Fluid co-loading or preloading for the prevention of hypotension during spinal anesthesia for C-section: a narrative review

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Abstract

Background: Fluid management strategies are one of the potential strategies to prevent spinal induced hypotension in parturients scheduled for caesarean section.

Objectives: This review will assess the current evidence on fluid strategies as a prophylactic measure for spinal induced hypotension.

Methods: A narrative review was conducted where Pubmed, Embase and the Cochrane library were searched in November 2021 for RCTs, meta-analyses and systematic reviews, that compared different fluid regimen in ASA classification one or two women scheduled for elective caesarean section.

Results: 77 studies were selected from initial screening, based on titles and abstracts. Out of the 77 initial studies, 37 were considered eligible for inclusion. Crystalloid preloading seemed ineffective in the prevention of spinal hypotension. Crystalloid co-loading, colloid pre- and co-loading all proved to reduce the incidence of spinal hypotension, as well as the incidence of nausea and vomiting and vasopressor use. There was no significant difference in neonatal outcome, regardless of the fluid regimen.

Conclusion: Crystalloid co-loading, colloid co-loading and colloid preloading all have been shown to be effective in the prevention of spinal hypotension.

Introduction

Spinal anesthesia is considered to be the anesthetic technique of choice in healthy pregnant women undergoing a routine caesarean section. Unfortunately associated hypotension is a common side effect, that can lead to undesirable maternal and fetal effects1-4. This is mainly due to a pharmacological sympathectomy, induced by spinal anesthesia resulting in arterial vasodilation and decreased systemic vascular resistance5,6. Parturients are more prone to hypotension due to the required high level of block and the pregnancy related physiological and anatomical changes. There is limited autoregulation in the uteroplacental circulation and therefore flow is almost directly related to the mean uterine perfusion pressure. When maternal hypotension occurs, blood flow in the uteroplacental circulation consequently is reduced and this can lead to fetal distress6. In addition to fetal distress, spinal hypotension can also cause maternal adverse outcomes like nausea and vomiting. Treating and particularly preventing spinal hypotension is therefore a very important part of the anesthetic management of a caesarean section. A range of strategies have been identified, including physical interventions such as left lateral tilt or compression stockings, the prophylactic use of vasopressors, low dose-spinal anesthesia, fluid management and recently the use of ondansetron has also been found to be effective7. This review will focus on fluid loading strategies during spinal anesthesia in order to prevent spinal anesthesia-induced hypotension, by increasing the venous return8. Different types and timings of fluids have been studied. Intravascular volume expansion can be achieved by either fluid preloading (before spinal anesthesia) or co-loading (after spinal anesthesia). Therefore, this review is divided into two parts: preloading and co-loading.
Methods

PubMed, Embase and the Cochrane library were searched in November 2021 and the following keywords were used: colloid, crystalloid, preload, co-load, spinal anesthesia, caesarean section, spinal hypotension. Also synonyms like: succinylated gelatin, albumin, hydroxyethyl starch, HES, 2-hydroxyethyl starches, hydroxyethyl starch 130-0.4, hydrocolloids, volulyte, Ringer’s lactate, plasmalyte, preloading, co-loading, caesarean delivery, abdominal delivery, C-section, and post-caesarean section, were included in our search. Only RCTs, meta-analyses, systematic reviews, which compared different fluid regimen in ASA classification one or two women scheduled for elective caesarean section, without a complicated pregnancy, were eligible for inclusion. Exclusion criteria consisted of language (only studies in Dutch, French or English were included), retracted studies, studies where only the abstract was available, studies without a p-value or an exact volume description, studies without an obstetric population, studies older than 30 years and studies that included urgent caesarean sections. Additionally, guidelines concerning fluid regimen during elective caesarean section were also searched. Our primary outcome was the incidence of hypotension, as defined by individual authors, but the most common definition of hypotension used in research studies are either a decrease to 80% of the baseline blood pressure value or a drop of the systolic pressure below 100 mmHg.

I. Preload

The use of fluid preloading in the prevention of spinal hypotension can be divided into two categories: preloading with crystalloids or preloading with colloids.

A. Crystalloid preload

Twenty studies were included looking at crystalloid preloading as a prophylactic measurement for spinal hypotension. A subcategorization was made comparing crystalloid preload with a control group (three studies), with a colloid preload group (16 studies) and with a crystalloid co-load group (one study). Details can be found in Table I to III. Table I shows the results of three studies that compared crystalloid preload with a control group (no preload or different volumes of preloading). Efficacy of preloading was poor.10-12. There was no difference in vasopressor use or the incidence of nausea and vomiting between both groups and neonatal outcome was also similar. The details of the comparison between crystalloid and colloid preloading are summarized in table two. Colloid preloading appears to be preferable in preventing spinal hypotension. In eight studies13,14,19,21-24,28 where hetastarch 6% was given as a preload, there was a significant reduction in the incidence of spinal hypotension or in the percentage of reduction in systolic blood pressure. In three other studies14,25,26, preloading with hetastarch 6% demonstrated a better hemodynamic stability (higher overall

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| (1) RCT10    | Plasmalyte 20 ml/kg preload vs control | 1993 | 140                | *Incidence of hypotension: significant difference of 16%  
 * No significant difference in dose of vasopressor (ephedrine)  
 * No significant difference in neonatal outcome |
| (2) RCT, single blinded 11 | Hartmann 200 ml vs Hartmann 1000 ml preload. Prophylactic ephedrine infusion | 1995 | 60                | *Incidence of hypotension: no significant difference  
 * No significant difference in dose of vasopressor (ephedrine)  
 * No significant difference in the incidence of nausea and vomiting  
 * No significant difference in neonatal outcome |
| (3) RCT, double blinded 12 | Ringer’s lactate 10 mg/kg vs 20 ml/kg vs 30 ml/kg | 1996 | 55                | *Incidence of hypotension: no significant difference  
 * No significant difference in the dose of vasopressor (ephedrine)  
 * No significant difference in neonatal outcome |
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| (4) RCT, blinded | 6% hetastarch 500 ml (+1L RL) vs RL 2L. Prophylactic 10 mg ephedrine. | 1995 | 40 | *Incidence of hypotension: 45% vs 85% (p<0.05)  
* Ephedrine use: 0mg vs 2mg (p <0.05)  
* No significant difference in nausea and vomiting  
* No significant difference in neonatal outcome |
| (5) RCT | 6% HES 500 ml vs RL 1L | 1995 | 26 | * Incidence of hypotension: 38% vs 62% => no statistical analysis  
* Decrease systolic BP: 27.6 (95 %CI 20.5-34.7)% in the crystalloid group and 21.3(16.0-26.6)% in the colloid group (p=0.15)  
* Neonatal outcomes were similar |
| (6) RCT | RL 1.5L vs 6% HES 500 ml vs 6% HES 1000 ml + a 500 ml RL co-load in all the groups | 1999 | 36 | *Incidence of hypotension: 75% vs 58% vs 17% (p<0.05) |
| (7) RCT, double blinded | Hartmann 15 ml/kg vs 15 ml/kg pentastarch | 1999 | 160 | *Incidence of hypotension: 47.5 vs 12.5% (p<0.0001)  
* Ephedrine use: 8.35 mg (12.56) [0–57] vs 1.35 mg (3.93) [0–18], P < 0.05  
* Neonatal outcomes were similar |
| (8) RCT | HES 10% 500 ml vs RL 1L | 2000 | 40 | *Incidence of hypotension: 40% vs 80% (p<0.05)  
* Ephedrine use: 10.6 mg ± 8.6 vs 35.3 mg ± 18.4 (p<0.05)  
* Nausea and vomiting: 20% vs 50% (p<0.05)  
* Neonatal outcomes were similar |
| (9) RCT, double blinded | RL 1L vs dextran 3% 1L | 2005 | 110 | *Incidence of hypotension: 85% vs 66% (p= 0.03)  
* Ephedrine use: 8.5-9.7 mg (SD) vs 15.0-11.9 mg (SD), (p<0.05)  
* Neonatal outcomes were similar |
| (10) RCT, Blinded | HES 6% 500 ml vs RL 20 ml/kg | 2007 | 200 | *Incidence of hypotension: when both under spinal: 44% vs 18% (p = 0.023), crystalloid under spinal vs colloid under CSE: 24% vs 18% (p = 0.047)  
* Ephedrine use: no statistical difference  
* Nausea: significant lower incidence in colloid preloading (p<0.05) |
| (11) RCT, double blinded | Hartmann 1.5 L vs HES 6% 0.5L vs HES 6% 1L | 2009 | 60 | *Incidence of hypotension: 70% vs 35% vs 65% P= 0.069  
* Ephedrine use: no significant difference  
* Nausea and vomiting: no significant difference  
* Neonatal outcomes were similar |
| (12) RCT | HES 130/0.45 500 ml vs NaCl 0.9% 1L | 2012 | 60 | *Incidence of hypotension: 40% vs 66% (P=0.03)  
* Ephedrine: 7.6 - 13 mg vs 16.4 - 15 mg (p<0.05)  
* Nausea: no significant difference  
* Neonatal outcomes were similar |
| (13) RCT, double blinded | HES 6% 7.5 ml/kg vs RL 1L vs NaCl 0.9% 1L | 2014 | 90 | *Incidence of hypotension: 13.3% vs. 46.6% vs 40% (p<0.05)  
* Ephedrine: 13.3% vs. 46.6% and 40%, (P<0.05)  
* Neonatal outcomes were similar |
| (14) RCT | HES 6% 500 ml vs NaCl 0.9% 1.5L | 2014 | 105 | *Incidence of hypotension: 69% vs 87 (p = 0.028)  
* No significant difference in ephedrine dose, incidence of nausea nor neonatal outcome |
| (15) RCT, double blinded, multi-centered | 500 ml of 6% HES + 500 ml of RL vs RL 1L | 2014 | 167 | *Incidence of hypotension: 36.6% vs 55.3% (P<0.025)  
* No significant difference between total phenylephrine use  
* Neonatal outcomes were similar |
| (16) RCT | RL 1L vs HES 6% 0.5L | 2015 | 32 | *Incidence of hypotension: 73.3 % vs 46.7 %, p= 0.26  
* A significant difference in usage of ephedrine and phenylephrine (p = 0.015 and p = 0.029, respectively)  
* Neonatal outcomes were similar |
blood pressure and less usage of vasopressors) compared to preloading with crystalloids, despite a nonsignificant reduction in hypotension.

In two studies20,27 no significant reduction in hypotension was seen when hetastarch 6% as preload was given. One study compared crystalloid and colloid preloading when giving a prophylactic phenylephrine infusion and concluded no significant difference in the incidence of hypotension, nevertheless a lower dose of the vasopressor was needed in the colloid group26. Ueyama et al15 compared two doses of HES 6% and discovered a dose-dependent evidence in the incidence of hypotension, in comparison with crystalloid preloading. The incidence of nausea and vomiting differed between studies with similar results between both groups in six studies12,20,21,23,26,28 and with a decrease in incidence in the crystalloid group in two studies17,19. Vasopressor use was overall higher in the crystalloid group compared to a colloid group13,16-18,21,22,23,26,28, although in some studies a statistical significance was not reached19,20,23,24,27. Neonatal outcome was consistently similar in all of the studies. One study29, as seen in table three, demonstrated that crystalloid co-loading is more efficient in the prevention of maternal hypotension then administering crystalloids before the spinal anesthesia. There also was a lower incidence of nausea and vomiting and of the administration of ephedrine in het co-load group. Neonatal outcome was similar.

### B. Colloid preload

Twenty-four studies were included looking at colloid preloading. A subcategorization was made comparing colloid preloading with a control group (two studies), with a crystalloid preload group (16 studies), with a colloid co-load group (five studies) and with a crystalloid co-load group (one study). Details can be found in Table II + IV to VI. The comparison between colloid preloading and crystalloid preloading has already been mentioned above. A significant difference in the incidence of hypotension was found when comparing a colloid preload (gelofusine 15 ml/kg) with giving no preload30. When comparing two doses of colloid preloading (pentastarch 10 ml/kg vs pentastarch 5 ml/kg), a dose-dependent significant reduction in hypotension was seen31. Nausea was less frequent in the colloid group15 and there was a reduction in vasopressor use. Neonatal outcome was similar in

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| (17)         | RCT26      | 2016 | 82                 | *Incidence of hypotension: 27%  
Vs 0.8% (P = 0.12)  
*No significant difference in the incidence of nausea nor neonatal outcomes.  
* Significantly less phenylephrine (1077.5 ± 514 mcg) was used in the colloid group than the crystalloid group (1477 ± 591 mcg, P = 0.003). |
| (18)         | RCT27      | 2017 | 120               | *Incidence of hypotension: 60% vs 65% (P > 0.05)  
* No significant difference in total ephedrine uses or neonatal outcomes |
| (19)         | RCT, double blinded28 | 2018 | 96                | *Decrease systolic BP: -4.501 ± 8.120 vs HES 6% 0.5l  
* Ephedrine: 8.979 +/- 6.045 mg vs 14.63 +/- 7.27 mg (p<0.05)  
* Nausea: no significant difference  
* Neonatal outcomes were similar |

### Table III. — Comparison of colloid preload with crystalloid preload 2/2.

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| (20)         | RCT29      | 2014 | 60                 | *Incidence of hypotension: 53% vs 83%, P = 0.026  
* Smaller dose of ephedrine in the co-load group compared to the preload group (7.5% vs 15%, P=0.015)  
* The incidence of nausea was lower in the co-load group (27% vs. 60%, P = 0.019).  
*Neonatal outcome measures were comparable between two groups. |
both groups. Colloid co-loading and preloading seem equally effective in preventing spinal induced hypotension, following five studies where HES 6% was used in different volumes as a colloid. One study showed a significant increase in cardiac output during the first five minutes after colloid preloading and not after colloid co-loading. Nausea and vomiting, the use of a vasopressor and neonatal outcome were similar in all groups. One study compared the use of colloid preloading with crystalloid co-loading, but showed no significant difference in the prevention of spinal hypotension, nor the vasopressor use, the incidence of nausea and vomiting or neonatal outcome.  

### 2. Co-load

The use of fluid co-loading in the prevention of spinal hypotension can be divided into two categories: co-loading with crystalloids or co-loading with colloids.  

#### A. Crystalloid co-load

The difference in hemodynamic profile between crystalloid co-loading and crystalloid or colloid preloading has already been discussed in the previous sections. Comparing crystalloid co-loading with a control group, showed a significant reduction in hypotension when using crystalloid co-loading in combination with a
B. Colloid co-load

A comparison of colloid co-loading with colloid and crystalloid co-loading and preloading has already been mentioned before.

Discussion

Different fluid regimens have been studied, fluid preloading and co-loading. Both fluid management strategies can occur with either a colloid solution or a crystalloid solution.

Crystalloid preloading showed to be ineffective in preventing hypotension despite high infusing volumes. Studies suggested the role of ANP release with its diuretic and vasodilating effects as a cause of its ineffectiveness, but also the fact that crystalloids immediately redistribute, with only 28% of the infused crystalloids remaining.
intravascular\textsuperscript{15}. The rapid administration of a crystalloid preload (10 min instead of 20 min) also failed to reduce the incidence of hypotension\textsuperscript{46}. Colloid preloading on the other hand, demonstrated to be an adequate prophylactic measure in the prevention of spinal hypotension. When comparing colloid preloading with a lower dose of the same colloid, the incidence of hypotension was reduced. This suggests a dose dependent effect and the importance that the volume of fluid must be large enough to result in a significant increase in cardiac output. A systematic review from 2002\textsuperscript{44} where the two types of preloading were investigated, supported the efficacy of colloid preloading in reducing spinal hypotension whereas crystalloid preloading seemed uniformly ineffective. Another systematic review and meta-analysis from 2015\textsuperscript{45}, including 990 patients,\textit{et al.} also noted the difference between crystalloids and colloids (where most of the included trials involved preloading) and showed that colloids reduced the incidence of hypotension more than crystalloids. The most recent systematic review and meta-analysis from 2021\textsuperscript{46}, which included 2566 patients, again confirmed the superiority of colloid preloading to crystalloid preloading in reduction of spinal hypotension and nausea and vomiting. HES 6\% in a dose of 7-10 ml/kg or 500 ml, was the fluid regimen of choice according to a subgroup analysis in this review.\textit{et al.} The fact that colloid preloading is more effective than crystalloid preloading probably is because colloids have a longer intravascular life than crystalloids. They consist of larger molecules that do not immediately redistribute through the interstitial space. Therefore, they do not decrease plasma colloid oncotic pressure so much and intravascular volume is better maintained\textsuperscript{15}, with less occurrence of tissue edema and electrolyte abnormalities\textsuperscript{43}. One study also found that the protective effect of the colloid solution was more pronounced for severe than for less severe hypotension\textsuperscript{18}.\textit{et al.} Hetastarch, pentastarch, dextran and albumin are all considered effective in the prevention of hypotension. Pentastarch may be slightly preferable because of its shorter plasma expansion effect (12h vs 36h)\textsuperscript{48}. Crystalloid and colloid co-loading both showed to be effective in the prevention of spinal hypotension. When both were compared with each other, no significant difference was seen. Unlike crystalloid preloading, crystalloid co-loading achieves its maximum effect during the time of spinal anesthesia, when the vasodilation\textit{et al.evolves}, plus it results in a rapid circulation of the vasopressor.

No fluid regimen alone has proven to be effective enough in eliminating spinal hypotension following neuraxial anesthesia for caesarean delivery. A combination of prophylactic measurements is therefore the golden standard\textsuperscript{47}. The simultaneous use of vasopressors, like the alfa-agonist phenylephrine which directly counteracts the decrease in arterial resistance, or noradrenaline have been proven to be effective\textsuperscript{16}. Left lateral tilt, low dose spinal anesthesia and the use of 5-HT\textsubscript{3} antagonists like ondansetron are other potential strategies to prevent hypotension\textsuperscript{17}. Ondansetron has shown to reduce spinal hypotension by blocking the Bezold-Jarisch reflex, induced by a reduced venous return\textsuperscript{16}.\textit{et al.} In this narrative review colloid preloading, co-loading and crystalloid co-loading showed to be effective as a part of the prophylactic management. In a meta-analysis from 2020\textsuperscript{48} where a forest plot was created, the effectiveness was showed in descending order, with colloid co-load more effective than colloid preload and crystalloid co-load more than crystalloid preload. A systematic review from 2020\textsuperscript{7} where 125 studies involving 9469 women were included, supported the use of crystalloids co-loading in higher volumes, as well as colloid pre- or co-loading. NICE guidelines on caesarean section from 2021\textsuperscript{19} recommend the use of crystalloid co-loading, in addition to the prophylactic use of vasopressors as the golden standard. Colloids were not supported because of cost and risk of side-effects such as anaphylaxis, hemostatic impairment and renal impairment. However, in none of the obstetric studies any serious side-effects were noted. The use of colloids therefore seems safe especially in this healthy pregnant population receiving low volumes of colloids (up to maximum 15 ml/kg or 1000 ml)\textsuperscript{49-52}.

An important note is that none of the included studies were able to demonstrate any adverse fetal outcome (based on Apgar scores and fetal pH), this is probably due to the rapid treatment of hypotension, with preservation of cardiac output and\textit{et al.uteroplacental perfusion}\textsuperscript{53}.

Limitations of the studies are the use of ephedrine as a vasopressor in the treatment of hypotension in most studies, which is no longer relevant to current recommended practice, with phenylephrine or noradrenaline now established as a first line vasopressor treatment. Also almost no study compared fluid regimen in women under prophylactic vasopressor administration, which is now recommended and as recent literature underscores: the most important fundament in the prevention. Following this limitation, other studies need to be set up to assess the impact of a fluid regimen as a adjuvants to a prophylactic vasopressor for the prevention of spinal induced hypotension.
Conclusion

No fluid regimen alone has proven to be effective enough in the elimination of spinal hypotension following neuraxial anesthesia for caesarean delivery. Crystalloid preloading is ineffective for prevention of hypotension despite high infusing volumes. Crystalloid co-loading, colloid co-loading and colloid preloading all have been shown to be effective looking at individual RCT’s, as well as systematic reviews and meta-analyses. NICE guidelines support the use of crystalloid co-loading because of the better safety profile, however no adverse effects were reported in previous studies regarding colloid administration et al.

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