Fluid Loading for Cesarean Delivery Under Spinal Anesthesia: Have We Studied All the Options?

Frédéric J. Mercier, MD, PhD

Single-shot spinal anesthesia has become the technique of choice for routine scheduled cesarean delivery. It is a simple, fast, reliable, and cost-effective technique.[1] However, a significant concern is maternal hypotension, which is associated with undesirable maternal and fetal/neonatal effects. Clinical studies confirm that the "spontaneous" incidence of hypotension is approximately 80%, despite left uterine displacement.[2]

Maternal morbidity from hypotension consists mainly of nausea and vomiting,[3] although severe hypotension may lead to altered consciousness, cardiovascular collapse, and/or other major complications. Additionally, maternal hypotension may cause a decrease in uteroplacental blood flow and potential deleterious consequences for the fetus. Although usually limited to transient neonatal acidosis in healthy term infants,[2,4] compromised and/or very premature fetuses may not tolerate the decrease in uteroplacental perfusion.[5] Thus, the aim of anesthesiologists should be to treat maternal hypotension quickly and efficaciously, or better yet, to actively prevent it.[6]

In current practice, vasopressor administration to sustain arteriolar tone has become the most important strategy to prevent spinal anesthesia–induced hypotension,[7] although strategies to increase venous return, such as prevention of aortocaval compression and fluid loading, are also routinely used (leg wrapping or thromboembolic stockings are also effective but are underutilized methods[6,8]). Combining the 2 approaches seems intuitively better than using either technique in isolation; of note, the use of fluid therapy has been shown to decrease the vasopressor dose needed to prevent hypotension.[6] This may be important because, although a high dose of phenylephrine does not induce neonatal acidemia in healthy low-risk parturients (in contrast to ephedrine), it has significant effects on maternal heart rate and cardiac output (up to a 20% reduction). Therefore, in compromised fetuses, the margin of safety for uteroplacental perfusion in the face of decreases in cardiac output might be reduced.[6,9,10] In addition, neonatal acidosis is merely a surrogate marker and little is known about the potential consequences of high doses of vasopressor on more relevant short- and long-term neonatal outcomes.

Conceptually, several variables can be manipulated with regard to fluid administration. In addition to volume and rate of administration, these include the type of fluid (crystalloid versus colloid) and the timing of administration (before the initiation of anesthesia—preload, or coincident with the initiation of anesthesia—coload). Schematically, combining these 2 variables, 4 different methods of intravascular fluid loading are possible: (1) *crystalloid pre*loading, (2) *colloid pre*loading, (3) *crystalloid co*loading, and (4) *colloid co*loading. Figure 1 depicts the 4 methods (in order of appearance in clinical practice) and possible comparisons among methods, labeled chronologically types I to IV, based approximately on the timing of their appearance in the literature. It is worth noting that the study by McDonald et al.[11] in the current issue of *Anesthesia & Analgesia* is the first study to address method 4 versus method 3, i.e., colloid coloading versus crystalloid coloading.

CRYSTALLOID PRELOAD (VERSUS CONTROL OF NO FLUID)

Crystalloid preloading (10–20 mL/kg Ringer lactate solution) has been widely used for decades for the prevention of hypotension. However, the 1993 landmark study by Rout et al.[12] demonstrated that the incidence of hypotension was only slightly reduced in the group receiving 20 mL/kg crystalloid preload compared with a control group without a preload (55% vs 71%, respectively), whereas the severity of hypotension was unchanged and the ephedrine requirements were not reduced. Jackson et al.[13] reached the same conclusion regarding crystalloid preloading inefficacy (1000 vs 200 mL), despite the concomitant use of prophylactic ephedrine infusion in both groups. Moreover, Park et al.[14] found no benefit of crystalloid preload even when increasing volumes from 10 up to 30 mL/kg. In addition, umbilical arterial pH was not improved. Thus, the minimal effectiveness, if any, of crystalloid preload was clearly confirmed during the 1990s, and this technique is no longer recommended.[6,8]

From the Département d'Anesthésie-Réanimation, APHP–Hôpital Antoine Béclère, and Université Paris-Sud, Clamart, France.

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Address correspondence to Frédéric J. Mercier, MD, PhD, Département d'anesthésie-Réanimation, Hopital A. Béclère, 157 rue de la Porte de Trivaux, 92141 Clamart Cedex BP405, France. Address e-mail to frederic.mercier@abc.aphp.fr.

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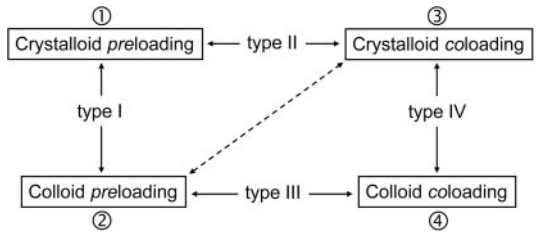

Figure 1. Diagram representing investigation of the 4 methods of intravascular fluid loading during cesarean delivery under single-shot spinal anesthesia. The arrows indicate the comparisons between methods, labeled chronologically types I to IV, based approximately on the timing of their appearance in the literature. The dashed arrow represents a further comparison that remains to be studied.

COLLOID PRELOAD VERSUS CRYSTALLOID PRELOAD

In contrast to crystalloids, colloid preloading consistently reduces the incidence and the severity of hypotension (Fig. 1; type I).[8,15] For example, Riley et al.[16] studied 40 parturients who were randomized to receive 500 mL of 6% hydroxyethylstarch (HES) combined with 1000 mL Ringer lactate solution or 2000 mL Ringer lactate solution without HES. They found a 45% incidence of hypotension in the colloid group versus 85% in the crystalloid group. In another study, increasing the colloid volume from 500 to 1000 mL further reduced the incidence of hypotension and improved maternal cardiac output, as compared with 1500 mL Ringer lactate.[17] The effect on cardiac output may be particularly beneficial, because umbilical arterial pH seems poorly correlated with maternal arterial blood pressure and better correlated with maternal cardiac output.[18] In most of these studies, ephedrine requirements were also markedly reduced with the use of colloid compared with crystalloid preload. A review of recent studies has confirmed that preloading with HES is clearly more effective for maintaining hemodynamic control than preloading with crystalloids.[6]

Currently, many experts and some national agencies discourage or ban the use of dextrans and gelatins primarily because of the risk of severe allergic risks. Although the allergic risk is much lower (both in incidence and severity) with HES, routine prophylactic use of colloids continues to be debated because of other potential disadvantages such as cost, pruritus, and mild coagulation defects associated with first-generation HES (average molecular weight, 670 kDa/molar substitution 0.75).[19] In addition, placental transfer and potential neonatal adverse effects of HES beyond the birth period are not documented in humans. Additional safety data with the latest-generation HES (130/0.4) are expected to clarify this aspect of the debate.

CRYSTALLOID COLOAD VERSUS CRYSTALLOID PRELOAD

Crystalloid administration seems to be more effective in preventing hypotension when the fluid is administered at a very rapid rate beginning at the time of the intrathecal injection; this crystalloid "*co*loading" technique was described in an elegant kinetic study by Ewaldsson and Hahn[20] in 2001 and seemed to dramatically improve mean arterial blood pressure after spinal anesthesia in 5 non-obstetric patients when compared with a conventional crystalloid preloading technique (Fig. 1; type II). A larger study in non-obstetric patients ($n = 46$) found significantly improved cardiac output in the coload group, but no difference in blood pressure.[21] At the same time, another study in women undergoing spinal anesthesia for cesarean delivery found no beneficial effect on blood pressure; however, the study was not powered for this specific outcome.[22] Crystalloid coloading for cesarean delivery was then studied in a landmark trial by Dyer et al.[23] Fifty parturients undergoing scheduled cesarean delivery were randomized to receive 20 mL/kg Ringer lactate solution IV either by rapid infusion (on average in 10 minutes) immediately after induction (coload) or for 20 minutes before induction of spinal anesthesia (preload). The incidence of hypotension (systolic blood pressure <80% of baseline) was significantly decreased in the coload versus preload group (36% vs 60%) and ephedrine requirements before delivery were also reduced (median: 0 vs 10 mg). This benefit in coloading was not observed by Cardoso et al.,[24] but these authors used half the volume (10 mL/kg Ringer lactate solution) of the Dyer et al. study. A slightly different design was used in the study by Ngan Kee et al.,[25] in which the authors compared no fluid with a coload technique with 2 L Ringer lactate solution and added a prophylactic phenylephrine infusion in both groups. The incidence of hypotension was dramatically reduced from 28% to 2% ($P < 0.001$) in the coload group. Phenylephrine requirements were also significantly reduced in the coload group, although the total dose was still impressively large (median: 1160 vs 1400 μg, $P = 0.008$). Because this study used no fluid rather than a crystalloid preload in the control group, it was not included in a meta-analysis that concluded there was no benefit in crystalloid coloading versus preloading.[26] Although this meta-analysis is a useful collection of studies on fluid loading techniques, I do not entirely share the conclusion of the authors. Rather, based on the 6 studies I detailed above, I conclude that crystalloid coloading is likely more effective than crystalloid preload or no fluid administration for preventing hypotension, provided that the amount/infusion rate of crystalloid coload infusion is high enough during the first 5 to 7 minutes after spinal anesthesia, the period during which sympathetic block is established.

COLLOID COLOAD VERSUS COLLOID PRELOAD

Rapid colloid coloading was initially compared with the same fluid (i.e., colloid) administered as preload (Fig. 1; type III). Four studies have been published from 2007 to 2009, all with HES as the colloid.[27–30] Each of these 4 studies showed no difference in incidence of hypotension between the 2 modalities of fluid loading. As pointed out by McDonald et al.,[11] this consistent result makes sense because colloid redistribution takes much longer than crystalloid redistribution. Thus, preloading with colloids is effective (in contrast to crystalloids) and there seems to be no additional benefit to delaying colloid administration until after the initiation of spinal anesthesia.

COLLOID COLOAD VERSUS CRYSTALLOID COLOAD

Until the study by McDonald et al.[11] in the current issue of *Anesthesia & Analgesia*, a direct comparison between crystalloids and colloids, both administered as a coload, had not been studied (Fig. 1; type IV). Thus, this new study adds useful information to our knowledge about fluid management during spinal anesthesia for cesarean delivery. The primary outcome of the study was maternal cardiac output assessed by Doppler measurements during the first 20 minutes after spinal anesthesia. This randomized, double-blind, controlled study was carefully designed and included a sample size calculation on this primary outcome. The authors concluded that there was no advantage in using colloid (HES) over crystalloid (Hartmann solution [HS]) as a coload when used in combination with a phenylephrine infusion. Nonetheless, when looking at some secondary outcomes (in Tables 2 and 3), there may be a trend toward better results in the HES coload group. For example: (a) the incidence of hypotension was 40% in the HES group versus 60% in the HS group ($P = 0.20$), (b) 4 times fewer patients experienced >1 episode of hypotension in the HES group versus HS group ($P = 0.08$), and (c) peak velocity increased significantly at 5, 10, and 15 minutes compared with baseline in the HES group but not in the HS group.

To summarize the results of the comparisons we have up to now, we know that:

- Crystalloid preload is ineffective or very poorly effective.
- Colloid (HES) preload is partly but consistently effective (comparison type I).
- Crystalloid coload seems to be partly effective, in contrast to crystalloid preload (comparison type II), but this benefit is inconsistent and may depend on the volume and rate of administration at the onset of sympathetic spinal block.
- Colloid (HES) coload is as effective as colloid (HES) preload (4 consistent studies, comparison type III).
- Colloid (HES) coload is as effective or more effective than crystalloid coload (comparison type IV = the new study by McDonald et al.[11]).

On the basis of this information, by "triangulation" among these comparisons, we might anticipate that colloid (HES) preload is more or as effective as crystalloid coloading. Personally, I suspect colloid (HES) preload will offer some advantages with regard to efficacy and reliability compared with crystalloid coload, but studies on this direct comparison (Fig. 1, dashed arrow) are needed to clarify the issue. In the meantime, I think we can provide the following recommendations:

1. It is useful to add a fluid loading technique to the vasopressor prophylaxis to prevent or mitigate hypotension in the setting of spinal anesthesia for cesarean delivery.
2. Crystalloid preloading is ineffective or poorly effective and should be replaced by 1 of the 3 other available fluid loading techniques (i.e., colloid [HES] preload or crystalloid coload or colloid [HES] coload).
3. In some specific maternal situations that may promote overload (some cardiovascular diseases, multiple pregnancies, severe preeclampsia), fluid loading is best avoided. In emergency cases in which hemodynamic instability is less frequent[6] and in which there may be little or no time for preloading fluid, coloading seems to be the preferable option.
4. Whichever the current fluid therapies chosen, none is completely effective and thus use of some sort of vasopressor regimen should always be considered.

Perhaps in the future, we will be better able to tailor our prophylaxis technique based on the anticipated risk of hypotension. Tools for this prediction already exist, but they are not very accurate,[31] not yet available for routine clinical practice,[32] too time-consuming for routine use,[33] or require spinal anesthesia to be performed in the lateral rather than sitting position.[34] Finally, when the risk of hypotension is thought to be high, or the consequences of hypotension might be dire, perhaps the combination of colloid (HES) preloading and crystalloid coloading will be the best option. This hypothesis will also need to be addressed by new studies. Other new worthwhile research could focus on optimal rate and volume of coloading and on safety (rather than solely on well-documented efficacy) of HES colloids.

In conclusion, we have improved our knowledge of fluid administration during cesarean delivery under spinal anesthesia and we are heading toward optimal management to prevent hypotension. However, additional studies are still needed before reaching the end of this track.

DISCLOSURES

Name: Frédéric J. Mercier, MD, PhD.
Contribution: This author wrote the entire manuscript.
Conflicts of Interest: Frédéric J. Mercier received honoraria from Kabi-Fresenius and received research funding from Kabi-Fresenius. I do not feel I have a conflict of interest with regard to the coloading study specifically addressed by my Editorial. I worked as a coordinating investigator in a preloading hydroxyethylstarch (HES) study in cesarean delivery under spinal anesthesia sponsored by Kabi-Fresenius and sometimes as a lecturer for Kabi-Fresenius. I support the use of HES in preloading technique (versus crystalloid preloading), which is in accordance with most of the studies published on this issue. However, I consider that coloading is a completely different issue, in which the benefit of HES versus crystalloids might not apply.
Attestation: Frédéric J. Mercier approved the final manuscript.

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