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# The Crystalloid Co-Load: Clinically as Effective as Colloid Preload for Preventing Hypotension from Spinal Anaesthesia for Caesarean Delivery

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## Abstract

**Objective:** Colloid preloading diminishes post-spinal hypotension. However, whether colloid preloading is superior to crystalloid co-loading is uncertain. In this retrospective study, we compared the effects of a colloid preload versus a crystalloid co-load on vasopressor requirements and maternal haemodynamics among women undergoing elective caesarean delivery (CD) with spinal anaesthesia.

**Methods:** We extracted data from the medical records of 160 healthy women who underwent elective CD with spinal anaesthesia at an academic obstetric centre before and after an institutional fluid-loading protocol change. Patients received a 500 mL 6% hydroxyethyl starch preload or a 1000 mL crystalloid co-load. The primary outcome was the total phenylephrine dose administered from spinal block placement to delivery.

**Results:** Our cohort comprised 79 women in the colloid group and 77 women in the crystalloid group. The mean phenylephrine use was significantly lower in the colloid group than in the crystalloid group (489±403 μg vs. 647±464 μg, respectively, p=0.02). The maximal drop in systolic blood pressure was greater in the colloid group than in the crystalloid group (36±20 mmHg vs. 29±16 mmHg, respectively, p=0.02). There were no clinically significant differences between the groups in heart rate, blood loss, temperature and Apgar scores.

**Conclusion:** Vasopressor use was lower in colloid preloading than in crystalloid co-loading. However, differences in all outcome measures were minimal and likely clinically insignificant, suggesting that both fluid-loading techniques are appropriate to use for the prevention of spinal hypotension in women undergoing CD.

**Keywords:** Co-load, crystalloid, hetastarch, phenylephrine, preload, spinal anaesthesia

## Introduction

Hypotension is a common side effect of spinal anaesthesia for caesarean delivery (CD). Spinal hypotension can result in perioperative morbidity, such as severe nausea and vomiting, foetal acidosis and cardiovascular instability (1). Different fluid-loading regimens have been studied for preventing spinal hypotension (2, 3). Compared with crystalloid preloading, colloid preloading is associated with less hypotension, nausea and vasopressor use after spinal placement (2, 3). This effect is explained by colloids having a longer intravascular half-life than crystalloids (4). In contrast, rapidly infusing crystalloid fluids after the induction of spinal anaesthesia (co-loading) may be more effective than preloading (5, 6). Given as a co-load, crystalloids fill the intravascular space as it expands secondary to the spinal anaesthesia-induced sympathectomy (7). Preloading and co-loading colloids are equally effective since colloids remain in the intravascular space long enough to be effective during the spinal-induced sympathectomy (5). Mercier predicted that crystalloid co-loading would not be as effective as colloid preloading; however, Tawfik et al.

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found that the two fluid-loading regimens are equivalent in preventing spinal hypotension (8, 9).

Preloading with hetastarch has been our standard regimen for elective CD for over two decades in our institution (10). Owing to an increased risk of mortality and morbidity in non-obstetric critically ill patients who received hetastarch, in 2013, the Food and Drug Administration issued a black box warning for hetastarch (11, 12). Therefore, in September 2013, we decided to modify our fluid-loading regimens from a preload of 500 mL hetastarch to a co-load of 1000 ml lactated Ringer's (LR) solution.

In this retrospective comparative effectiveness impact study, we compared vasopressor use and maternal haemodynamics among women undergoing elective CD under spinal anaesthesia who received a colloid preload versus a crystalloid co-load. We hypothesised that crystalloid co-loading is less effective than hetastarch preloading in preventing spinal hypotension.

## Methods

Approval was obtained from the Stanford University institutional review board for this quality assurance review and change of practice impact analysis. Informed consent was not necessary since data were collected retrospectively. The study location was the Lucile Packard Children's Hospital, a tertiary academic obstetric centre, in California, USA. We retrospectively collected data of patients who received colloid preloading between May 2013 and August 2013 and patients who received crystalloid co-loading between December 2013 and March 2014. We did not collect data between September 2013 and November 2013 to allow a period of familiarisation with the new protocol. We included the medical records of patients who underwent elective CD under spinal or combined spinal-epidural anaesthesia. Exclusion criteria were maternal age <18 years and >40 years, women who delivered at <37 weeks of gestation, multiple gestation, hypertensive disorders associated with pregnancy, diabetes, other significant medical or obstetric co-morbidities and failed spinal or combined spinal-epidural blocks requiring epidural supplementation.

In September 2013, the fluid-loading regimen for spinal anaesthesia for CD was changed from a colloid preload of 500 ml hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride; B. Braun, Bethlehem, PA, USA) to a crystalloid co-load of 1000 mL LR solution. Intravenous access consisted of an 18-gauge peripheral catheter. Colloid preloading was administered prior to spinal anaesthesia >15-30 min. Crystalloid co-loading was administered immediately after injection of spinal medication and as rapidly as possible using a pressurised inflatable bag inflated to an initial pressure of 300 mmHg. Spinal anaesthesia was performed in the sitting position and preferably inserted in the L3/4 interspace. It consisted of hyperbaric bupivacaine 12 mg, fentanyl 10 µg and preservative-free morphine 200 µg. Our standard clinical practice is for blood pressure (BP) to be measured non-invasively every minute after spinal anaesthesia until delivery. During the study period, our conventional practice was to treat post-spinal hypotension with phenylephrine boluses (50-200 µg). Our practice was to maintain the systolic BP (SBP) close to baseline and to administer phenylephrine if the SBP decreased by >10% of the baseline value. Prophylactic phenylephrine infusions were not used during the study period. Small doses of ephedrine (5-10 mg) were given in preference or in addition to phenylephrine to treat hypotension if bradycardia (defined as a heart rate <40 bpm) was present. Apart from the fluid-loading regimen, the anaesthetic protocol did not change over the two-study periods. After fluid loading, both regimens received crystalloid fluid infused without pressure at a rate determined by an anaesthesiologist as appropriate for the case. An anaesthesia resident or fellow supervised by an attending obstetric anaesthesiologist provided anaesthesia care for all women who underwent elective CD.

Our primary outcome was the total phenylephrine dose administered for the period between spinal block placement and delivery. We selected vasopressor as our primary outcome as our clinical practice goal is to maintain BP at baseline, so differences in phenylephrine doses rather than hypotension between the groups would be expected if this goal was obtained. Secondary outcomes included SBP and heart rate in the first 20 min after induction of spinal anaesthesia, quantified blood loss (QBL), Apgar scores, maternal temperature prior to surgery and on post-anaesthesia care unit admission and change in maternal haemoglobin level from prior to surgery to the first day after surgery. In our hospital, QBL is calculated by adding the volume of the post-delivery blood collected in the suction canisters and drapes to the blood absorbed in the swabs used during surgery. The weight of blood absorbed in the swabs is estimated by weighing the swabs after surgery and subtracting the weight of an equivalent number of dry swabs. One gram of weight change in the swabs is considered equivalent to 1 mL of blood.

### Statistical analyses

An a priori power analysis using data from a previous study (6) at our institution indicated that a minimum sample size of 57 patients per group would be required to show a 25% difference in phenylephrine requirements between the groups ($\alpha$=0.05 and $\beta$=0.80). Student's t-test, Mann-Whitney U test and Pearson's $\chi^2$ test were applied as appropriate for between-group comparisons. Repeated measures ANOVA was used to test for differences in SBP and heart rate between the groups over time. SBP was averaged >5 min epochs for the

repeated measures ANOVA to minimise the missing values. All statistical analyses were performed using the JMP™ Pro 10.0.2. A P value <0.05 was considered as significant. Data were presented as mean (±SD), median (interquartile range) and number (%).

## Results

We reviewed 160 (80 for colloid preloading and 80 for crystalloid co-loading) consecutive medical records in each study period cohort that met the inclusion criteria. After data collection, we excluded four patients; one woman was >40 years, one woman was <37 weeks of gestation at delivery, and two women underwent non-elective CD. Our final study cohort was composed of 79 women who received colloid preloading and 77 women who received crystalloid co-loading.

Maternal demographics and obstetric characteristics were similar between the study groups (Table 1). Successful spinal anaesthesia (defined as block height with pinprick to at least T4) was achieved in all patients. No epidural catheters in those receiving combined spinal-epidural anaesthesia were bolused during the time frame of the study (i.e. period between spinal block placement and delivery). The mean total dose of phenylephrine administered was significantly lower in the colloid group than in the crystalloid group (489±403 µg vs. 647±464 µg, respectively, p=0.02). The frequency of phenylephrine administration was similar in both groups (98% vs. 92% in the colloid versus crystalloid groups, p=0.14). Figure 1 shows the SBP and heart rate changes during the first 20 min after spinal injection. There was no difference in the mean SBP between the colloid group versus the crystalloid group. However, the maximal drop in SBP was greater in the colloid group than in the crystalloid group (36±20 vs. 29±16, respectively, p=0.02) (Table 2). Although the QBL values were not significantly different between the groups, there was a greater drop in haemoglobin concentration in the colloid group (Table 2). Every baby in both groups had 5-minute Apgar scores ≥7. The proportion of babies who had 1-minute Apgar scores

**Table 1. Demographic and obstetric data**

| | Colloid (n=79) | Crystalloid (n=77) |
|---|---|---|
| Age (years) | 33±5 | 33±6 |
| Weight (kg) | 79±14 | 77±14 |
| Height (cm) | 162±7 | 161±7 |
| Gravida | 3±5[A] | 3±7[A] |
| Primiparous (%) | 15.2% | 16.9% |
| Indication for caesarean (%) | | |
| Repeat | 77% | 77% |
| Breach | 10% | 16% |
| Other | 13% | 7% |

Data are presented as mean±SD or percentages. There were no significant differences between the groups. p<0.05 was considered as significant. [A]Data are presented as median±difference from max and min.

**Table 2. Haemodynamic and other outcome measures**

| | Colloid (n=79) | Crystalloid (n=77) | p |
|---|---|---|---|
| Phenylephrine use (spinal to delivery, µg) | 489±403 | 647±464 | 0.02 |
| Phenylephrine use (delivery until surgical end, µg) | 267±316 | 355±456 | 0.16 |
| Patients who required ephedrine (%) | 12.7% | 9.1% | 0.61 |
| Baseline heart rate (bpm) | 84±12 | 85±13 | 0.44 |
| Mean intraoperative heart rate (bpm) | 77±10 | 79±9 | 0.13 |
| Baseline SBP (mmHg) | 116±11 | 116±11 | 0.92 |
| Mean intraoperative SBP (mmHg) | 111±9 | 114±10 | 0.10 |
| Maximum drop in SBP (mmHg) | 36±20 | 29±16 | 0.02 |
| Quantified blood loss (mL) | 657±326 | 688±238 | 0.51 |
| Volume of crystalloid (mL) | 1548±810 | 2372±983 | <0.0001 |
| Baseline haemoglobin (g $dL^{-1}$) | 12.2±1.1 | 12.2±1.1 | 0.98 |
| Delta haemoglobin (g $dL^{-1}$) | 1.9±1.1 | 1.5±0.8 | 0.02 |
| Preoperative temperature prior to spinal anaesthesia (°C) | 36.6±0.2 | 36.6±0.2 | 0.49 |
| PACU admission temperature (°C) | 36.5±0.2 | 36.4±0.3 | 0.06 |

Data are presented as mean±SD or percentages. SBP: systolic blood pressure; PACU: post-anaesthesia care unit. Delta haemoglobin is haemoglobin change from preoperative to postoperative.

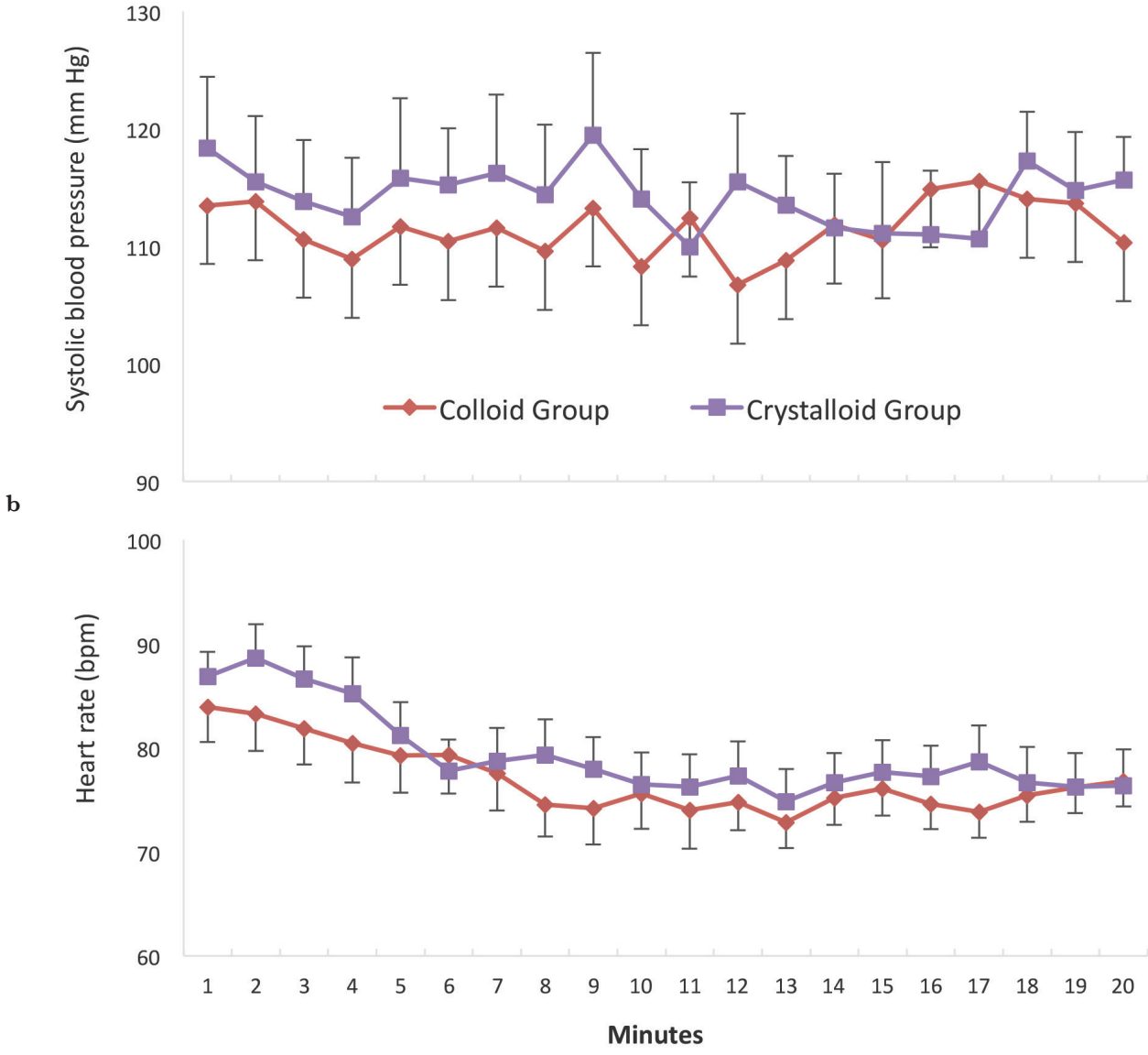


**Figure 1. a, b. Systolic blood pressure (a) and heart rate (b) for the first 20 min after spinal anaesthesia induction in patients who received either a preload of 500 ml of hetastarch (colloid group) or a co-load of 1000 mL of lactated Ringer's (crystalloid group). Data are presented as mean±SD. Systolic blood pressure and heart rate were not different between the groups (p=0.47 and p=0.11, respectively; repeated measures ANOVA). BL: baseline.**

≥7 were 95% and 93% in the colloid and crystalloid groups, respectively (p=0.45).

## Discussion

In this retrospective impact study, we observed that women who received colloid preloading required less vasopressor post-spinal anaesthesia than those who received crystalloid co-loading. Owing to longer intravascular half-life, colloid should expand the intravascular space for longer than crystalloid, and the colloid preload is expected to be present within the intravascular space at the time of spinal anaesthesia. For co-loading with crystalloids to be effective, the fluid needs to expand the intravascular space created by spinal anaesthesia-induced sympathectomy. Although the crystalloid solution was delivered rapidly, the rate of fluid expansion of the intravascular space with crystalloid may have been less than that of arterio- and veno-dilation induced by the spinal block (8). This may explain why, within the early period after spinal blockade, the vasopressor requirement was greater in the crystalloid co-loading group than in the colloid preload group.

Although we found a statistically significant reduction in total vasopressor use in the colloid preloading group, we believe

that the difference (approximately 150 µg phenylephrine) is not significant from a clinical perspective. However, by rapidly infusing crystalloid as a co-load, phenylephrine boluses can be administered quickly to correct systolic hypotension. This may explain why the maximal drop in SBP was less among women in the crystalloid group than those in the colloid group. Rapid delivery of vasopressor likely explains why co-loading crystalloids have been found to be especially effective when combined with vasopressor infusions (13).

We found no between-group difference in the incidence of spinal hypotension. In addition, maternal SBP during the first 20 min post-spinal anaesthesia was similar in both groups. Similar observations were reported by Tawfik et al. who observed that hypotension occurs in 42% and 52% of women who received crystalloid co-loading compared with colloid preloading, respectively (p=0.18) (9). However, in the present study, vasopressor was administered once the SBP decreased at least 20% from baseline. In addition, ephedrine was the primary vasopressor in their study.

The use of phenylephrine with crystalloid co-loading or colloid preloading has not been associated with neonatal acidosis or differences in Apgar scores (14). Although we did not measure umbilical cord gases, previous authors have demonstrated that neonatal acid/base status is not influenced by maternal exposure to phenylephrine, even with total doses two times greater than the mean total dose given to the crystalloid patients in our study (14). We are unable to find any evidence in the medical literature that fluid-loading regimens have any significant effect on neonatal or maternal outcomes when hypotension is corrected by the appropriate use of phenylephrine. Our findings substantiate those from other studies, indicating that maternal and neonatal outcomes can be optimised using phenylephrine to maintain baseline BP and treat spinal hypotension (15).

There was a slightly greater drop in haemoglobin concentration in the colloid group, but we did not observe a significant between-group difference in intraoperative blood loss. A likely explanation is the greater dilutional effect from the long-lasting volume expansion induced by colloid preloading compared with crystalloid co-loading. A 500 mL hydroxyethyl starch would be equivalent to 1500 mL crystalloid for equivalent volume expansion (4). It is unlikely that the change in haemoglobin was due to any kind of coagulopathy associated with hydroxyethyl starch. Previous authors did not find significant changes in the maternal coagulation profiles among women who received hydroxyethyl starch compared with crystalloid preloading during CD (16).

Our study has several potential limitations. Outcomes in retrospective design may be influenced by confounders. However, our study design allowed us to assess maternal outcomes within a typical clinical practice and to determine the impact of a clinical practice change on a cohort of women who undergo elective CD. There were no other personnel or practice changes over the study period, making our results unlikely to be affected by factors other than changes in fluid-loading techniques. However, we acknowledge that measured and unmeasured confounders may potentially have influenced some outcome measures. The goal of the present study was to assess whether vasopressor use, as a surrogate indicator of hypotension and haemodynamic stability, was different between those receiving colloid preloading compared with crystalloid co-loading. We believe that impact studies are an effective way to make this assessment because these provide a true reflection of clinical practice and are not limited by artificial protocols and limitations inherent in randomised controlled trials. We utilised intermittent phenylephrine boluses to treat maternal hypotension; therefore, it is uncertain whether our findings are applicable to women who receive prophylactic phenylephrine infusions. Previous studies of women having CD have found that a phenylephrine infusion is the most effective method for preventing spinal hypotension and may be preferable to using intermittent boluses for treating hypotension (17). Additionally, although we found that the fluid-loading technique utilised did not impact blood loss, we acknowledge that our study was not powered to assess these secondary outcomes.

## Conclusion

In this retrospective observational study, women who received colloid preloading required a lower total dose of phenylephrine than those who received crystalloid co-loading. However, the between-group difference in vasopressor dose was modest, and both fluid-loading regimens had similar efficacy in preventing hypotension and maintaining haemodynamic stability. In light of these findings and the black box warning for hydroxyethyl starch, crystalloid co-loading may be preferable to colloid preloading for the prevention of post-spinal hypotension during elective CD. Despite the ongoing institutional availability of hydroxyethyl starch, based on our study results, we now routinely administer crystalloid co-load in preference to preloading to all our patients undergoing elective CD with spinal anaesthesia.

**Informed Consent:** Due to the retrospective design of the study, informed consent was not taken.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - K.M., A.J.B., B.C., E.T.R.; Design - K.M., A.J.B., B.C., E.T.R.; Supervision - K.M., A.J.B., B.C., E.T.R.; Resources - K.M., A.J.B., B.C., E.T.R.; Materials - K.M., A.J.B., B.C., E.T.R.; Data Collection and/or Processing - K.M.,

A.J.B., B.C., E.T.R.; Analysis and/or Interpretation - K.M., A.J.B., B.C., E.T.R.; Literature Search - K.M., A.J.B., B.C., E.T.R.; Writing Manuscript - K.M., A.J.B., B.C., E.T.R.; Critical Review - K.M., A.J.B., B.C., E.T.R.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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