Original Investigation

Crystalloid versus Colloid in Stabilizing Hemodynamic of Patients Undergoing Cesarean Section with Neuraxial Anesthesia

A Randomized Controlled Trial

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SUMMARY

Background: Neuraxial anesthesia-associated maternal hypotension in cesarean delivery is the most frequent and troublesome complication poses serious risks to mother and compromises neonatal well-being. The use of intravenous fluid loading as the preventive strategy in this context has been challenged because inconsistent results cause doubt on its real efficacy. We compared hypotension-preventing effect of crystalloid and colloid with different loading regimens given in a volume-escalation manner in neuraxial anesthetized cesarean parturients.
Methods: One thousand parturients with American Society of Anesthesiologists (ASA) physical status I/II undergoing selective cesarean delivery were screened and 939 were assigned into different fluid loading regimens with a multi-stage randomization. The volume of crystalloid or colloid in each loading regimen was determined by an up-and-down sequential method. Rate of hypotension was recorded as the primary outcome, and the median (EV50) and 90% effective volumes (EV90) of fluids were calculated in epidural and spinal blockades.
Results: A total of 469 subjects were analyzed in the crystalloid group and 470 in the colloid group. The numbers of patients developed clinically significant and severe hypotension are significantly decreased, and the effective volume of colloid required in preventing hypotension in both anesthetized populations is relatively lower than that of crystalloid on the intention-to-treat analyses. There is still an occurrence of hypotension at a rate of about 10%-20% even when the EV90 was reached.
Conclusions: Fluid loading is an effective maneuver in balancing maternal circulation when reaching the effective volume of different neuraxial anesthesia, but prophylactic or therapeutic vasoconstrictors should also be prepared and be given at an appropriate time because a significant proportion of women can still develop hypotension.■

KEYWORDS C-Section; Fluid; Neuraxial Anesthesia; Hemodynamic; Outcomes

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THE rate of Cesarean delivery remains an upward trend worldwide, especially among women in low-resource countries. Approximately one third labor deliveries are performed by using cesarean section every year, of which takes over 80% of all the cases that are done under the neuraxial anesthesia (1, 2). Neuraxial anesthesia-associated maternal hypotension is the major circulation-unbalancing factor, and also the most frequent and troublesome complication resulted from sympathetic blockade, of which poses serious risks to mother, such as unconsciousness, pulmonary aspiration, hepatic dysfunction, apnea or even cardiac arrest, and compromises neonatal well-being, such as impaired uteroplacental blood perfusion leading to hypoxia, significant fetal acidosis and neurological injury (3-6). Prophylaxis, thereby, has been being a decades-long issue debated, but the optimal maneuver for preventing such an incidence is still not acquired.

Multiple strategies are currently used to guard against the occurrence of hypotension during regional anesthesia for elective or emergency cesarean delivery, but no definitive consensus has been reached on the best treatment strategy. Physical interventions, for instance, a left-lateral tilt position proceeded to increase the venous return blood volume through displacing gravid uterus off the inferior vena cava (7) and lower limb compression carried out by wrapping legs to minimize venous pooling blood (8), can produce unintentional effects on mothers such as unacceptable discomfort, localized ischemia or nerve injury. Pharmaceutical therapies including ephedrine, phenylephrine, metaraminol and mephentermine are prescribed to constrict the peripheral circulation and increase cardiac output (9, 10), however, they have potential dangers to evoke maternal supraventricular dysrhythmia, tachyphylaxis, anaphylaxis and hypertension, and also increase the risk of fetal acidosis for impaired uteroplacental flow secondary to vasoconstriction. Intravenous fluid management is now accepted as a standard means in preventing neuraxial block-induced hypotension, though, the choice of fluid type (crystalloid or colloid) (11-15), intervention timing (pre-, co- or post-anesthesia loading) (16-19), titrating speed (pressured-fast, fast or slow) (20, 21) and volumes given (high or low) (22, 23) are still the debated topics and different choices have yielded different results.

Clinical guidelines recommend that intravenous fluid preloading should be used to reduce the risk of maternal hypotension after neuraxial anesthesia for cesarean delivery, but no detailed strategies were given concerning how to realize this purpose (24, 25). A recent Cochrane systematic review showed an effectiveness sequence of fluids in reducing the frequency of hypotension underwent spinal anesthesia: colloids > crystalloids > no fluids, but no differences were found for different doses, rates or methods of administering colloids or crystalloids (26), in which the included studies did not do any calculating investigation on the minimal effective volume of fluids under spinal block. Pre-loading the circulation is aimed at the volume expansion that alleviates the vasodilation induced by regional anesthesia, nonetheless, co-loading or post-loading regimen has been proposed due to a much more effective role in decreasing the rate of hypotension (16-19). In addition, given the fact of a significantly increased blood volume in parturients plus a relatively reduced effective circulation volume after neuraxial anesthesia, conventional methods of fluid management, either 'liberal' (2,000 ml/person) or 'restricted' (500 ml/person), all did not produce ideal effects on preventing hypotension and ameliorating circulation balance.

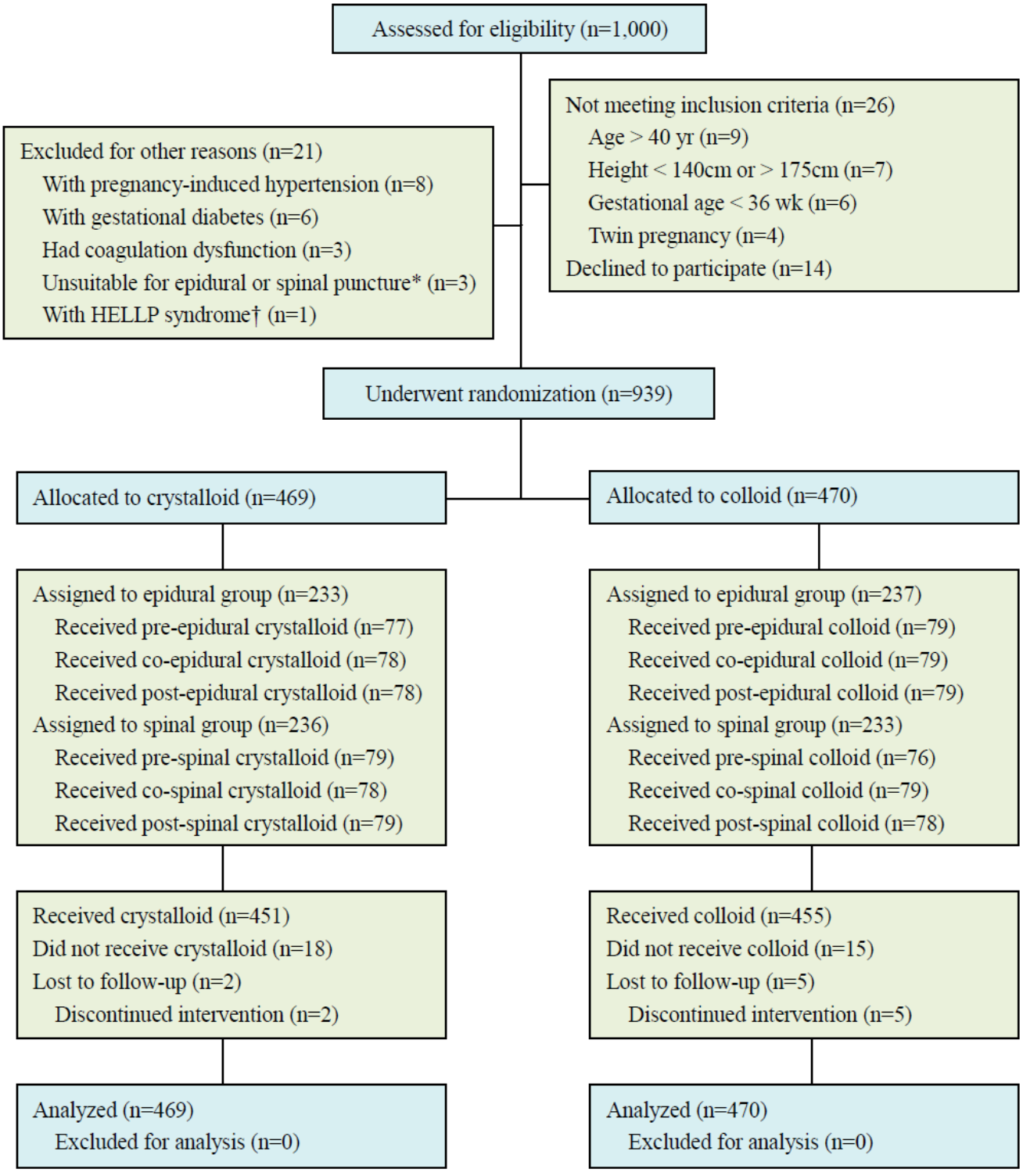
In January 2009, we initiated a randomized controlled trial to assess the effectiveness of crystalloid and colloid in balancing circulation by preventing hypotension in cesarean parturients at different fluid loading regimens under epidural or spinal anesthesia and calculate the effective volumes of fluids through an up-down volume-escalation method.

METHODS

Participants and Ethics

Ethical approval obtained from the Institutional Ethics Examining Committee of Human Research before recruiting patients. All participants signed an informed consent and a full explanation was given to those willing to accept neuraxial anesthesia (epidural or spinal block) with respect to epidural puncture and catheterization, lumbar spinal puncture, the opioid and local anesthetics used in this study, and possible risks and complications might appear during study. Recruitment for the trial took place between January 2009 and March 2011. Screened-for-participating parturients were eligible if they were undergoing elective cesarean delivery, were ages between 19 and 40 yr, and fulfilled the following criteria: gestational age >= 36 wk, American So-

Figure 1. Trial Profiles of Enrollment, Screening, and Randomization.



* Detailed reasons for those unsuitable for performing epidural or spinal puncture were displayed in the text

† HELLP syndrome refers to hemolysis, elevated liver enzyme and low platelets syndrome

ciety of Anesthesiologists (ASA) physical status I to II, uncomplicated singleton pregnancy.

Randomization

When patients entered operating room, a further assessment based on the overall previously-initiated evaluation was done. After confirmation of the signed anesthetic information, a multi-stage randomization was carried out (flow of the patient allocation see Supplementary Materials **Figure S-1**). First of all, the patients were randomized into either crystalloid or colloid intervention, of which followed by a second-stage random allocation into epidural or spinal anesthesia, respectively. Subsequently, the third-stage randomization was performed to assign subjects to pre- (20 min prior to anesthesia induction), co- (simultaneous administration with anesthesia performance) or post-anesthesia (immediately given after completion of anesthetic injection) fluid loading subgroup. The random number lists of the three stages were generated by means of the QuickCalcs (Online Calculators for Scientists, available at http://www.graphpad.com/quickcalcs/RandMenu.cfm; last accessed March 29, 2016. GraphPad Software Inc., La Jolla, San Diego, CA). Finally, the last-stage randomized patient received crystalloid or colloid with different doses determined by following an up-and-down sequential method (number of patients assigned to each subgroup is listed in Supplementary Materials **Table S-1**) (27). The healthcare providers, data-collecting members, and parturients were not masked to the group allocation except for data-analyzing members and outcome adjudicators.

Demographic Characteristics

The following data were collected as demographic characteristics of the subjects: age at delivery, weight, height, gestational age of fetus, current status of smoking, nulliparous or multiparous status and maternal vital signs (blood pressure, heart rate, respiratory rate and oral temperature).

Exclusion Criteria

Parturients were excluded from the study if one or more of the following criteria were met: (i) allergy to local anesthetics or opioids; (ii) a history of psychiatric diseases records; (iii) participants younger than 18 yr or older than 40 yr; (iv) those who were not willing to or could not finish the whole study; (v) primary hypertension, gestation-induced hypertension or preeclampsia; (vi) diagnosed diabetes mellitus or gestation-associated diabetes mellitus; (vii) subjects with a nonvertex presentation or scheduled induction of labor; (viii) emergency cesarean section or parturients failed vaginal delivery with neuraxial analgesia; (ix) twin gestation and breech presentation; (x) contraindications for performing neuraxial anesthesia (detailed list of the contents see Supplementary Materials **Table S-2**).

Study Procedures

After completion of the randomization, patients were given the initial volume of fluids: crystalloid (5 ml/kg of Lactated Ringer's solution) and colloid (4 ml/kg of hydroxyethyl (HES) 130/0.4 (Voluven® 6%, Fresenius Kabi, Bad Homburg, Germany). These volumes were chosen based on our clinical experience and statistical simulation at various doses from previous observation (Data are not shown). Each subsequent volume was relying on the response of the preceding subject via following Dixon's biased-coin design up-and-down sequential method (27). The changing volumes of both fluids were in an increment of 1ml/kg. The anesthesia provider was blinded to the volume of the given fluids, as was the parturient. If a given volume, in our study, encountered a failure in preventing hypotension, the following subject would be given the same volume of the fluids again, and the volume would not be stepped up in the next subject until the third patient still failed to response to the same volume. All response-failed women were prescribed a repeatable ephedrine 6-10 mg intravenously. If a successful prevention was observed, the next parturient was randomly assigned to the next lower volume with a probability of 0.1 and to the same volume with a probability of 0.9 as described elsewhere (28). The infusion of all fluids must be completed within 15 min whenever pre-, co- or post-anesthesia. Ringer's lactate solution at a titrating rate of 10 ml/min was followed after completion of all interventional fluid regimens and the total volume was calculated at the end of the study.

In the epidural anesthesia section, all parturients received extradural puncture and catheterization between L2 and L3 in the left-lateral position. The test dose of 3.0 ml of lidocaine 1.5% (45 mg) plus 5 μg/ml epinephrine was given. After delivering a test dose, all

Table 1. Baseline Characteristics of Subjects.*

Characteristic	Crystalloid		Colloid	
	Epidural (n=233)	Spinal (n=236)	Epidural (n=237)	Spinal (n=236)
Age at delivery, yr	26 ± 8	27 ± 7	28 ± 9	25 ± 6
Weight, kg	60 ± 11	58 ± 12	59 ± 13	61 ± 14
Height, cm	161 ± 12	158 ± 7	159 ± 10	162 ± 11
Nullipara/Multipara, n	223/10	224/12	220/17	227/9
Gestational age, wk	38 (37 – 40)	39 (37 – 40)	37 (36 – 40)	39 (37 – 40)
Current smoker	12 (5.2)	9 (3.8)	10 (4.2)	14 (5.9)
Blood pressure, mmHg				
Systolic pressure	117 ± 15	108 ± 11	121 ± 19	119 ± 16
Diastolic pressure	70 ± 8	68 ± 6	65 ± 6	67 ± 8
Heart rate, bpm	77 ± 12	73 ± 10	75 ± 11	78 ± 12
Respiratory rate, bpm	17 ± 3	19 ± 4	19 ± 3	19 ± 4
Oral temperature, ºC	37.1 ± 0.3	36.9 ± 0.4	37.0 ± 0.3	36.8 ± 0.5

* Data are presented as the means ± standard deviation (SD), media (interquartile range) or number (%), unless otherwise indicated.
bmp = beats per minutes of heart rate and breaths per minutes of respiratory rate.

participants received a 12-15 ml epidural analgesic mixture in a single bolus of 0.75% (7.5 mg/ml) ropivacaine with 10 μg/ml preservative-free morphine. In the spinal anesthesia section, all women received spinal anesthetic administered between L3 and L4 in the left-lateral position using hyperbaric 0.5% bupivacaine 2 ml (10 mg) plus morphine 50 μg. After completion of the anesthetic procedures, patients were immediately repositioned supine with a 15° left lateral tilt. The highest sensory block was checked and confirmed at the level of T6-T7 determined with loss-to-pinprick method bilaterally. Motor block was measured with modified Bromage scale (0, no block; 1, inability to raise extended leg; 2, inability to flex knee; 3, inability to flex ankle and foot).

After the anesthetic procedures were completed, arterial blood pressure was measured every minute for 10 min and then every 3 min for the duration of the study. In our study, hypotension was defined as systolic blood pressure (SBP) < 20% of baseline or SBP < 90 mmHg. Baseline arterial blood pressure was determined by measuring three time of the patient every 2 min at supine position with left uterine displacement.

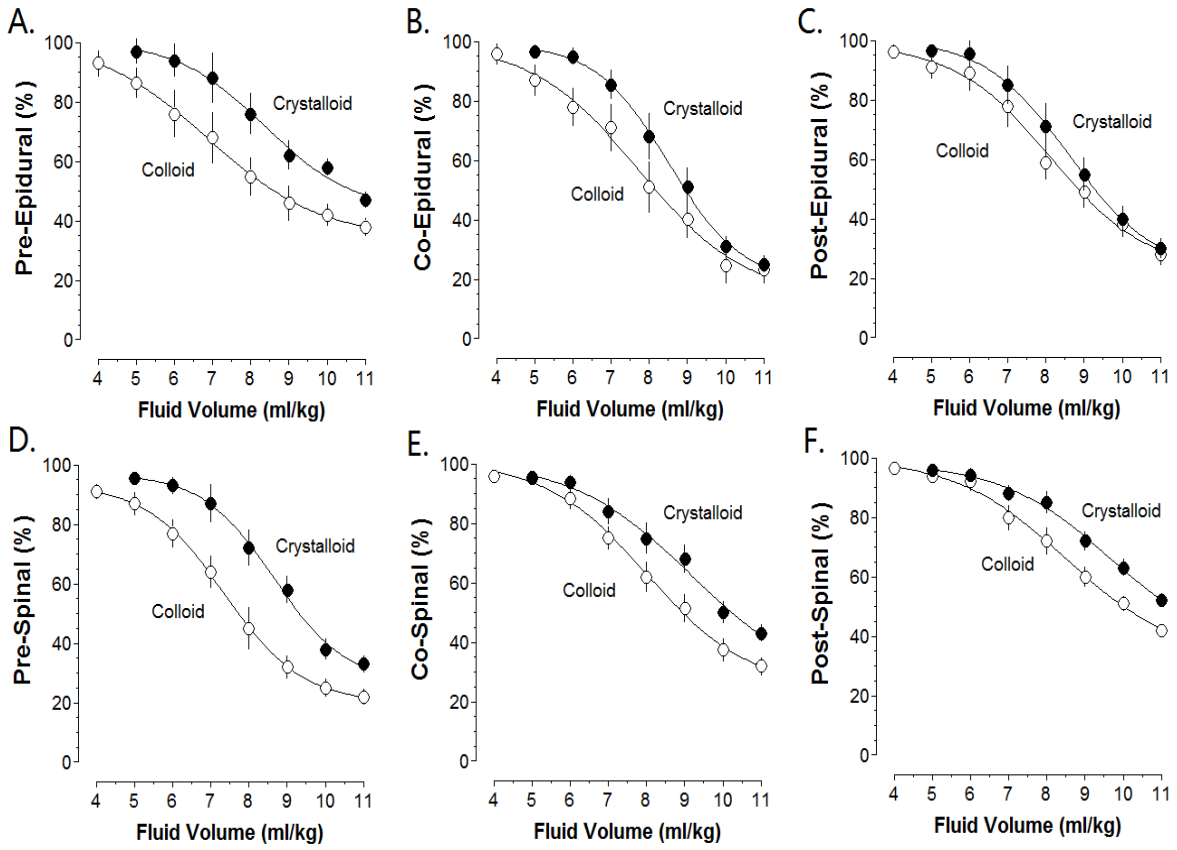
Peripartum Management and Monitoring

A catheter was inserted in a right or left antecubital vein for fluid and drug administration. The maternal parameters monitored during the whole study included the heart rate by three-lead electrocardiograph, respiratory rate, noninvasive systolic and diastolic blood pressure, mean arterial pressure, oral temperature and fingertip pulse oximetry. The incidence of the maternal adverse events, such as nausea, vomiting, pruritus, shivering, fatigue, hemorrhage, headache, somnolence, hallucination, sweating, hypothermia, and pulmonary edema throughout the study were recorded. Metoclopramide 10 mg can be administered intravenously if nausea or vomiting was unrelated to hypotension.

The following time intervals were recorded: titrating time of fluids (overall time of target fluids infused), induction of neuraxial anesthesia (from puncture positioning to successful injection of testing dose in epidural or anesthetic mixture in spinal), anesthetic induction to skin incision (from completion of anesthetic mixture injection to beginning of skin incision), uterine incision to delivery (from the start of uterine incision to umbilical-cord broken after baby delivered), duration of anesthesia (from completion of anesthetic mixture injection to sensory block disappeared) and surgery (from skin incision to the last skin suture). After delivery of the baby, 20 IU of oxytocin was titrated following Ringer's lactate solution.

Fetal and Neonatal Management

Figure 2. Volume-Effect Relationship.



Probabilities of hypotension response to fluid volumes, crystalloid 5-11 ml/kg and colloid 4-11 ml/kg, analyzed using logistic regression and maximum likelihood estimation of raw data after fitted to a sigmoidal maximum efficacy model. EV50 and EV90 of each curve are calculated and presented in Table 3. Panel A to F display an estimated proportion of the hypotension developed even if a large amount of fluid (11 ml/kg) was given.

Apgar scores at 1 and 5 min and neurobehavioral assessment scale (NBAS; detailed criteria were listed in Supplementary Materials **Table S-3**) were rated by the pediatric personnel according to the standard assessment. Umbilical-cord blood gas analysis was performed by the investigators.

Trial Outcomes

The rate of hypotension with different severity including overall hypotension, clinically significant hypotension (hypotension associated with maternal discomfort defined as nausea, retching/vomiting, dizziness or chest symptoms) and severe hypotension (SBP less than 80 mmHg) was selected as the primary outcome of the different fluid intervention procedures in CHOPIN trial. Secondary outcomes include recurrence of hypotension after ephedrine correction, obstetric and anesthetic variables described above as time intervals, total volume of intraoperative fluids with the exception of interventional target fluids, and the incidence of side effects from epidural or spinal puncture and drug delivery. Infant outcomes include the body weight, Apgar scorings, umbilical-cord blood gas measurement and NBAS scales.

Outcome Adjudication

A committee of physicians who are blinded to the group allocation adjudicated the aforementioned outcomes. We used the decisions from the Adjudication Committee for all statistical analyses involving these outcomes.

Sample Size

Table 2. Primary Maternal Outcomes.

Outcome	Crystalloid (n=469)	Colloid (n=470)	p Value
Overall hypotension, n (%)			
Epidural			
Pre-loading	52 (11.0)	45 (9.6)	0.45
Co-loading	47 (10.0)	42 (8.9)	0.57
Post-loading	49 (10.4)	47 (10.0)	0.82
Spinal			
Pre-loading	50 (10.7)	34 (7.2)	0.066
Co-loading	54 (11.5)	46 (9.8)	0.39
Post-loading	60 (12.8)	53 (11.3)	0.47
Clinically significant hypotension, n (%) *			
Epidural			
Pre-loading	8 (15.3)	6 (13.3)	0.77
Co-loading	11 (23.4)	7 (16.7)	0.43
Post-loading	9 (18.4)	9 (19.1)	0.92
Spinal			
Pre-loading	10 (20.0)	8 (23.5)	0.69
Co-loading	12 (22.2)	11 (23.9)	0.84
Post-loading	14 (23.3)	12 (22.6)	0.93
Severe hypotension, n (%) †			
Epidural			
Pre-loading	4 (7.7)	3 (6.7)	0.85
Co-loading	5 (10.6)	4 (9.5)	0.86
Post-loading	6 (12.2)	7 (14.9)	0.70
Spinal			
Pre-loading	5 (10.0)	4 (11.8)	0.80
Co-loading	7 (12.9)	6 (13.0)	0.99
Post-loading	8 (13.3)	6 (11.3)	0.75
Recurrence of hypotension after ephedrine, n (%) ‡			
Epidural			
Pre-loading	7 (13.4)	5 (11.1)	0.73
Co-loading	6 (12.8)	6 (14.3)	0.83
Post-loading	8 (16.3)	5 (10.6)	0.42
Spinal			
Pre-loading	8 (16.0)	5 (14.7)	0.87
Co-loading	9 (16.7)	8 (17.4)	0.94
Post-loading	9 (15.0)	7 (13.2)	0.79

* Clinically significant hypotension means the hypotension is associated with maternal discomfort such as nausea, retching/vomiting, dizziness or chest symptoms, and calculated from the overall incidence of hypotension.

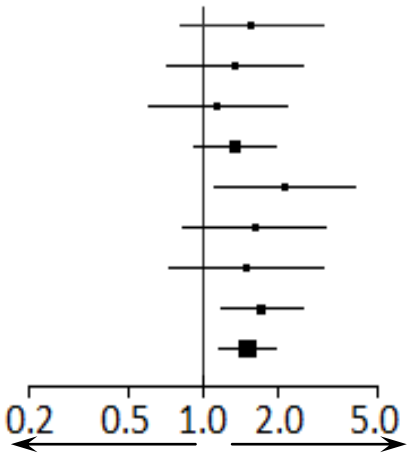
† Severe hypotension refers to the systolic blood pressure (SBP) less than 80 mmHg. The percentage of severe hypotension was calculated from the overall incidence of hypotension.

‡ Denotes the percentage was calculated from the overall occurrence of hypotension.

According to previously reported studies on the reduction in the cumulative rate of hypotension from regional anesthesia (29, 30) and the institutional early database, the mean difference in hypotension decrease was 2.5 per cent, i.e., 17.5 % in the crystalloid group and 20 % in the colloid group under neuraxial anesthesia; we set the two-sided $\alpha = 0.05$, one-sided $\beta = 0.10$, and the power of test = 0.90. Therefore, a minimal sample size of 65 subjects per group was needed to detect the difference. We increased the sample size to 75 in each group to account for potential missing data and dropout during the study course. The 15%increase in sample size was mainly on the basis of the institutional database that round 11% [median; interquartile range (IQR), 9-15%] patients dropped out or their data were lost during studying period. Therefore, we increased the sample size to 75 per group following the upper limit 15%.

Figure 3. Odds Ratios for Hypotension.

	Events of Hypotension/Total Number of Subjects		Odds Ratio (95% CI)
	Crystalloid	Colloid	
Pre-Epidural	52/77	45/79	1.57 (0.82-3.02)
Co-Epidural	47/78	42/79	1.34 (0.71-2.52)
Post-Epidural	49/78	47/79	1.15 (0.61-2.19)
Subtotal	148/233	134/237	1.34 (0.92-1.94)
Pre-Spinal	50/79	34/76	2.13 (1.12-4.05)
Co-Spinal	54/78	46/79	1.61 (0.84-3.11)
Post-Spinal	60/79	53/78	1.49 (0.74-3.00)
Subtotal	164/236	133/233	1.71 (1.17-2.50)
Overall	312/469	267/470	1.51 (1.16-1.97)



In overall, colloid is better in preventing hypotension than crystalloid with an OR of 1.51, 95% CI 1.16-1.97.

Statistical Analyses

Analyses were done using GraphPad Prism version 5.0 (GraphPad Software, Inc., San Diego, CA) or SPSS version 13.0 (SPSS Inc., Chicago, IL). Values are expressed as the mean, SD, IQR, or numbers. All our data assessment primarily was based on an intention-to-treat (ITT) analysis. Meanwhile, a per protocol (PP) analysis was done, in which the subjects excluded, withdrawn, and lost follow-up were precluded. All statistical tests were two-sided and the statistical significance was accepted at the level of $p < 0.05$.

All categorical data were analyzed with a chi-square test or Fisher's exact test (as appropriate) to indicate the trend. The difference in parametric data ere compared with Student t test. The one-way analysis of variance (ANOVA) was used to examine the multi-group differences in the demographic data. The ANOVA tests were always followed by the Bonferroni post hoc tests. Mann-Whitney U test was used in analyzing non Gaussian distributed variables and presented as the medians and IQRs, including gestational age of fetus, the highest sensory block level, time intervals of obstetrics and anesthesia. The number needed to treat (NNT) with repeated ephedrine and corresponding 95% confidence interval (95% CI) were calculated based on the absolute risk reduction (ARR): NNT = 1/ARR. The ARR was the reduction in the proportion of the patients who developed hypotension in the crystalloid or colloid group after firstly prescribed ephedrine.

Volume-effect data were fitted to a sigmoidal maximum efficacy model by means of GraphPad Prism software. The median effective volume (EV50), 90% effective volume (EV90) and corresponding 95% CIs were calculated using maximum likelihood estimation and logistic regression with Firth's correction. Odds ratios (ORs) for hypotension and their 95% CIs were estimated in the ITT population and in the predefined subgroups with different fluid volumes.

RESULTS

One thousand gravidas were screened for eligibility and 61 subjects were excluded during the screening period because of the reasons appeared in **Figure 1**. Of the three patients unsuitable for performing epidural or spinal puncture, two were spinal deformity and one has undergone back surgery at the site of needle insertion.

Table 3. EV50 and EV90 of Different Interventions.

	EV_{50} (95% CI)			EV_{90} (95% CI)		
	Crystalloid	Colloid	p Value	Crystalloid	Colloid	p Value
Epidural						
Pre-loading	8.37 (7.32 – 9.41)	6.87 (6.36 – 7.39)	0.039	9.11 (8.72 – 11.61)	7.52 (6.83 – 9.07)	0.019
Co-loading	8.51 (8.09 – 8.93)	7.73 (6.89 – 8.58)	0.087	9.47 (9.01 – 12.49)	8.03 (7.25 – 11.06)	0.004
Post-loading	8.62 (8.20 – 9.05)	8.12 (7.42 – 8.84)	0.095	9.84 (9.25 – 13.00)	8.88 (7.73 – 11.82)	0.017
Spinal						
Pre-loading	8.66 (8.11 – 9.22)	7.35 (7.22 – 7.49)	0.033	9.37 (8.69 – 12.23)	8.54 (7.70 – 10.84)	0.023
Co-loading	9.21 (6.26 – 12.16)	8.02 (7.47 – 8.56)	0.48	10.46 (9.52 – 13.65)	9.09 (8.60 – 12.33)	0.014
Post-loading	9.67 (7.21 – 12.13)	8.50 (7.66 – 9.34)	0.34	12.31 (10.47 – 15.59)	10.58 (9.17 – 13.28)	0.026

EV50: median effective volume; EV90: 90% effective volume; 95% CI: 95% confidence interval

A total of 939 women were firstly randomized to receive crystalloid or colloid intervention, and then the second- and third-stage randomizations were proceeded to performing epidural or spinal anesthesia with different fluid regimens, of them 33 subjects did not received targeted fluids and seven were lost follow-up because of a discontinued fluid-delivering for the investigators reasons. In the epidural anesthesia, a total of seven participants encountered inadvertent dural puncture without any post-anesthesia treatment. Finally, 469 subjects in the crystalloid group and 470 subjects in the colloid group were analysed. All those excluded patients after randomization were treated as the ITT analysis.

Table 1 summarizes the demographic, background characteristics, and baseline vital signs (all were within the physiologic ranges). They were comparable each other among the subgroups.

Subjects who developed hypotension per study protocol are presented in **Table 2**, and no statistically significant differences were observed between crystalloid and colloid interventions. The numbers of patients developed clinically significant and severe hypotension are much lower in both fluids than the overall occurrence of hypotension. The percentage of hypotension in different intervention regimens is showed in **Figure 2**. The EV50 and EV90 of crystalloid and colloid in each subgroup are showed in **Table 3**. The volume of colloid required in preventing hypotension either in the epidural or the spinal population is relatively lower than that of crystalloid. In addition, the values of EV50 in pre-loading groups and all the EV90 in three loading regimens showed statistical significance ($p < 0.05$). Moreover, both EV50 and EV90 of crystalloid and colloid, respectively, appeared a significant increase from pre-loading to co-loading to post-loading subgroup. Patients who developed hypotension were treated with ephedrine, and repeated ephedrine can be prescribed if the subject encountered hypotension again. The NNTs with repeated ephedrine in different intervention groups were calculated and showed that only in the pre-loading spinal anesthesia patients who were given less ephedrine in the colloid than that in the crystalloid ($p = 0.002$, see Supplementary Materials **Table S-4**). Besides, similar results received when analyzing the rate of hypotension on the PP population basis.

There were no statistically significant differences in obstetric and anesthetic data compared between crystalloid and colloid showed in Supplementary Materials **Table S-5**. Infant outcomes in both intervention fluids showed in Supplementary Materials **Table S-6** displayed no significant differences in each subgroup.

In both fluids, patients underwent spinal anesthesia experienced more adverse events than that of epidural anesthesia (38 vs. 27 in spinal and epidural with crystalloid, respectively; 36 vs. 28 in spinal and epidural with colloid, respectively). One patient in the pre-spinal crystalloid underwent hysterectomy because of mass perfuse hemorrhage. But, overall, no statistical significance was observed in the two fluid interventions (see Supplementary Materials **Table S-7**).

Figure 3 summarizes the ORs of hypotension in the ITT population and in the predefined subgroups with different fluid volumes. The overall effect of colloid on hypotension prevention is superior to crystalloid with an OR 1.51 (95% CI, 1.16 – 1.97; $p = 0.002$). Furthermore, we calculated the ORs of hypotension by subdividing the volumes of fluids into three parts, i.e. 5-7, 7-9 and 9-11 ml/kg of crystalloid, and 4-7, 7-9 and 9-11 ml/kg of colloid, and found volume of both fluids less

than 7 ml/kg had a higher ORs than those over 7 ml/kg (see Supplementary Materials Figure S-2).

DISCUSSION

In this study, we calculated the EV50 and EV90 of crystalloid and colloid in preventing hypotension in patients undergoing cesarean delivery with epidural or spinal anesthesia, and compared the effectiveness of both fluids given at different regimens (pre-, co- or post-anesthesia loading) in affecting infant outcomes. The median and 90% effective volumes of colloid are relatively lower by 1.5-2.0 ml/kg compared with crystalloid when reaching similar role in balancing circulation by preventing the occurrence of hypotension in cesarean parturients undergoing neuraxial block, and both crystalloid and colloid produced little influence on infant outcomes. Overall, colloid is superior to crystalloid in hypotension prevention with an OR of 1.51 (95% CI 1.16-1.97).

Volumes of fluids, crystalloid or colloid, given for against regional anesthesia-induced hypotension in cesarean section has been discussing for decades, but the precise volumes how much can produce optimal effect are still not reached (16-19, 31). Those who praise the 'liberal' fluid therapy suggested that the augmentation of blood volume with pre-loading, regardless of the fluid used, must be large enough to result in a significant increase in cardiac output for effective prevention of hypotension, and in their studies, at least 1,500-2,000 ml crystalloid or 1,000 ml colloid was recommended (11-13, 32). Nevertheless, the 'restricted' party considered that extreme expansion of the blood volume with prophylactic fluids would exert negative effects on maternal and infant outcomes, thus they proposed a relative lower volume of fluids, i.e. 1,000 ml crystalloid or 500 ml colloid was good enough (33-35). In addition, contrary data demonstrated that no matter what type or what volume of fluids infused, the incidence of hypotension appeared without significant difference between crystalloid and colloid, and in both high and low dose of volumes (18, 23, 36). All these studies used an estimated volume of fluids. In our study, we calculated the EV50 and EV90 of crystalloid and colloid in different study protocols, and found that both EV50 and EV90 of crystalloid are higher than those of colloid in the two types of anesthetized population. Besides, patients underwent spinal anesthesia required more fluids than whom with epidural anesthesia. The possible reason for such a difference is mainly because epidural block needs longer time when the local anesthetic diffusing and reaching the spinal cord through the meninges than spinal anesthesia alone (37). Therefore, epidural anesthesia allows patients with more time to adapt and endure the sympathetic blockade-induced decrease in blood pressure or fluctuation of circulation, but spinal anesthesia with rapid onset of blockade cannot give enough time to do so.

Pre-loading regimen of fluids is recommended for its prophylactic role of hypotension through prior augmentation of the circulation, though, recent studies displayed similar effect of co-loading and post-loading maneuvers in against the incidence of hypotension (17, 18, 38). Williamson et al. suggested the combined method of pre-loading and co-loading means as a substitute for the simple pre-loading crystalloid fluid administration (19). In our study, three fluid-delivering protocols produced similar effect on the reduction of hypotension when they reached corresponding effective volumes. This is also the major difference of our study from previous reports because we used a volume-incremental manner to realize an optimal effect of hypotension prevention, but not merely a fixed volume of fluids. This design, on the one hand, can increase the sensitivity of the study intervention by enlarging the selective window; and on the other hand, additional outcome analyses can still be performed as the traditional design did.

Hypotension is the major manifest of circulation imbalance induced by neuraxial anesthesia, from which series of maternal and neonatal severe adverse events can result (3-6). While clinical guidelines recommend a prophylactic administration of fluids for preventing this complication, different studies displayed controversial results on this issue, i.e. in effect versus in vain. Dyer and colleagues considered that the timing of fluid administration is the reason for ineffectiveness of traditional pre-loading method with an over (20) min period of fluid titration before anesthesia induction, and they emphasized a rapid crystalloid infusion after spinal anesthesia (21). Dahlgren et al. found that parturients with a positive preoperative supine stress test are more easily developed clinically significant hypotension than the negative comparisons, and the stress positive women are more likely to benefit from prophylactic colloid solution than the negative ones (39). In addition, they also found that the more severe of hypotension the patients encountered, the more protective effect of the colloid solution appeared in spinal anesthetized women (13). As

Ueyama et al. presented that large dose of fluid can effectively prevent the occurrence of hypotension, but a rate of hypotension at least 15% was still observed in those received large-dose colloid (12). This is in accordance with the results of a systematic review (40) that colloid administration is the effective means of hypotension prevention, though, it still cannot totally eliminates the occurrence of this anesthesia-associated complication. In our study, crystalloid and colloid given with different loading regimens all produce effective role in preventing hypotension, especially in the clinically significant and severe hypotension, but, overall, there is yet an occurrence of hypotension at a rate of about 10% to 20% even when the EV90 was reached. Besides, the NNTs with repeated ephedrine in the colloid participants are much lower compared with the crystalloid ones, especially in the pre-spinal loading patients.

Neonatal outcomes are major consideration for cesarean parturients under regional anesthesia due to the threatening from hypotension, but recent literatures showed that despite the high prevalence of maternal hypotension, term infants can tolerate this placental blood perfusion challenge without any major negative consequences (41-43). Meanwhile, a range of studies also did not find any sequel from the fluid interventions in patients undergoing cesarean section with neuraxial blockade (36, 44-47). Our results are consistent with these findings that various fluid loadings produced little effect on infants' Apgar and NBAS scorings, and also no significant difference was observed in the umbilical-cord artery pH values in both crystalloid and colloid.

Maternal adverse events in each loading group were recorded and found that nausea/vomiting, fatigue, itching and shivering are four major events in both fluid interventions. Although one woman in the co-spinal colloid loading regimen found with mild pulmonary edema, this does not seem to be associated with colloid administration because the women merely received 7 ml/kg fluid and no intraoperative hypotension developed diagnosed with following clinical manifestations: breathing difficulty especially shortness of breath worse on lying down, lung crackling sounds in stethoscope, and positive results in chest X-ray; and recovered after treating with diuretics, morphine sulphate and antibiotics. The incidences of adverse events are similar in all types of fluid loadings.

In summary, this study provides robust evidence that the hypotension-preventing effect of both crystalloid and colloid in parturients undergoing cesarean delivery with neuraxial anesthesia is reliable, and this effect displays a volume-dependent manner in a limited scope, of which is concordant with other previous reports that large amount of fluids are not necessarily useful in balancing maternal hemodynamic (22, 48). Second, different fluid loading regimens have their own corresponding EV50 and EV90 for stabilizing circulation under different regional anesthesia, epidural or spinal, but not the traditionally used means of crystalloid 1,000 ml or colloid 500 ml. At last, while fluid loading is an effective method of preventing neuraxial block-induced hypotension in cesarean parturients, it cannot total eliminate its occurrence with a final rate of 10% to 20% as suggested by a systematic review that surgical procedures should not be delayed regardless of the fluid loading strategy because the incidence of maternal hypotension is still high (49). Therefore, fluid loading is an effective maneuver in balancing maternal circulation when reaching the effective volume of different neuraxial anesthesia, but prophylactic or therapeutic vasopressors should also be prepared and be given at an appropriate time because a significant proportion of parturients can still develop hypotension.■

ARTICLE INFORMATION

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Supplementary Materials

Crystalloid versus Colloid in Stabilizing Hemodynamic of Patients Undergoing Cesarean Section with Neuraxial Anesthesia A Randomized Controlled Trial

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Table S-1. Number of Patients Randomized into Different Subgroups.

Total randomisation (n=939)		
Crystalloid intervention (n=469)		
Epidural group (n=233)		
Pre-epidural part (n=77)	Co-epidural part (n=78)	Post-epidural part (n=78)
5 ml/kg (n=8)	5 ml/kg (n=7)	5 ml/kg (n=5)
6 ml/kg (n=7)	6 ml/kg (n=9)	6 ml/kg (n=9)
7 ml/kg (n=17)	7 ml/kg (n=14)	7 ml/kg (n=16)
8 ml/kg (n=13)	8 ml/kg (n=18)	8 ml/kg (n=17)
9 ml/kg (n=14)	9 ml/kg (n=12)	9 ml/kg (n=16)
10 ml/kg (n=10)	10 ml/kg (n=11)	10 ml/kg (n=9)
11 ml/kg (n=8)	11 ml/kg (n=7)	11 ml/kg (n=6)
Spinal group (n=236)		
Pre-spinal part (n=79)	Co-spinal part (n=78)	Post-spinal part (n=79)
5 ml/kg (n=7)	5 ml/kg (n=9)	5 ml/kg (n=6)
6 ml/kg (n=9)	6 ml/kg (n=6)	6 ml/kg (n=11)
7 ml/kg (n=13)	7 ml/kg (n=15)	7 ml/kg (n=17)
8 ml/kg (n=18)	8 ml/kg (n=14)	8 ml/kg (n=13)
9 ml/kg (n=15)	9 ml/kg (n=19)	9 ml/kg (n=18)
10 ml/kg (n=9)	10 ml/kg (n=10)	10 ml/kg (n=8)
11 ml/kg (n=8)	11 ml/kg (n=5)	11 ml/kg (n=6)
Colloid intervention (n=470)		
Epidural group (n=237)		
Pre-epidural part (n=79)	Co-epidural part (n=79)	Post-epidural part (n=79)
4 ml/kg (n=5)	4 ml/kg (n=7)	4 ml/kg (n=4)
5 ml/kg (n=9)	5 ml/kg (n=7)	5 ml/kg (n=8)
6 ml/kg (n=15)	6 ml/kg (n=9)	6 ml/kg (n=11)
7 ml/kg (n=11)	7 ml/kg (n=15)	7 ml/kg (n=13)
8 ml/kg (n=16)	8 ml/kg (n=13)	8 ml/kg (n=11)
9 ml/kg (n=10)	9 ml/kg (n=12)	9 ml/kg (n=16)
10 ml/kg (n=6)	10 ml/kg (n=9)	10 ml/kg (n=11)
11 ml/kg (n=7)	11 ml/kg (n=7)	11 ml/kg (n=5)
Spinal group (n=233)		
Pre-spinal part (n=76)	Co-spinal part (n=79)	Post-spinal part (n=78)
4 ml/kg (n=6)	4 ml/kg (n=5)	4 ml/kg (n=7)
5 ml/kg (n=4)	5 ml/kg (n=5)	5 ml/kg (n=5)
6 ml/kg (n=8)	6 ml/kg (n=10)	6 ml/kg (n=9)
7 ml/kg (n=12)	7 ml/kg (n=15)	7 ml/kg (n=14)
8 ml/kg (n=16)	8 ml/kg (n=13)	8 ml/kg (n=15)
9 ml/kg (n=15)	9 ml/kg (n=17)	9 ml/kg (n=14)
10 ml/kg (n=7)	10 ml/kg (n=8)	10 ml/kg (n=9)
11 ml/kg (n=8)	11 ml/kg (n=6)	11 ml/kg (n=5)

Table S-2. Contraindications for Neuraxial Anesthesia.

Absolute contraindications
Patient refusal
Infection
Localized active infection at the site of needle insertion
Systemic infection
Sepsis
Coagulopathy and other bleeding diathesis
Full anticoagulation therapy
Heparin
Antithrombolytics
Partial anticoagulation therapy
Preoperative antiplatelet drugs – asprin, NSAIDs or clopidogrel
Low dose warfarin, subcutaneous heparin
Low molecular weight heparin
Temporary intraoperative anticoagulation
Severe hypovolemia
Increased intracranial pressure
Severe aortic or mitral stenosis
Relative contraindications
Lack of cooperation
Pre-existing neurological deficits
Multiple sclerosis
Other demyelinating lesions
Severe spinal deformity
Stenotic valvular heart lesions
Prior back surgery at the site of needle injection
Diseases states
Respiratory failure
Major blood loss

NSAIDs: non-steroidal anti-inflammatory drugs

Table S-3. Criteria for NBAS Scale. *

The Neurobehavioral Assessment Scale (NBAS) is intended to test the modifiability of an infant's performance in response to activities specific to the newborn or young infant. The NBAS can be used for neurobehavioral examination over the first months of life (0-18 months). Its underlying principles can be applied at any age. Note that each score indexes the quality of the infant's performance and the responsiveness of the infant to the maneuvers performed by the examiner. The examiner does not just carry out standard maneuvers to obtain responses (reflexes) which are judged normal or abnormal according to a standard criterion. The examiner plays an active role modifying his/her behavior in order to elicit the infant's 'best performance'. In this way the NBAS tests the modifiability of the infant's performance in response to changes of environmental inputs, *i.e.* affordances and the examiner's scaffolding behavior. This procedure permits the examiner to test the effectiveness of his/her maneuvers in modifying the infant's performance. Below the 11 neurobehavioral areas assessed are illustrated with the descriptions of the extreme scores.

No.	Item	Criterion
1	Autonomic System Control	A score of 1 is assigned when the infant shows good autonomic control during the entire examination. No change in skin color or respiratory rate is observed. By contrast, a score of 5 is given when the infant is never able to control his autonomic subsystem, not even following prolonged examiner attempts to console him/her.
2	Behavioral Stale Control	A score of 1 is assigned when the infant shows a prompt reaction to the more disturbing maneuvers. Although he will eventually reach a crying state, he is able to self quiet or be comforted by minimal examiner intervention (face or voice) and achieves an alert state. By contrast, a score of 5 is given when the infant shows a noncontrollable alteration in his behavioral states. Consolation is not achieved, even following prolonged examiner attempts.
3	Motor Activity Control	A score of 1 is given when startles, tremors and clonus are practically absent throughout the entire examination, or if present, do not influence the infant's performances and thus do not alter behavioral, autonomic and orientation responses. Motor activity is fluent and active for most of the exam. By contrast, a score of 5 is given when control is never reached.
4	Visual and Auditory Orientation (Interactive/Attention Subsystem)	A score of 1 is assigned when the infant orients towards the examiner's face and voice for over 30 seconds, while head and trunk are supported by the examiner. The infant is able to follow with eyes and head horizontally over an arc of 180°. By contrast, a score of 5 is given when the infant never succeeds in orienting.
5	Morol Startle Reaction	Typically thought of solely in reflexive terms it is often unrecognized that when the startle reaction is overactive, the infant cannot achieve a good head control. Consequently, this item is scored on the basis of the infant's capacity to control the influence of Moro/startle and then lift his head to follow a stimulus in a vertical position (sitting position helped by the examiner). A score of 1 is

		given when the infant is able to gain head control and follow an object for more than 30 seconds. Moro/startle reaction will be evident only infrequently in the sitting position, but does not interfere with performance. By contrast, a score of 5 is given when this performance is never achieved. Moro/startle reactions are always evident and stereotyped.
6	Asymmetric Tonic Neck Reflex (ATNR)	This item is scored on the basis of the infant's capacity to align and realign his head in a supine position in order to follow a stimulus. A score of 1 is given when the infant follows over a horizontal arc of not less than 180°. The ATNR is evident only intermittently but does not interfere with performance. By contrast, a score of 5 is assigned when the performance is never achieved. The ATNR is always evident and stereotyped and the infant never realigns his head to follow a stimulus.
7	Head Righting Reactions in a Prone Position	This item is scored according to the duration the infant is able to keep his head raised in order to follow an object or a face. A score of 1 is given when the time for following is greater than 30 seconds. By contrast, a score of 5 is given when the performance is never accomplished.
8	Head-Righting Reactions During 'Pull-to-Sit' Maneuver	The score for this item is based on the infant's ability to control his head during the pull-to-sit. A score of 1 is given when the head is held in a straight line with the trunk. By contrast, a score of 5 is given when the head flops completely.
9	Body-Righting Reactions in Prone Position	This item addresses the infant's ability to extend his head and the upper part of his trunk and bear weight on his forearms in order to follow a stimulus; this ensures the possibility of shifting weight to one side and thus freeing one hand for manipulation. The score is based on the length of time the infant extends his head and the upper part of his trunk and supports his weight. A score of 1 is given when the duration is greater than 30 seconds. By contrast, a score of 5 is given when the performance is never achieved.
10	Grasp Reflex	This item is scored on the basis of the infant's capacity to bring his hands to the midline in a supine position; scores from 1 to 4 depend on the number of facilitations needed to accomplish this performance (e.g., gentle caressing of the dorsal surface may facilitate hand opening when the hands are clenched). A score of I is given when the infant is able to open his hands and bring them to the midline with smooth, well-directed movements, isolated finger movements, without facilitation. The grasp reflex is evident only intermittently but does not interfere with the performance. By contrast, a score of 5 is given when the performance is never achieved; the grasp reflex is always evident and stereotyped or the movement of the upper limbs is so poor that no functional activity can be performed.
11	Positive Supporting Reaction	This item is scored on the basis of the infant's capacity to interrupt the typical pattern of this reaction (i.e., simultaneous extension of hip and knee associated with plantiflexion of the ankle joint) and its reversal (simultaneous flexion of hip and knee associated

		with dorsiflexion of the ankle joint) showing isolated hip, knee, ankle movements. A score of 1 is given when the infant is actively kicking and shows isolated hip, knee, and ankle movements throughout the examination. Simultaneous hip, knee, and ankle extension and flexion are evident only intermittently but they do not interfere with isolated movements. By contrast, a score of 5 is given if active kicking is absent or occurs only and exclusively as part of a total extension or total flexion pattern, while isolated movements are never observed.

* Adopted from: Bottos M, Dalla Barba B, D'Este A, Tronick EZ. The Neurobehavioral Assessment Scale as an instrument for early long-term prognosis and intervention in major disability in high-risk infants. *J Pediatr Psychol.* 1996;21: 755-769, and reprinted with permission.

Table S-4. NNT with Repeated Ephedrine.*

NNT	Crystalloid (n=469)	Colloid (n=470)	p Value
Epidural			
Pre-loading	19 (4.1)	10 (2.1)	0.088
Co-loading	35 (7.5)	28 (6.0)	0.36
Post-loading	41 (8.7)	34 (7.2)	0.39
Spinal			
Pre-loading	25 (5.3)	8 (1.7)	0.002
Co-loading	46 (9.8)	30 (6.4)	0.054
Post-loading	53 (11.3)	42 (8.9)	0.23

***** Data are presented as the number (%). NNT: number-needed-to-treat

Table S-5. Obstetric and Anesthetic Data.*

Variable	Crystalloid	Colloid	p Value
Duration of fluid infusion, min			
Pre-epidural	8 (7 – 11)	9 (6 – 12)	0.67
Co-epidural	8 (6 – 11)	8 (7 – 12)	0.18
Post-epidural	9 (7 – 13)	10 (7 – 13)	0.42
Pre-spinal	7 (5 – 11)	8 (7 – 11)	0.23
Co-spinal	9 (7 – 12)	9 (7 – 12)	0.81
Post-spinal	7 (5 – 13)	8 (6 – 11)	0.72
Induction of neuraxial anaesthesia, min			
Pre-epidural	10 (8 – 13)	9 (8 – 14)	0.88
Co-epidural	9 (7 – 11)	9 (8 – 12)	0.49
Post-epidural	11 (8 – 13)	10 (7 – 13)	0.78
Pre-spinal	9 (6 -12)	11 (8 – 13)	0.31
Co-spinal	10 (9 – 14)	10 (7 – 12)	0.70
Post-spinal	9 (7 – 13)	10 (7 – 13)	0.42
Anaesthetic induction to skin incision, min			
Pre-epidural	16 (14 – 21)	18 (13 - 22)	0.55
Co-epidural	19 (16 – 25)	17 (14 – 22)	0.40
Post-epidural	18 (15 – 23)	17 (15 – 24)	0.38
Pre-spinal	9 (8 – 12)	11 (7 – 12)	0.84
Co-spinal	10 (7 – 12)	10 (8 – 13)	0.17
Post-spinal	8 (7 – 13)	9 (7 – 12)	0.74
Uterine incision to delivery, min			
Pre-epidural	3 (2 – 4)	3 (2 – 5)	0.54
Co-epidural	3 (2 – 4)	3 (2 – 4)	0.42
Post-epidural	2 (2 – 4)	3 (2 – 5)	0.84
Pre-spinal	3 (2 – 5)	3 (2 – 5)	0.69
Co-spinal	3 (3 – 5)	3 (2 – 4)	0.78
Post-spinal	3 (2 – 4)	2 (2 -5)	0.84
Duration of anaesthesia, min			
Pre-epidural	145 (123 – 169)	152 (136 – 177)	0.62
Co-epidural	150 (131 – 182)	142 (130 – 180)	0.49
Post-epidural	138 (120 – 156)	144 (127 – 168)	0.89
Pre-spinal	121 (113 – 142)	132 (127 – 159)	0.69
Co-spinal	130 (128 – 148)	125 (110 – 146)	0.36
Post-spinal	128 (116 – 154)	120 (114 – 137)	0.41
Duration of surgery, min			
Pre-epidural	48 (40 – 55)	50 (45 – 61)	0.68
Co-epidural	44 (38 – 51)	46 (40 – 60)	0.31
Post-epidural	52 (42 – 68)	55 (41 – 67)	0.69
Pre-spinal	46 (42 – 54)	53 (40 – 62)	0.55
Co-spinal	55 (46 – 60)	47 (39 – 58)	0.84

Post-spinal	46 (40 – 58)	50 (44 – 67)	0.42
Highest sensory block level			
Pre-epidural	T7 (T6 – T8)	T7 (T7 – T8)	0.91
Co-epidural	T6 (T6 – T8)	T7 (T6 – T7)	0.88
Post-epidural	T7 (T6 – T8)	T6 (T6 – T8)	0.89
Pre-spinal	T8 (T6 – T9)	T7 (T7 – T8)	0.94
Co-spinal	T7 (T6 – T8)	T7 (T7 – T8)	0.99
Post-spinal	T7 (T6 – T7)	T8 (T6 – T8)	0.87
Estimated blood loss, ml			
Pre-epidural	340 (310 – 380)	350 (330 – 400)	0.48
Co-epidural	320 (280 – 410)	300 (270 – 370)	0.57
Post-epidural	360 (330 – 400)	320 (300 – 380)	0.54
Pre-spinal	350 (330 – 420)	340 (310 – 430)	0.95
Co-spinal	330 (300 – 410)	300 (290 – 350)	0.17
Post-spinal	360 (320 – 430)	370 (340 – 450)	0.35
Additional fluid volume, ml			
Pre-epidural	525 (481 – 666)	550 (512 – 693)	0.64
Co-epidural	538 (504 – 635)	517 (476 – 640)	0.37
Post-epidural	574 (522 – 703)	556 (508 – 686)	0.47
Pre-spinal	543 (516 – 687)	589 (530 – 721)	0.59
Co-spinal	572 (542 – 710)	554 (470 – 673)	0.22
Post-spinal	521 (490 – 687)	561 (531 – 692)	0.79

***** Data denotes median and interquartile range (IQR) analyzed with Mann-Whitney U test.

Table S-6. Infant Outcomes.

Outcome	Crystalloid (n=469)	Colloid (n=470)	p Value
Pre-epidural			
Weight, g	3310 ± 450	3230 ± 380	0.83
1-min Apgar < 7, n (%)	5 (1.1)	6 (1.3)	0.64
5-min Apgar < 7, n (%)	0	0	-
Low umbilical cord pH (artery < 7.20), n (%)	12 (2.6)	9 (1.9)	0.50
NBAS scorings (median [IQR])	18 (12 – 27)	15 (12 – 30)	0.69
Co-epidural			
Weight,g	3420 ± 290	3270 ± 360	0.60
1-min Apgar < 7, n (%)	7 (1.5)	5 (1.1)	0.56
5-min Apgar < 7, n (%)	0	0	-
Low umbilical cord pH (artery < 7.20), n (%)	13 (2.8)	11 (2.3)	0.67
NBAS scorings (median [IQR])	17 (13 – 31)	16 (11 – 28)	0.55
Post-epidural			
Weight, g	3300 ± 315	3410 ± 280	0.56
1-min Apgar < 7, n (%)	9 (1.9)	8 (1.7)	0.80
5-min Apgar < 7, n (%)	1 (0.2)	0	0.32
Low umbilical cord pH (artery < 7.20), n (%)	15 (3.2)	17 (3.6)	0.72
NBAS scorings (median [IQR])	21 (15 – 36)	19 (14 - 34)	0.70
Pre-spinal			
Weight, g	3150 ± 340	3210 ± 270	0.78
1-min Apgar < 7, n (%)	3 (0.6)	3 (0.6)	0.99
5-min Apgar < 7, n (%)	0	0	-
Low umbilical cord pH (artery < 7.20), n (%)	8 (1.7)	5 (1.1)	0.40
NBAS scorings (median [IQR])	13 (11 – 21)	14 (11 – 23)	0.58
Co-spinal			
Weight, g	3290 ± 310	3310 ± 270	0.69
1-min Apgar < 7, n (%)	6 (1.3)	4 (0.8)	0.52
5-min Apgar < 7, n (%)	0	1 (0.2)	0.31
Low umbilical cord pH (artery < 7.20), n (%)	11 (2.3)	9 (1.9)	0.65
NBAS scorings (median [IQR])	17 (13 – 25)	18 (12 - 29)	0.70
Post-spinal			
Weight, g	3320 ± 280	3200 ± 300	0.64
1-min Apgar < 7, n (%)	8 (1.7)	7 (1.5)	0.79
5-min Apgar < 7, n (%)	1 (0.2)	0	0.32
Low umbilical cord pH (artery < 7.20), n (%)	15 (3.2)	12 (2.6)	0.55
NBAS scorings (median [IQR])	17 (15 – 30)	19 (16 – 36)	0.31

NBAS: neurobehavioral assessment scale; IQR: interquartile range

Table S-7. Maternal Adverse Events during Intervention Period.

	Crystalloid						Colloid					
	Epidural			Spinal			Epidural			Spinal		
Adverse Event	Pre	Co	Post	Pre	Co	Post	Pre	Co	Post	Pre	Co	Post
Nausea/Vomiting	3	3	5	2	6	8	2	5	7	6	4	6
Fatigue	2	1	1	2	3	1	2	1	1	0	2	1
Haemorrhage	0	0	1	2	0	0	0	1	0	0	1	1
Pruritus	2	1	1	1	0	1	1	2	1	2	2	1
Headache	0	1	0	1	1	0	1	0	0	0	0	2
Somnolence	0	0	0	0	1	0	0	1	0	0	0	1
Hallucination	1	0	0	0	0	0	0	0	0	0	0	0
Sweating	2	0	0	1	1	0	0	0	0	0	2	0
Shivering	1	1	3	1	2	3	1	2	2	3	4	1
Hypothermia	0	1	1	0	2	1	1	1	0	0	0	1
Pulmonary aedema	0	0	0	0	0	0	0	0	0	0	1	0
Total	9	7	11	9	16	13	7	11	10	9	14	13

Figure S-1. Flow of Multi-Stage Randomization.

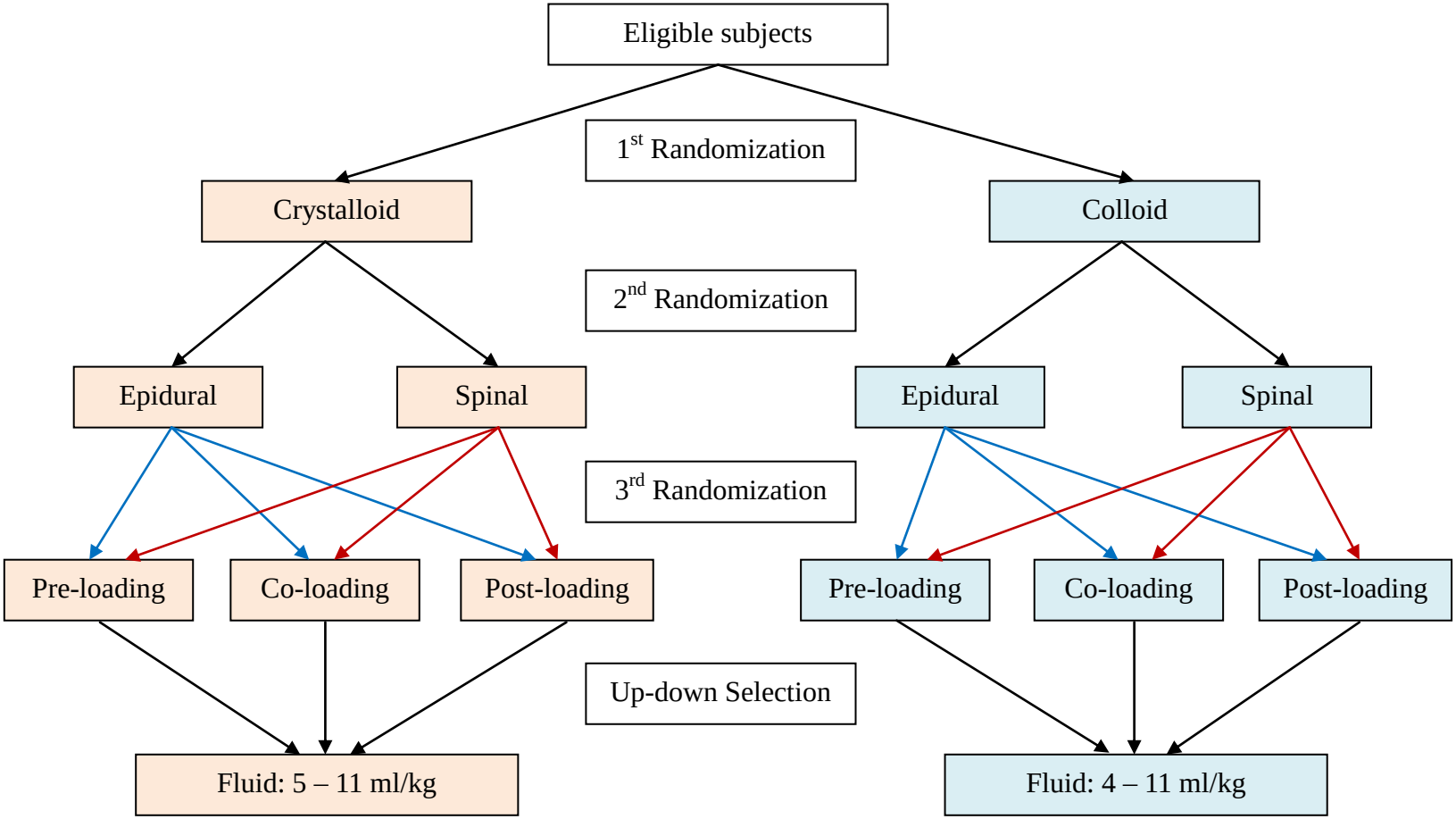
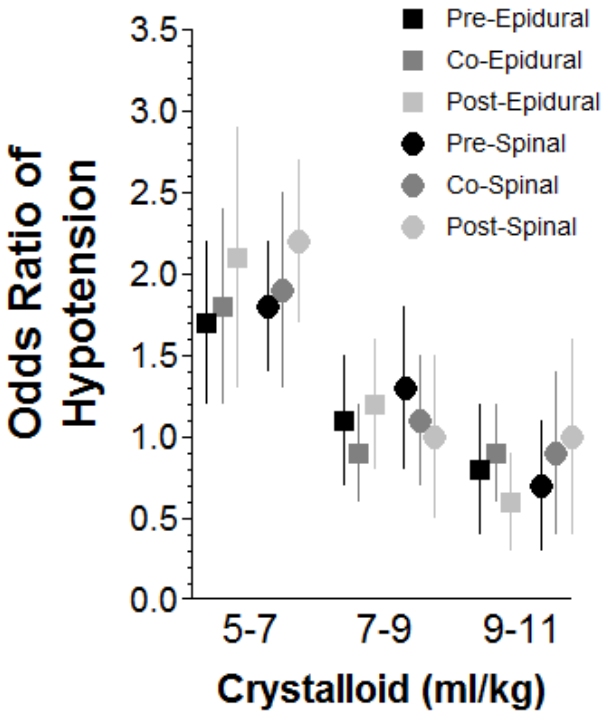


Figure S-2. Odds Ratios for Hypotension in Stratified Fluid Volumes.

Crystalloid and colloid all have a higher tendency of developing hypotension at the volume of less than 7 ml/kg compared with those received relatively larger dose of fluids.

A



B