.5% HB bupivacaine and 20 µg fentanyl	SBP < 95 mmHg or decrease > 20% from baseline	Incidence of hypotension	Double
Lin *et al.*[52]	1999	Colloid preload vs. Crystalloid preload	30 / 30	10% Dextran 40 0.5 l	Lactated Ringers 1 l	Ephedrine 8 mg	Therapeutic	Right lateral position L3/4 or L4/5, 11 mg of 0.5% bupivacaine	SBP decrease of < 70% of baseline	Incidence of hypotension	Double
Madi-Jebara *et al.*[53]	2008	Colloid preload vs. Crystalloid preload	61 / 59	6% HES 0.5 l	Lactated Ringer 1l	Ephedrine 3 mg	Therapeutic	Sitting position L2/3 or L3/4, 10 mg of 0.5% HB bupivacaine and 2.5 µg of sufentanil and 0.1 mg of morphine	SBP < 100 mmHg or decrease > 20% from baseline	Incidence of hypotension	Not mentioned
Matsota *et al.*[54]	2015	Colloid preload vs. Crystalloid preload	15 / 15	6% HES 0.5 l	Lactated Ringers 1l	Ephedrine 5 mg	Therapeutic	Sitting position L3/4 or L4/5, 0.75% ropivacaine and 20 µg of fentanyl	SBP < 100 mmHg or decrease > 20% from baseline	Incidence of hypotension	Single
McDonald *et al.*[55]	2011	Colloid coload vs. Crystalloid coload	30 / 30	6% HES 1 l	Lactated Ringers 1 l	Phenylephrine 100 µg	Therapeutic and prophylactic	Sitting position L3/4, 12 mg of 0.5% HB bupivacaine and 15 µg fentanyl	SBP decrease < 80% of baseline	Cardiac output	Double
Mitra *et al.*[56]	2014	Colloid preload vs. Crystalloid preload	64 / 32	1. 6% HES $10\,ml\,kg^{-1}$ 2.4% modified fluid gelatin $10\,ml\,kg^{-1}$	Lactated Ringers $20\,ml\,kg^{-1}$	Phenylephrine 80 µg	Therapeutic	Sitting position L3/4, 2 ml of 0.5% HB bupivacaine and 25 µg fentanyl	SBP < 100 mmHg or decrease > 20% from baseline	Incidence of hypotension	Double
Nishikawa *et al.*[57]	2007	Colloid coload vs. Colloid preload	18 / 18	6% HES $15\,ml\,kg^{-1}$ as coload or preload	NA	Ephedrine 4 mg	Therapeutic	Lateral position L3/4, 11.5 to 13.5 mg 0.5% HB bupivacaine	SBP decrease < 80% of baseline	Incidence of hypotension	Double
Oh *et al.*[58]	2014	Crystalloid preload vs. Crystalloid coload	30 / 30	NA	Hartmann's solution $15\,ml\,kg^{-1}$ as coload or preload	Ephedrine 5 mg	Therapeutic	Right lateral position L3/4, 8 mg of 0.5% HB bupivacaine and fentanyl 15 µg	SBP decrease > 20% from baseline	Incidence of hypotension	Not blinded
Razavi *et al.*[59]	2018	Crystalloid preload vs. Crystalloid coload vs. Colloid preload vs. Colloid coload	24 / 25 / 24 / 25	Voluven $7\,ml\,kg^{-1}$ as preload or coload	Ringers solution $15\,ml\,kg^{-1}$ as preload or coload	Ephedrine 5 mg	Therapeutic	Sitting position L2/3 or L3/4, 12 mg of 0.5% HB bupivacaine with 20 µg fentanyl	SBP < 90 mmHg or decrease > 20% of baseline	Incidence of hypotension	Double
Romdhani *et al.*[60]	2014	Colloid preload vs. Crystalloid preload	48 / 53	6% HES 0.5 l	0.9% saline solution 1.5 l	Ephedrine 6 mg	Therapeutic	Sitting position L2/3 or L3/4, 10 mg of 0.5% HB bupivacaine and 2.5 µg of sufentanil and 100 µg of morphine	SBP > 20% from baseline	Incidence of hypotension	Not blinded

Table 1 (*continued*)

Ref.	Year	Comparison	Number of patients comparison 1 vs. 2	Colloid	Crystalloid	Vasopressor and amount	Vasopressor given as	Spinal anaesthesia	Definition of hypotension	Primary outcome	Blinding
Rupnar *et al.*[61]	2018	Crystalloid preload vs. Crystalloid coload	150 / 150	NA	Lactated Ringers 15 ml kg^{-1} as coload or preload	Ephedrine 6 mg	Therapeutic	Sitting position L3/4, 10 to 12 mg of 0.5% HB bupivacaine	SBP < 20% below baseline	Incidence of hypotension	Single
Saghafinia *et al.*[62]	2017	Colloid preload vs. Crystalloid preload	60 / 60	6% HES 7 ml kg^{-1}	Normal saline 15 ml kg^{-1}	Ephedrine 5 to 10 mg	Therapeutic	Sitting position L3/4 or L4/5, 12 to 15 mg of 0.5% bupivacaine	SBP < 100 mmHg or decrease > 20% from baseline	Incidence of hypotension	Single
Saleem *et al.*[63]	2016	Colloid preload vs. Crystalloid preload	100 / 100	3% Haemacel 0.5l	Lactated Ringers 20 ml kg^{-1}	Phenylephrine	Therapeutic	0.75% HB bupivacaine with standard technique	SBP < 70% of baseline	Incidence of hypotension	Not mentioned
Shah *et al.*[64]	2015	Crystalloid preload vs. Crystalloid coload	50 / 50	NA	Lactated Ringers 10 ml kg^{-1} as coload or preload	Ephedrine or phenylephrine	Therapeutic	Not mentioned	MAP decrease >20% form baseline	Incidence of hypotension	Not mentioned
Sharma *et al.*[65]	1997	Colloid preload vs. Crystalloid preload	19 / 21	6% HES 0.5 l	Lactated Ringers 1 l	Ephedrine 5 mg	Therapeutic	Sitting position L2/3 or L3/4, 75 mg of 5% HB lidocaine and 10 μg fentanyl	SBP decrease of < 75% of baseline	Incidence of hypotension	Single
Siddik *et al.*[66]	2000	Colloid preload vs. Crystalloid preload	20 / 20	10% HES 0.5l	Lactated Ringers 1l	Ephedrine 5 mg	Therapeutic	Sitting position L2/3 or L3/4, 13 mg of 0.75% bupivacaine in 8.5% dextrose	SBP < 100 mmHg or < 80% of baseline	Incidence of hypotension	Single
Siddik-Sayid *et al.*[67]	2009	Colloid coload vs. Colloid preload	88 / 90	6% HES 0.5 l as coload or preload	NA	Ephedrine 6 mg	Therapeutic	Sitting position L2/3 or L3/4, 12.75 mg of 0.75% HB bupivacaine in dextrose and 0.2 mg morphine	SBP < 100 mmHg or decrease < 80% from baseline	Incidence of hypotension	Double
Singh *et al.*[68]	2009	Colloid preload vs Crystalloid preload	30 / 30	6% HES 10 ml kg^{-1}	Lactated Ringers 20 ml kg^{-1}	Mephentermine 3 mg	Therapeutic	Right lateral position L3/4, 1.8 to 2.2 ml of 0.5% HB bupivacaine	SBP < 90 mmHg or decrease >30% from baseline	Incidence of hypotension	Not mentioned
Tamilselvan *et al.*[69]	2009	Colloid preload vs. Crystalloid preload	40 / 20	1. 6% HES 0.5 l, 2. 6% HES 1 l	Lactated Ringers 1.5 l	Ephedrine 6 mg	Therapeutic	Sitting position L3/4, 12.5 mg of 0.5% HB bupivacaine and 15 μg fentanyl	SBP < 90 mmHg or decrease >20% of baseline	Maternal cardiac output	Double
Tawfik *et al.*[70]	2014	Colloid preload vs. Crystalloid coload	103 / 102	6% HES in 0.9% NaCl 0.5 l	Acetated Ringers 1l	Ephedrine 5 mg	Therapeutic	Sitting position L2/3 or L3/4, 12.5 mg of 0.5% HB bupivacaine and 10 μg fentanyl	SBP < 90 mmHg or decrease < 80% of baseline	Incidence of hypotension	Double
Teoh *et al.*[71]	2009	Colloid coload vs. Colloid preload	20 / 20	6% HES 15 ml kg^{-1} as coload or preload	NA	Phenylephrine 50 μg	Therapeutic	Right lateral position L3/4, 10 mg of 0.5% HB bupivacaine and 100 μg morphine	SBP decrease < 90% from baseline	Incidence of hypotension	Single
Ueyama *et al.*[72]	1999	Colloid preload vs. Crystalloid preload	24 / 12	6% HES 0.5 l; 6% HES 1 l	Lactated Ringers 1.5 l	Ephedrine 10 mg	Therapeutic	Right lateral position L3/4, 8 mg tetracaine hydrochloride and 100 μg morphine in 10% dextrose	SBP < 100 mmHg or < 80% of baseline	Changes in blood volume and cardiac output	Not mentioned
Unlugenc *et al.*[73]	2015	Colloid coload vs. Crystalloid coload	30 / 30	6% HES 1 l	Lactated Ringers 1l	Ephedrine 10 mg	Therapeutic	Sitting position L3/4 or L4/5, 10 mg of 0.5% HB bupivacaine and 25 μg fentanyl	SBP < 90 mmHg or < 80% of baseline	Incidence of hypotension and ephedrine use	Double
Upadya *et al.*[74]	2016	Colloid preload vs. Crystalloid preload	25 / 25	6% HES 0.5 l	Lactated Ringers 1 l	Ephedrine 5 mg	Therapeutic	Left lateral position L2/3 or L3/4, 10 mg of 0.5% HB bupivacaine in dextrose	SBP <100 mmHg or < 80% of baseline	Incidence of hypotension	Not mentioned
Varshney *et al.*[75]	2013	Colloid coload vs. Colloid preload	20 / 20	6% HES 10 ml kg^{-1} as coload or preload	NA	Phenylephrine 25 μg	Therapeutic	Sitting position L3/4 or L4/5, 5.5 mg of 0.5% HB bupivacaine and 25 μg fentanyl	SBP < 90 mmHg or decrease >25% of baseline	Incidence of hypotension	Double
Wani *et al.*[76]	2018	Colloid coload vs. Crystalloid coload	48 / 49	6% HES 1 l	Lactated Ringers 1 l	Ephedrine 5 mg	Therapeutic	Sitting position L3/4, 3 ml of 0.5% HB bupivacaine	SBP <90 mHg or 20% decrease from baseline	Incidence of hypotension	Double
Yalcinkaya *et al.*[77]	2010	Colloid preload vs. Crystalloid preload	40 / 40	6% HES 10 ml kg^{-1}	Lactated Ringers 10 ml kg^{-1}	Ephedrine 5 mg	Therapeutic	Lateral position L2/3 or L3/4, 1.8 ml of HB bupivacaine 0.5% and 20 μg fentanyl	SBP <90 mmHg of decrease >25% from baseline	Incidence of hypotension	Not mentioned
Yorozu *et al.*[78]	2002	Colloid preload vs. Crystalloid preload	32 / 35		Lactated Ringer	Ephedrine 5 mg	Therapeutic	Right lateral position L3/4, 0.3% dibucaine	SBP <90 mmHg	Incidence of hypotension	Not mentioned

NA, not applicable; SBP, systolic blood pressure; HB, hyperbaric; IB, isobaric.

Fig. 2. Risk of bias summary

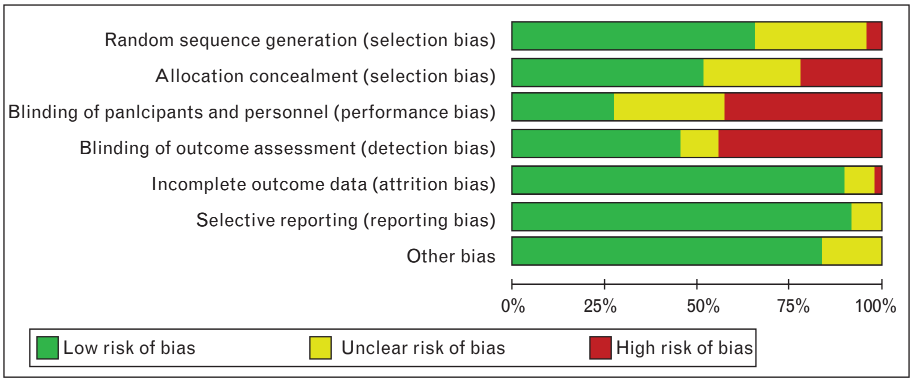


Table 2 GRADE assessment

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Outcome: Incidence of hypotension						
4317 (49 studies)	Moderate[a]	No serious inconsistency[b]	Moderate indirectness[c]	No imprecision	Not likely[d]	Low quality

[a] Not all studies were double-blind, possible selection bias. [b] No significant differences between direct and indirect comparison. [c] Due to differences in outcome measures. [d] There is a possibility of publication bias, but it was not considered sufficient to downgrade the overall quality of evidence.

best among all four treatments with the other treatments much lower: colloid preload (67%), crystalloid coload (36%) and crystalloid preload (0%). Colloid coload had a significantly lower incidence of hypotension when compared with crystalloid coload and crystalloid preload: risk ratio 0.76 (95% CI 0.61 to 0.95) and RR 0.59 (95% CI 0.47 to 0.73), respectively. There was no significant difference between colloid coload and colloid preload: risk ratio 0.87 (95% CI 0.71 to 1.07). Colloid preload lowers the incidence of hypotension significantly compared with crystalloid preload: risk ratio 0.68 (95% CI 0.60 to 0.76). Crystalloid coload lowers the incidence of hypotension significantly compared with crystalloid preload: risk ratio 0.77 (95% CI 0.65 to 0.92).

The tau^2 for the network model was 0.0475 and the I^2 statistic was 52.6%. No significant differences were found in the consistency analysis that compared the direct and indirect outcomes ($P = 0.63$).

Sensitivity analysis

In Figure S4a (supplementary material, http://links.lww.com/EJA/A403), we present the network graph. Conventional meta-analysis of the low-bias studies showed a nonsignificant difference between comparison colloid preload and colloid coload, RR 0.83 (95% CI 0.68 to 1.03, $P = 0.09$, $I^2 = 0\%$). Significant differences were found between the comparisons crystalloid coload and colloid coload, as well as between crystalloid preload and colloid preload: risk ratio 1.46 (95% CI 1.08 to 1.96, $P = 0.01$, $I^2 = 61\%$) and risk ratio 1.59 (95% CI 1.28 to 1.97, $P < 0.0001$, $I^2 = 61\%$), respectively (Figure S3b & S3c, supplementary material, http://links.lww.com/EJA/A403). For comparisons crystalloid preload with crystalloid coload, colloid coload with crystalloid preload and colloid preload with crystalloid coload, no forest plot is shown because less than three studies could be included.

As only a limited number of studies used a prophylactic vasopressor, we decided to not perform a sensitivity analysis.

Network meta-analysis results of the low-bias-studies can be found in Figure S4c (supplementary material, http://links.lww.com/EJA/A403). The ranking showed colloid preload had the highest chance of being the best (79%) followed by colloid coload (78%), crystalloid coload (37%) and crystalloid preload (6%). Colloid preload had a lower chance of hypotension if compared to crystalloid preload: risk ratio 0.64 (95% CI, 0.52 to 0.78). Colloid coload had a lower chance of hypotension if compared to crystalloid preload: risk ratio 0.64 (95% CI, 0.42 to 0.98). All other comparisons were not significant.

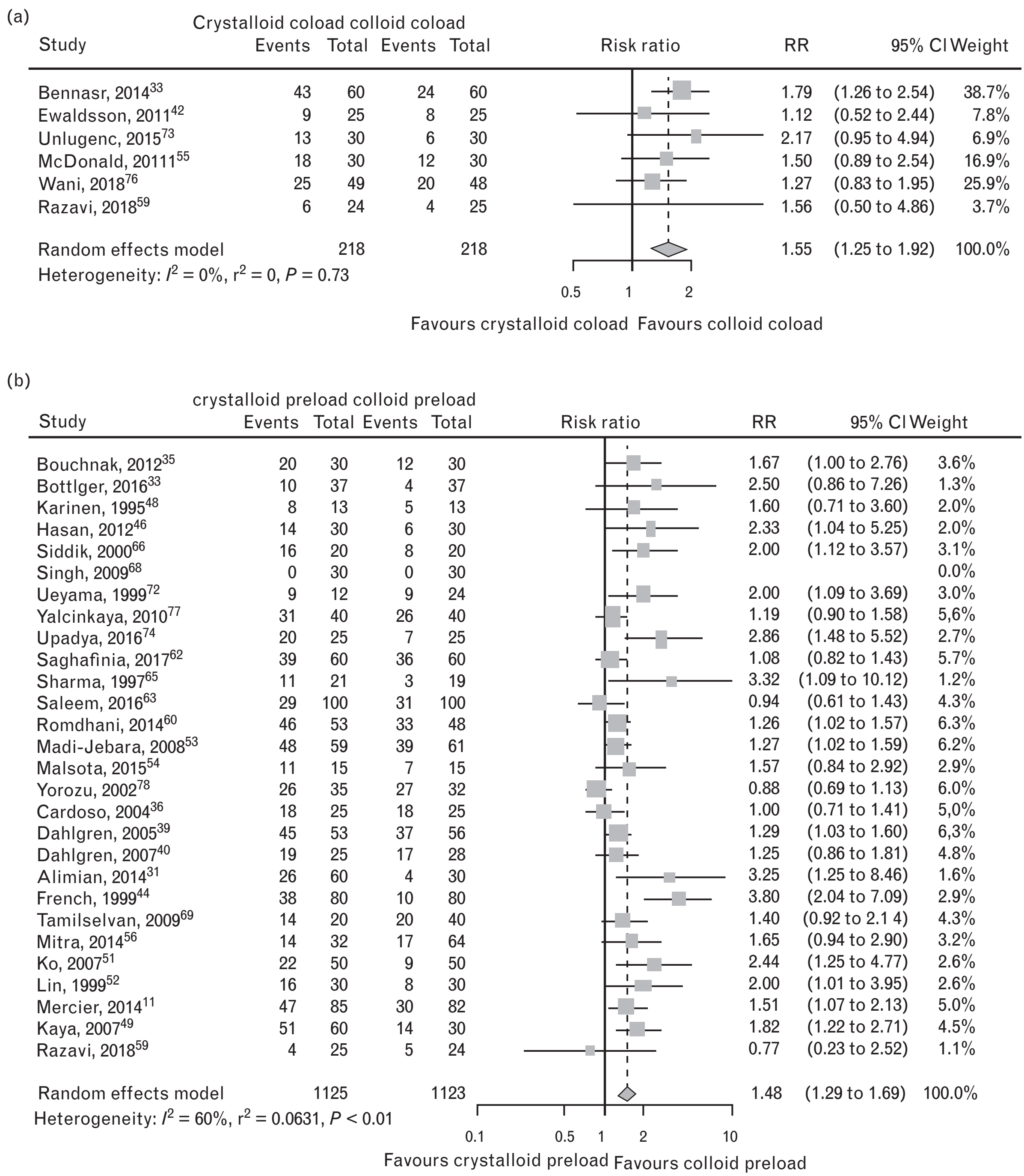
Publication bias

Comparison-adjusted funnel plots can be found in Fig. 5. The Egger test was significant if we included all studies ($P < 0.01$), suggesting possible publication bias. Sensitivity analysis with only double-blind studies showed a nonsignificant Egger test ($P = 0.14$), suggesting no publication bias.

Meta regression

The meta regression can be found in Figure S15 (supplementary material, http://links.lww.com/EJA/A403).

Fig. 3. Conventional meta-analysis of the primary outcome



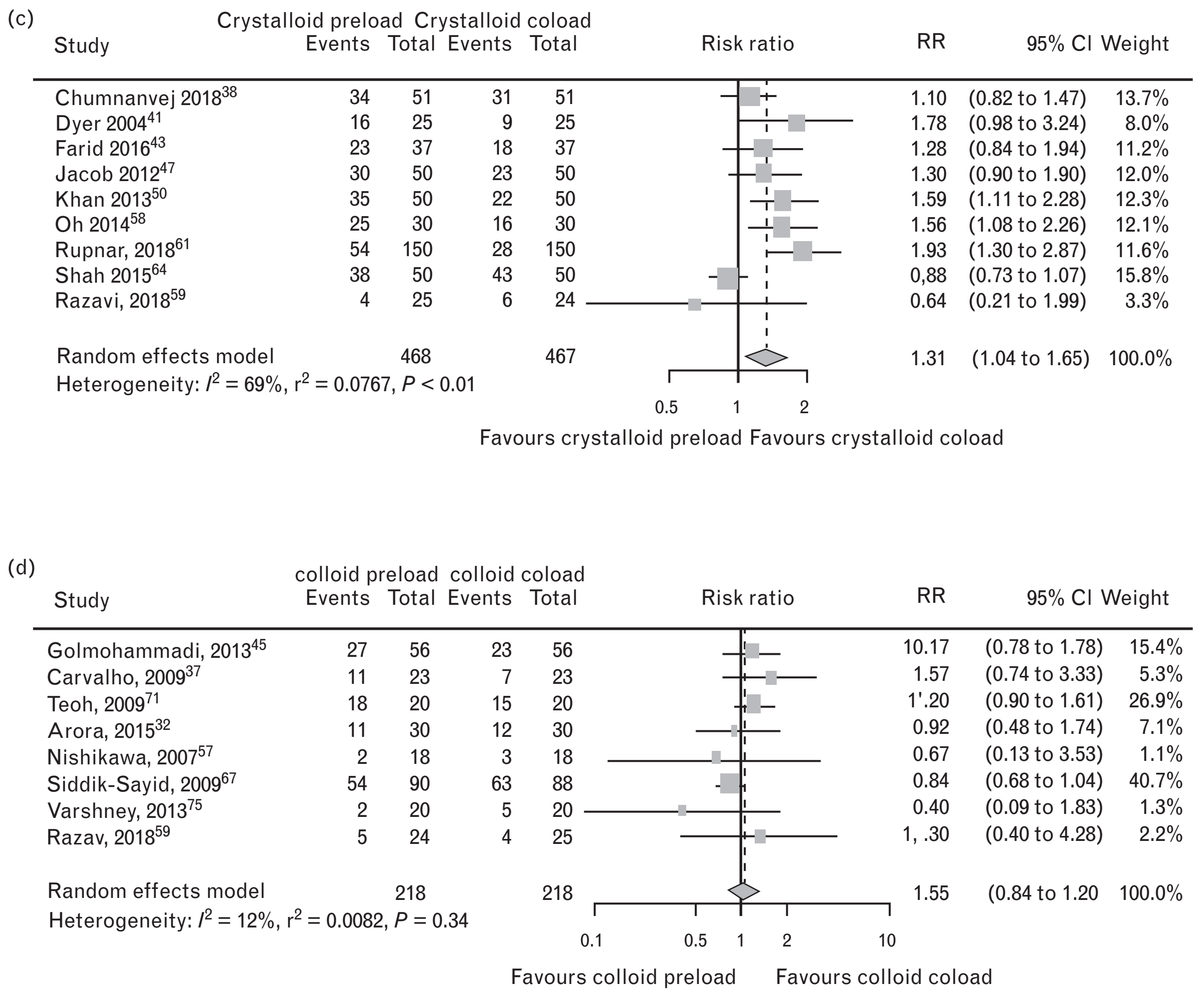
We found a significant dose–response relationship for the volume of crystalloid preload (regression coefficient = −0.073 (95% CI, −0.142 to −0.005), Figure S15a, http://links.lww.com/EJA/A403). Sensitivity analysis with only the double-blind studies found no such relationship (regression coefficient = −0.06 (95% CI, −0.175 to −0.055). No significant dose–response was found for crystalloid coload (Figure S15b, http://links.lww.com/EJA/A403), colloid preload (Figure S15c, http://links.lww.com/EJA/A403) or colloid coload (Figure S15d, http://links.lww.com/EJA/A403).

Secondary outcomes

Ephedrine use

Conventional analysis of studies comparing crystalloid preload with colloid preload found a lower requirement

Fig. 3 (Continued).



for ephedrine use in the colloid preload group, with a mean difference of 4.49 mg (95% CI 0.66 to 8.32, $P = 0.02$, $I^2 = 90\%$) (Figure S5b, http://links.lww.com/EJA/A403). Similarly, comparing crystalloid preload with crystalloid coload found a lower requirement for ephedrine use in the crystalloid coload group, with a mean difference of 7.77 mg (95% CI 1.34 to 14.20, $P = 0.02$, $I^2 = 90\%$) (Figure S5c, http://links.lww.com/EJA/A403). No significant differences were found between colloid preload and colloid coload (Figure S5a, http://links.lww.com/EJA/A403).

Network results are shown in Figure S10, http://links.lww.com/EJA/A403. Crystalloid preload required most additional ephedrine if compared to all other fluid regimes.

Phenylephrine use

There were only sufficient data for the comparison of colloid preload versus colloid coload, and crystalloid preload versus colloid preload. No significant differences were found for conventional and network meta-analysis (Figures S6 and S11, http://links.lww.com/EJA/A403).

Nausea and/or vomiting

A significant increase in the incidence of nausea was found in studies that compared crystalloid preload with crystalloid coload, with a risk ratio of 2.15 (95% CI 1.45 to 3.20, $P = 0.0002$, $I^2 = 0$) (Figure S7b, http://links.lww.com/EJA/A403). Network meta-analysis showed significantly less nausea with crystalloid coload compared with crystalloid preload, and colloid coload compared with crystalloid preload, with risk ratios of 0.51 (95% CI 0.31 to 0.85) and 0.51 (95% CI 0.26 to 0.99), respectively (Figure S12, http://links.lww.com/EJA/A403). For vomiting, there were no significant differences found in all comparisons (Figure S8 and S13, http://links.lww.com/EJA/A403). There were insufficient data for an analysis of nausea and vomiting as a combined outcome.

Neontatal outcomes

There were no significant differences in the analyses of umbilical artery pH (Figure S9 and S14, http://links.lww.com/EJA/A403). There were insufficient data for an analysis of neonatal acidosis.

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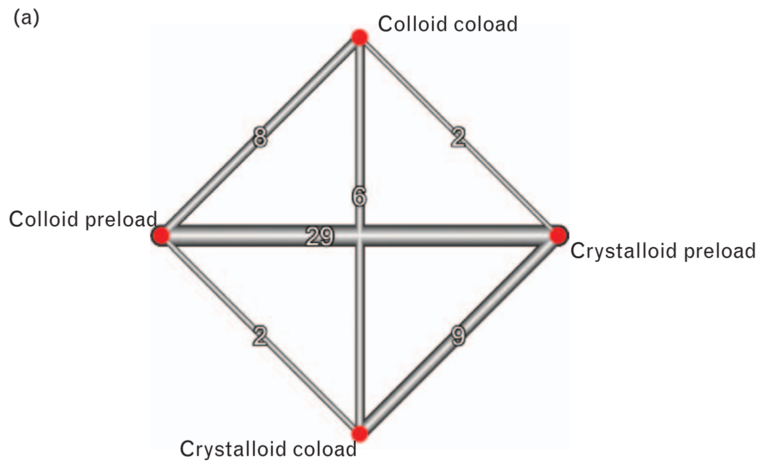
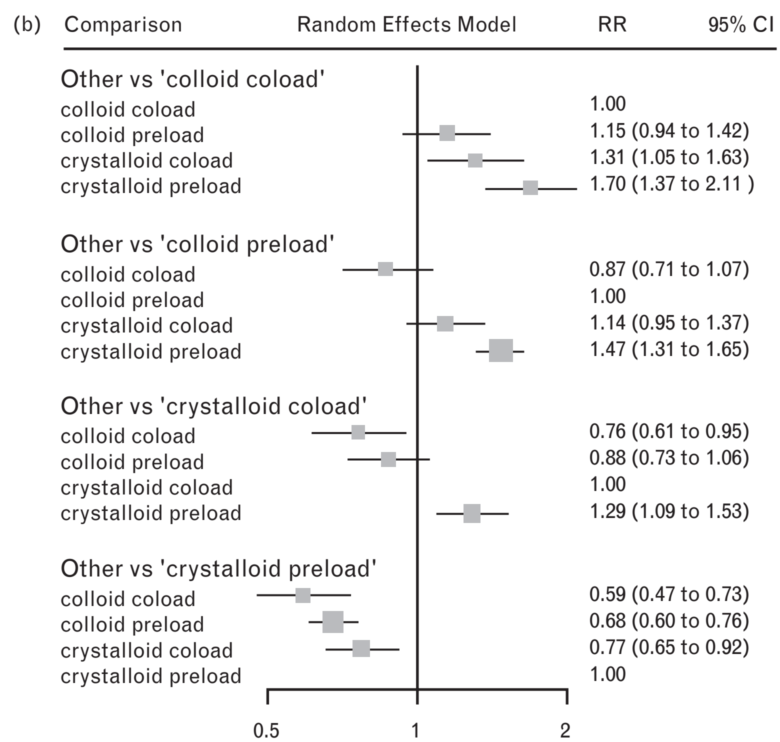
Fig. 4. Network meta-analysis



Line thickness and numbers represents the number of studies included in the analysis for the comparisons.



Forest plots for the network meta-analysis of incidence of hypotension. The size of the square indicates the weight of the effect size as determined by the number of studies and participants.

Discussion

As a major result, we found an effectiveness in descending order, of colloid coload more than colloid preload, and crystalloid coload more than crystalloid preload, for the management of spinal hypotension in women undergoing elective caesarean section (Fig. 4c). Differing slightly from this, the sensitivity analysis (including double-blind studies only) demonstrated that colloid coload and preload were almost equally effective 78 and 79%, respectively, whereas crystalloid coload and crystalloid preload only had a 37 and 6% chance, respectively, of success (league table: Figure S4c, http://links.lww.com/EJA/A403).

In direct comparisons, we found a significantly increased incidence of hypotension when comparing crystalloid

Fig. 4 (Continued).

(c)

0.97			
colloid coload	0.67		
0.87 (0.71 to 1.07)	colloid preload	0.36	
0.76 (0.61 to 0.95)	0.88 (0.73 to 1.06)	crystalloid coload	0.00
0.59 (0.47 to 0.73)	**0.68 (0.60 to 0.76)**	0.77 (0.65 to 0.92)	crystalloid preload

Treatments were ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores which are used to rank the treatments. Higher P scores indicate a greater chance of being the best treatment. The column treatment is compared with the row treatment. Treatment estimates are provided as risk ratios with 95% CIs. Significant pairwise comparisons are bold.

preload with colloid preload. However, the TSA showed that there were insufficient data for a definite conclusion that colloid preload is more effective than crystalloid preload in preventing hypotension.

Likewise, conventional meta-analysis showed that crystalloid coload was more effective in preventing hypotension than crystalloid preload, but again TSA did not confirm this finding.

Meta-regression suggested a dose–response effect for crystalloid preloading only. When nonblind and single-blind studies were excluded, no dose–response relationship could be found.

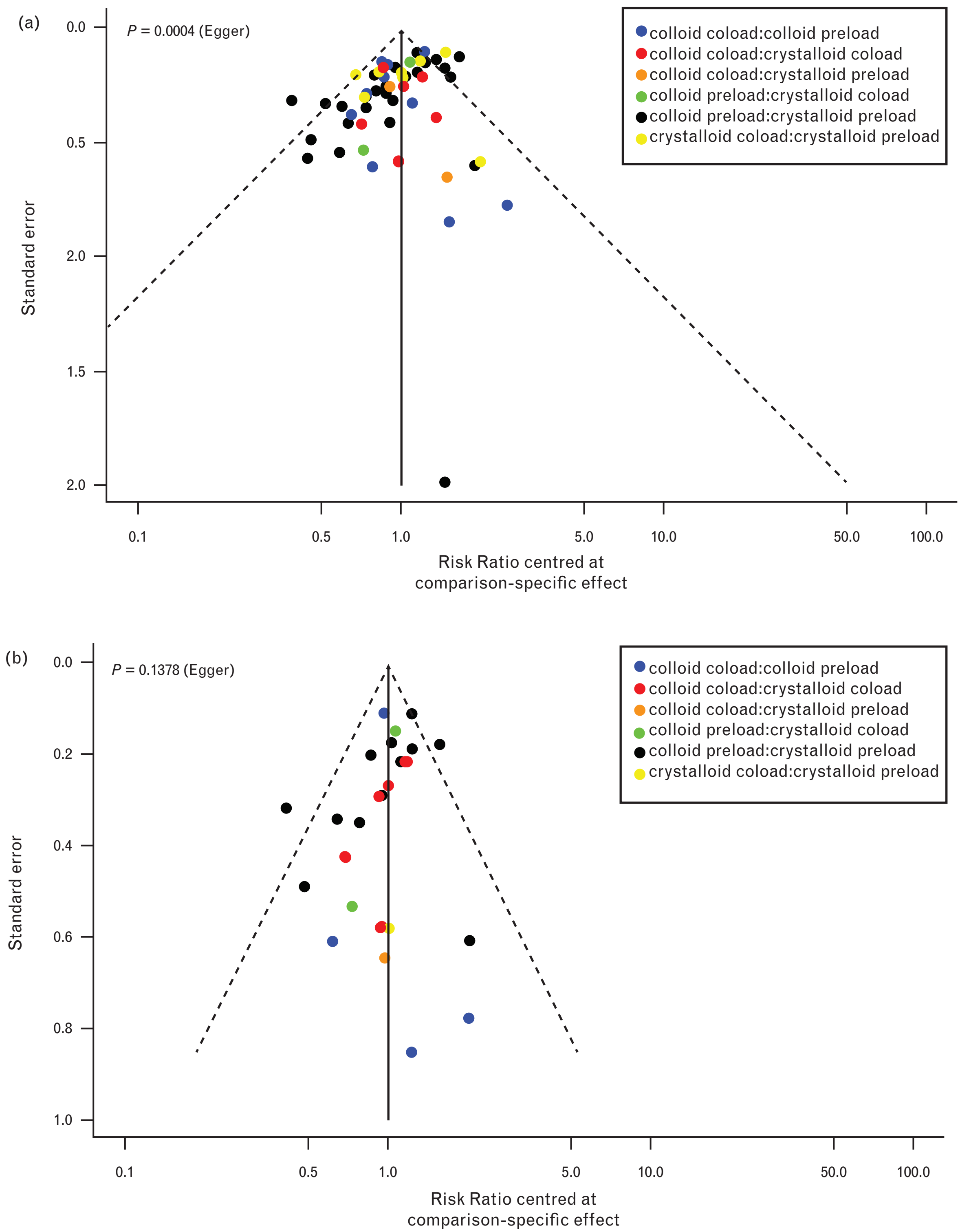
With this evaluation, we aimed to present the highest level of evidence by adding a sensitivity analysis with only double-blind studies. A total of 39% of our included articles were double-blind. We consider TSA to be the most robust statistical method to decide whether there is sufficient data to make a definite conclusion. In our study, there was insufficient evidence to draw any definite conclusion if we combined TSA with only double-blind studies for the primary outcome, namely the incidence of maternal hypotension. Despite years of research on this topic, based on the negative TSA, we still came to same conclusion as Banerjee *et al.*[79] in 2010 that no significant differences between any of the fluid loading groups can be confirmed.

Recently, a network meta-analysis on measures to prevent hypotension was published by Fitzgerald *et al.*[14] This focused mainly on vasopressors, therefore allowing for only limited comparisons with our study. Another major difference with our study is that those authors[14] defined the administration of 500 ml or less of a crystalloid fluid as an inactive control. In our analysis, studies with this comparator would have been included in comparisons with crystalloid administrations, either pre or coload depending on the time of infusion in the individual studies. Therefore, the number of studies in the comparisons differs between Fitzgerald *et al.*, and our analysis. Fitzgerald *et al.*[14] reported a significantly lower incidence of hypotension for colloid preload than crystalloid preload for low risk of bias studies. However, those authors used only conventional meta-analysis, while we added TSA, which did not confirm this finding. We therefore conclude that the evidence is too limited to draw a definite conclusion on differences between these two fluid regimens. Fitzgerald *et al.*[14] also reported significantly less hypotension after colloid coload compared with crystalloid coload. Again, our TSA analysis did not corroborate this finding. We feel our results are of clinical relevance because if there were a definite benefit of colloids, their use would have to be taken more into consideration despite their potential downsides.

Also, we cannot compare the magnitude of the effect estimate of the study of Fitzgerald *et al.*[14] and that of our study because those authors reported odds ratios whereas we report risk ratios. As the Cochrane Handbook for Systematic Reviews of Interventions points out, odds and risk ratio are different when the events of the outcomes investigated are frequent.[80] This is the case for hypotension, and thus, odds ratios overestimate the effect of the interventions.

A Cochrane analysis[81] from 2017 agrees with the findings of Fitzgerald *et al.*,[14] in that crystalloid coload is more effective than preload. Ripollés Melchor *et al.*[82] and the Cochrane review by Chooi *et al.*[81] compared crystalloids with colloids regardless of the time-point of administration and found a significantly reduced risk of hypotension

Fig. 5. Funnel plot



when colloids were used. Similar conclusions were drawn in another meta-analysis from 2013.[83]

Another advantage of our study is that we included meta-regressions in the analysis. The dose–response of volume effect that we established suggests that the more crystalloid that is given before spinal anaesthesia, the less maternal hypotension is seen. This is, however, of little clinical relevance because crystalloid preloading is the least effective fluid loading technique. In addition, sensitivity analyses including only double-blind studies did not find this relationship. This volume relationship was not found for either crystalloid or colloid coloading, perhaps because most of the haemodynamic effects of sympathetic blockade occur during the first 5 to 7 min after intrathecal injection and therefore, more volume would be of little help when given thereafter. From a practical perspective, this means that when using coloading, a moderate volume (1 l) is likely to be enough, and there is no benefit to prolonged i.v. fluid administration thereafter. Excessive fluid may be detrimental after caesarean section. The lack of a volume relationship for the colloid preload is more difficult to explain. A possible explanation could be the more potent volume expanding effect of colloids, that is reaching a ceiling volume effect rapidly. However, this would contrast with a study from Ueyama *et al.*,[72] who found a much lower incidence of maternal hypotension when preloading with 1 l of colloid instead of only 0.5 l (17% versus 58%, respectively).

Finally, our findings must be seen in the light of the growing ambition to include patients undergoing (elective) caesarean sections in enhanced recovery programmes with shortened starvation times and proactive oral fluid consumption prior to surgery. The available data are not convincing, that this form of oral prehydration really does prevent spinal anaesthesia-induced hypotension.[84,85] On the contrary, prevention of hypotension has been shown to contribute to enhanced recovery and therefore must be promoted.[86]

Limitations

The use of network meta-analysis is a valuable evolution of standard meta-analysis, although there are some limitations, and interpretation of the results must be undertaken with care. Transitivity and inconsistency of the model can have an impact on the results. We tested for inconsistency between direct and indirect results for all different comparisons and found no significant difference (see Figure S1, S2 (supplementary material, http://links.lww.com/EJA/A403)). Egger's test implied the possibility of publication bias. A sensitivity analysis restricted to double-blind studies only found no indication for publication bias. Therefore, the corresponding results may be seen as more robust.

Another limitation is the broad range of definitions of hypotension among the included studies, which can lead to different incidences of hypotension.[87] However, the majority of the studies used a decrease in SBP of more than 20% as the definition.

To analyse the possible confounding effect of vasopressors, we planned to do a subgroup analysis, but only three of the 49 included studies used a vasopressor prophylactically, although it has been suggested as best current practice.[3,88] Because of low sample size and different fluid comparisons, we decided that data were too scarce to perform such an analysis. Because vasopressors were mostly given therapeutically, we believe that the result presented must be considered as an effect of the fluids used. On the contrary, we think this is a major research gap and only studies that combine fluid with a prophylactic vasopressor allow one to define the added value of fluid.

Another cause of the heterogeneity may be due to the fact that we included all amounts of fluids and durations of administration as defined by the authors, because there is no minimal volume defined in the literature. Small volumes of fluid, especially crystalloids, given as a preload or coload are mostly less effective in controlling hypotension when compared with larger volumes. However, only two of the included studies reported using 500 ml of crystalloids, all other studies investigated larger volumes. Also, the exact timing and speed of the infusions play an important role in the treatment effect. For crystalloids, fluid may not remain in the circulation if the infusion is slow or is completed sometime before the spinal. In addition, for an 18-guage cannula a pressure bag might be required to infuse 500 ml of crystalloid in less than 7 min. Unfortunately, not all studies reported this type of important information.

A further limitation is the difficulty of translating the results of finding the highest protective efficacy with colloids into clinical practice. Regulatory restrictions have recently been imposed on hydroxyethylstarch solutions.[89] Secondly, only a small amount of data comes from gelatine solutions and its role in peri-operative care has also recently been seriously questioned.[90]

We only included studies on elective caesarean sections, largely conducted in healthy patients. Our conclusions therefore cannot be extrapolated to nonelective cases or women with complex pregnancies or preexisting comorbidities. Indeed, it has been reported that in some settings, for example pre-eclamptic patients, spinal-induced haemodynamic effects are less pronounced and that fluid loading may not be useful and may even be harmful.[91] More recently, Pretorius *et al.*[92] performed a meta-analysis on fluid therapy in pre-eclamptic women and could not provide a conclusion given the paucity of data.

Finally, there was a heterogeneity in the doses of the local anaesthetic used across the various studies. Bupivacaine was mainly used as the local anaesthetic in our included articles. Low doses of bupivacaine were found to be associated with less hypotension compared to higher doses and thus the dose of local anaesthetics may also play a significant role in the haemodynamic response to spinal anaesthesia.[93]

Conclusion

Our meta-analysis supports the efficacy of colloid pre-or coloading, and of crystalloid coloading to a lesser extent, for decreasing the incidence of hypotension during elective caesarean sections performed under spinal anaesthesia. However, TSA combined with sensitivity analysis (including only double-blind studies) showed no definite superiority of any fluid regimen. Due to european restrictions on the most studied colloid (HES), we recommend crystalloid coload as the most appropriate fluid regimen. More research is needed to exactly define the role of the prophylactic use of vasopressors in relation to fluid therapy.

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Presentation: none

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