ORIGINAL ARTICLE

Comparison of Colloid versus Crystalloid Co-Loading to Prevent Hypotension in Patients Undergoing Hip or Femoral Fracture Surgery under Spinal Anesthesia: A Randomized Controlled Trial

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Background: The incidence of hypotension in patients who undergo hip-fracture surgery is high and related to numerous complications.

Objective: To compare colloid and crystalloid during spinal anesthesia in terms of their ability to prevent intraoperative hypotension in patients who undergo hip or femoral fracture surgery.

Materials and Methods: The present study was a prospective, randomized, single-blind, controlled trial approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University. Sixty-eight patients who underwent hip or femoral fracture surgery under spinal anesthesia were recruited. The patients were randomized into the hydroxyethyl starch (Voluven®) group V and crystalloid fluid administration as lactated or acetated Ringer's solution, group C. After spinal anesthesia, the patients received 500 mL of one of these fluids over 25 minutes as co-load.

Results: Patient characteristics were similar in both groups. The incidence of hypotension was lower in group V than in group C at 28.9% in group V and 46.7% in group C. However, the difference was not statistically significant (p=0.211). Acute kidney injury did not occur in either group on postoperative day 1. Vasopressor requirement was not different between the groups with ephedrine (p=0.339) and norepinephrine (p=0.666) within one hour after spinal anesthesia.

Conclusion: Co-loading with colloids did not yield a significantly lower incidence of hypotension after spinal anesthesia in hip or femoral fracture surgery.

Keywords: Co-load fluid; Crystalloid; Colloid; Spinal anesthesia

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Hip or femoral fractures are a worldwide problem, especially in geriatric patients who are more susceptible to osteoporosis and falls[1]. Surgery and anesthesia, for example, regional anesthesia, spinal anesthesia, and general anesthesia, are required to correct these fractures. In the United Kingdom, the incidence of intraoperative hypotension among patients underwent hip fracture surgery was between 56% and 89%[2]. Intraoperative hypotension has been reported to be associated with postoperative adverse outcomes, such as acute kidney injury (AKI), myocardial infarction, or a higher mortality rate[3,4]. Administration of both crystalloid and colloid solutions can increase cardiac output (CO) rather than nothing[5]. Fluid administration can be categorized on the basis of the fluid type and the method.

A retrospective study reported that most hip fracture surgery patients received spinal anesthesia[6,7]. Hypotension during spinal anesthesia is caused by sympathetic blockage following arteriolar vasodilation that leads to decreased systemic vascular resistance (SVR) and reduced venous vasomotor tone with increased venous pooling, thereby reducing venous return[8].

Fluid administration can prevent intraoperative hypotension by increasing CO to counteract the

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reduction in SVR from spinal anesthesia.

Among assessments based on the type of fluid administration, a previous study reported that in comparison with preloading of crystalloid solutions, preloading of colloid solutions in patients who underwent femoral fracture surgery caused no statistically significant intraoperative hypotension[9]. A large-volume preload, especially with crystalloid solutions, caused fluid shifting from the intravascular space to the extravascular space, producing relative hypovolemia. In addition to the fluid-shifting effect, a large preload volume increased the atrial natriuretic peptide level, causing peripheral vasodilatation and initiating diuresis[10]. Thus, relative hypovolemia and hypotension commonly occur with crystalloid fluid administration. Colloid fluid administration also showed a lower incidence of intraoperative hypotension than crystalloid solution after preload and co-load fluid administration in caesarean sections[11,12].

In assessments based on the method of fluid administration, patients who underwent cesarean section[13-15] and non-obstetric operations[16] showed a lower incidence of intraoperative hypotension and vasopressor requirement in the co-load group than the preload group. The more beneficial effects of co-loading over preloading in preventing intraoperative hypotension can be attributed to the fact that the increasing CO outweighed the effect of sympathetic block and reached the highest value at 45 minutes after spinal anesthesia[17].

Previous studies have shown that co-loading with the colloid solution during spinal anesthesia may reduce intraoperative hypotension, but no prior study had evaluated this approach in patients who underwent hip or femoral fracture surgery. Therefore, the present study aimed to compare co-loading of colloid and crystalloid solutions during spinal anesthesia to prevent intraoperative hypotension in patients who underwent hip or femoral fracture surgery.

Materials and Methods

Ethical approval for the present study was obtained from the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University on March 12, 2021 (REC 63-405-8-1) and complied with declaration of Helsinki. The present study was registered at the Thai Clinical Trials Registry (TCTR20210316007) on 16 March 2021 before the first participant was enrolled. All participants were explained the study protocol before obtaining informed consent. A prospective, randomized, single-blind, controlled trial was conducted in Songklanagarind Hospital between July 2021 and August 2022. The targeted populations were patients aged at least 20 years with American Society of Anesthesiologists (ASA) physical status classification I to III who underwent elective or urgent hip or femoral fracture surgery.

Exclusion criteria included coagulopathy with an international normalized ratio greater than 1.50, severe aortic stenosis, congestive heart failure, pulmonary oedema, N-terminal pro-brain natriuretic peptide (NT-proBNP) level greater than 300 pg/mL, Mobitz type 2 second-degree to third-degree atrioventricular block, glomerular filtration rate less than 30 mL/min/1.73 m^2 allergy to hydroxyethyl starch (HES), hyponatremia as serum sodium of less than 130 mEq/L, and surgery under general anesthesia. Patients participating in other studies were also excluded.

Patients were randomly allocated into two groups, namely group V and group C, using a concealed, opaque, and computer-generated block of four randomizations. Patients in group V received a 500 mL co-load of colloid fluid at 6% HES-Voluven®, Fresenius Kabi for over 25 minutes, whereas those in group C received a 500-mL co-load of crystalloid fluid, lactated Ringer's solution or acetated Ringer's solution for patients with pre-existing diabetes, over 25 minutes. The patients were unaware of the co-load fluid administration. Demographic data and baseline patient characteristics were recorded the day before surgery.

On the day of the operation, the patient received preoperative intravenous fluid as determined by the attending anesthesiologist or surgeon. If the patient had underlying hypertension, an antihypertensive agent was administered preoperatively. In the preoperative holding area, three researchers who measured inter-rater reliability before study initiation confirmed the high reliability of inferior vena cava (IVC) ultrasonography for evaluation of the patients. The diameter and fluid responsiveness were evaluated by measuring the IVC diameter and collapsibility index that was calculated from: (maximum IVC diameter – minimum IVC diameter) / maximum IVC diameter, and cut-off value of greater than 50%, which represented fluid responsiveness using a SonoSite EDGE II device with a rP19x transducer.

Spinal anesthesia was performed at the L3-L4 intervertebral space using a 27-gauge Quincke spinal

needle in the lateral decubitus position by an attending anesthesiologist or resident. After free-flow aspiration of cerebrospinal fluid, a spinal anesthetic was injected using 0.5% hyperbaric bupivacaine (Marcaine® Spinal 0.5% Heavy) or 0.5% isobaric bupivacaine (Marcaine® Spinal 0.5% isobaric) without intrathecal opioids. Both types and dosages of the spinal local anesthetic were dependent on the anesthesiologist. Peripheral nerve block was performed by decision of anesthesiologist for example pericapsular nerve group (PENG) block, fascia iliaca nerve block, or femoral nerve block.

Using Terumo® Terufusion™ TE-LF600/700A, 500 mL of the study fluid was infused during spinal anesthetic drug injection through the spinal needle at an infusion rate of 1,200 mL per hour. Non-invasive blood pressure measurements were obtained at the arm every minute for 16 minutes as the standard of care and recorded every two minutes until 16 minutes after spinal anesthesia. Subsequently, measurements were obtained and recorded every five minutes for 30 minutes after spinal anesthesia. Anesthetic and analgesic levels were assessed and recorded by the attending anesthesiologist, resident, or nurse anesthetist using a toothpick every two minutes for 16 minutes after spinal anesthesia. After co-loading fluid infusion, all patients received fluid replacement by maintenance and replacement third space and blood loss with crystalloids.

Patients who developed hypotension received boluses of ephedrine 6 mg or norepinephrine 10 µg intravenously each time. Hypotension was defined as a reduction in mean arterial pressure (MAP) of less than 30% from the inpatient baseline record or less than 65 mmHg. Patients who develop hypotension will receive ephedrine or norepinephrine depending on decision of anesthesiologist.

The total vasopressor requirement for the first 60 minutes, amount of intraoperative blood loss, and fluid consumption were recorded at the end of the surgery. On the first postoperative day, blood samples were collected to measure serum creatinine levels for AKI evaluation. Urine output and fluid balance were also recorded.

The primary outcome of the present study was the incidence of intraoperative hypotension in the first 30 minutes after spinal anesthesia. The secondary outcomes were vasopressor requirement in the first 60 minutes after spinal anesthesia and the incidence of AKI on postoperative day 1.

Vasopressor requirement was recorded as an accumulative dose and divided into two groups,

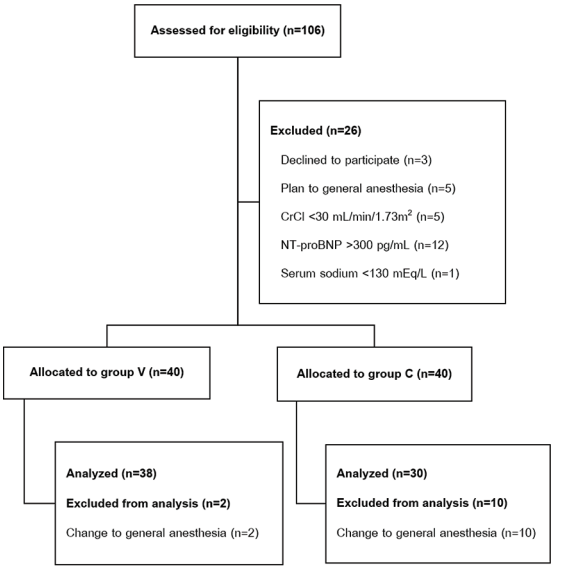

Figure 1. CONSORT flow diagram.

CrCl, creatinine clearance (using Cockcroft-Gault formula); NT-proBNP, N-terminal pro-brain natriuretic peptide

ephedrine and norepinephrine, indicating the severity of intraoperative hypotension. Moreover, AKI was defined as a serum creatinine level increment of 0.3 mg/dL or more according to Kidney Disease: Improving Global Outcomes (KDIGO). Similar to previous studies, the authors conducted post-hoc analyses of hemodynamic changes after spinal anesthesia[9,18,19].

The sample size was calculated from a previous study in patients underwent caesarean section[20], and the groups receiving preload of crystalloid and colloid solutions showed a hypotension incidence of 47.5% and 12.5%, respectively. The sample size was calculated using a two-independent proportion formula: the alpha (α) level was 0.05, and the power of the test or 1 – beta (β) was 90%. The total sample size of the study was 64 patients. Data analysis was performed using RStudio version 3.6.3. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as the number of patients and percentages. Student's t-test was used to analyze normally distributed continuous variables, and the Wilcoxon rank-sum test was used to analyze non-normal continuous variables. Categorical variables were analyzed using Fisher's exact test or the chi-square test. The authors also performed univariate and multivariate logistic regression analyses of the type of fluids, and the level of analgesia adjusted for gender, age, type of

Table 1. Baseline patient characteristics

	Colloid (n=38)	Crystalloid (n=30)	p-value
Demographic data			
Sex; n (%)			0.718
• Male	18 (47.4)	12 (40)	
• Female	20 (52.6)	18 (60)	
Age (years); mean±SD	52.2±19.6	53.7±19.5	0.756
Body weight (kg); mean±SD	61.3±12.3	64.2±15.9	0.405
Height (cm); median (IQR)	160.5 (155, 167)	159.0 (152, 166.2)	0.191
Underlying disease(s); n (%)			
• Hypertension	10 (41.7)	12 (52.2)	0.668
• Diabetic mellitus	3 (12.5)	4 (17.4)	0.701
ASA physical status classification; n (%)			0.603
• I	6 (15.8)	2 (6.7)	
• II	25 (65.8)	22 (73.3)	
• III	7 (18.4)	6 (20.0)	
Preoperative period			
Premedication; n (%)			
• Calcium channel blocker	4 (10.5)	8 (26.7)	0.158
• Beta-blocker	1 (2.6)	1 (3.3)	1
• Alpha-blocker	1 (2.6)	0 (0.0)	1
• ACEI	2 (5.3)	0 (0.0)	0.500
• ARB	1 (2.6)	1 (3.3)	1
• >1 type of antihypertensive drugs	2 (5.3)	2 (6.7)	1
NT-proBNP (pg/mL); median (IQR)	42 (18.5, 83.5)	63 (27.8, 102)	0.178
Creatinine (mg/dL); mean±SD	0.7±0.2	0.8±0.3	0.139
CrCl (mL/min/1.73 m^2); median (IQR)	103 (70.2, 126.8)	93.5 (66.8, 113)	0.317
IVC max. diameter (cm); median (IQR)	1.3 (1.1, 1.6)	1.2 (0.9, 1.5)	0.092
IVC collapsibility index (%); mean±SD	32.6±15.5	32.1±12.6	0.878
Intraoperative period			
Peripheral nerve blocks; n (%)	28 (73.7)	23 (76.7)	1
Type of spinal anaesthetics; n (%)			1
• Hyperbaric bupivacaine	17 (44.7)	14 (46.7)	
• Isobaric bupivacaine	21 (55.3)	16 (53.3)	
Dose of spinal anesthetics (mg); median (IQR)	15 (12.6, 17)	15 (12.6, 16)	0.531
Maximum analgesic level ≥T5; n (%)	20 (52.6)	21 (70.0)	0.229
Estimated blood loss (mL); median (IQR)	400 (150, 675)	400 (300, 487.5)	0.445
Intraoperative fluid consumption; median (IQR)			
• Crystalloid (mL)	750 (500, 1,400)	1,200 (900, 1,537.5)	0.006
• Colloid (mL)	500 (500, 500)	0 (0, 0)	<0.001
• Packed red cells (mL)	0 (0, 0)	0 (0, 0)	0.12

ASA=American Society of Anesthesiologists; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CrCl=creatinine clearance (using Cockcroft-Gault formula); IQR=interquartile range; IVC=inferior vena cava; NT-proBNP=N-terminal pro-brain natriuretic peptide; SD=standard deviation, T5=5th thoracic level

analgesic drugs, and dosage of analgesic drugs for predicting risk factors of intraoperative hypotension. Statistical significance was set at p-value less than 0.05. The power of the present study was 0.9. Inter-rater reliability in evaluations performed by the three researchers was assessed using the intraclass correlation coefficient that was high.

Results

One hundred and six patients were assessed for eligibility. Twenty-six patients were excluded, and 40 patients were randomly allocated to each group. After allocation, two patients in group V and ten in group C were changed to general anesthesia. They were excluded from the analysis. Thus, 68 patients were

Table 2. Comparison of incidence of hypotension, acute kidney injury, and vasopressor requirement outcomes

	Colloid (n=38)	Crystalloid (n=30)	p-value
Primary outcome			
Hypotension; n (%)	11 (28.9)	14 (46.7)	0.211
Secondary outcomes			
Acute kidney injury; n (%)	0 (0.0)	0 (0.0)	-
Vasopressor requirement (first 60 minutes); median (IQR)			
• Ephedrine (mg)	0 (0, 6)	6 (0, 12)	0.339
• Norepinephrine (mcg)	0 (0, 0)	0 (0, 0)	0.666

IQR=interquartile range

Table 3. Comparison of postoperative day 1 parameters

	Colloid (n=38)	Crystalloid (n=30)	p-value
Creatinine (mg/dL); mean±SD	0.7±0.2	0.8±0.3	0.095
CrCl (mL/min/1.73 m^2); median (IQR)	97.5 (79.5, 128)	91.5 (68.2, 128.2)	0.288
Urine output (mL/kg/hour); median (IQR)	1.6 (1.2, 2.1)	1.5 (1, 1.9)	0.302
Fluid balance (mL); median (IQR)	380 (–265.2, 857)	335 (22.5, 652.5)	0.897

CrCl=creatinine clearance (using Cockcrot-Gault formula); IQR=interquartile range; SD=standard deviation

thoroughly analyzed by intention to treat (Figure 1).

The two groups showed no significant differences in baseline patient characteristics such as gender, age, weight, height, underlying hypertension or diabetes mellitus, or ASA physical status classification. In addition, other preoperative parameters, such as type of antihypertensive premedication, NT-proBNP level, IVC maximum diameter, IVC collapsibility index, serum creatinine level, and creatinine clearance (CrCl), were not significantly different either (Table 1).

Among the intraoperative parameters, the two groups showed statistically significant fluid differences in colloid and crystalloid consumption. The colloid group showed higher colloid consumption and lower crystalloid consumption ($p<0.001$). Other intraoperative parameters in the colloid and crystalloid groups were not statistically significant, such as peripheral nerve block at 73.3% and 64.3%, respectively (p=0.7), type of spinal anesthetic with hyperbaric at 60% and 57.1%, respectively, and isobaric at 40% and 42.9%, respectively (p=1), dosage of spinal anesthetic at 13.8±1.9 mg and 14±1.7 mg, respectively (p=0.808), estimated blood loss (p=0.303), and packed red cell consumption (p=0.898).

Intraoperative hypotension in the first 30 minutes after spinal anesthesia developed in 28.9% of patients in the colloid group and 46.7% of those in the crystalloid group, but the difference was not statistically significant (p=0.211). None of the patients developed postoperative AKI on postoperative day 1. Vasopressor requirement, which was summarized as the accumulative dose in the first 60 minutes after spinal anesthesia, was not different between the groups (p=0.339 for ephedrine and 0.666 for norepinephrine) (Table 2).

On postoperative day 1, the colloid and crystalloid groups showed no significant difference in the serum creatinine level at 0.7±0.2 mg/dL versus 0.8±0.3 mg/dL (p=0.095), urine output at 1.6 (IQR 1.2, 2.1) mL/kg/hour versus 1.5 (IQR 1, 1.9) mL/kg/hour (p=0.302), and fluid balance at 380 (IQR –265.2, 857) mL versus 335 (IQR 22.5, 652.5) mL (p=0.948) (Table 3).

After administration of spinal anesthesia, systolic blood pressure, MAP, and diastolic blood pressure were not significantly different between the groups until 30 minutes. In the multivariable analysis, patients with a level of analgesia greater than T5 had a 6.44-fold higher risk of hypotension than patients who did not. In the present study, patients in both groups reported no adverse events from the study fluid infusion, such as skin itching, anaphylaxis, or pulmonary oedema.

Discussion

The present study demonstrated that incidence of hypotension in patients who received co-load with the colloid group compared to the co-load with the crystalloid group in the first 30 minutes after spinal anesthesia did not show statistically significant

difference at 28.9% in the colloid group and 46.7% in the crystalloid group (p=0.2111). This result was similar to that of a previous study that evaluated patients undergoing orthopedic surgeries of the lower extremities and showed the preload with the colloid group had a lower incidence of hypotension than the preload with the crystalloid group, but the difference was not statistically significant at 13.3% in the colloid group and 16.7% in the crystalloid group (p=0.50)[9]. The higher incidence of intraoperative hypotension in the present study could be attributed to two reasons. First, the average age of the participants was high. A higher age increases the risk of spinal anesthesia-induced hypotension through several mechanisms, such as decreased left ventricular compliance, cardiovascular reserve, and baroreceptor reflex activity[20]. The second rationale was that the authors included patients who underwent hip fracture surgery, which required a higher level of anesthesia and may create a higher risk of intraoperative hypotension. Therefore, these consequences influence hemodynamic changes after spinal anesthesia. However, in the present study, co-loading with colloids did not significantly prevent hypotension in comparison with crystalloid co-loading.

The present study results differ from those reported in cases involving caesarean sections. A recent systematic review reported that colloid fluid administration can prevent intraoperative hypotension better than crystalloid fluid administration[11]. However, the authors of that review did not mention the method of fluid administration. A recent prospective observational study reported that co-loading with crystalloids was associated with a higher incidence of intraoperative hypotension in comparison with co-loading using colloid solutions[10]. The incidence of intraoperative hypotension in the prior study was higher than that in the present study because caesarean sections required a higher anesthetic level. However, in the present study, more than 50% of patients had an analgesic level greater than thoracic level 5, and logistic regression showed that it is a risk factor for intraoperative hypotension, similar to other studies[17].

AKI did not occur in both groups in the present study, consistent with a previous study in elderly patients who underwent hip arthroplasty and a systematic review in which 6% HES administration did not increase the incidence of postoperative AKI[21,22]. Nevertheless, the present study evaluated only a short postoperative period. Moreover, the authors limited the volume of 6% HES to a level that did not exceed the maximum dose of 50 mL/kg/day and excluded participants with pre-existing renal impairment such as CrCl less than 30 mL/min/1.73 m^2. However, a longer follow-up period for serum creatinine levels should be considered.

Vasopressor requirements were not significantly different between the groups in the present study. This result was similar to that of the previous studies with cases involving caesarean sections[12,23]. However, the vasopressors used in the present study were different from those used in the previous studies. The authors used ephedrine or norepinephrine, while previous studies used phenylephrine and cafedrine or theodrenaline. Direct comparison of the effectiveness of different vasopressors is not possible because of the lack of studies on equivalent doses of ephedrine and phenylephrine.

The present study had limitations. First, this was a single-blind study because the authors could not cover fluid packaging, which was completely different between the two groups. This may introduce performance or detection bias by investigators, however, the authors used automatic blood pressure measurement, serum creatinine levels, and infusion pumps to control the rate of fluid administration in both groups, which helped reduce inaccurate results. Second, the authors did not control the dose and type of anesthetic drugs, which could affect hemodynamics and the level of anesthesia. Third, the researchers need to investigate the increase in CO through continuous CO monitoring, as it directly guides fluid administration for each patient. Finally, Colloid usage was not limited to surgery for replacement or resuscitation, and the amount was not controlled during the preoperative and intraoperative periods. This lack of control may have influenced kidney function and hemodynamics between groups.

Conclusion

Co-loading with colloid fluid administration cannot reduce the incidence of intraoperative hypotension in patients undergoing hip or femoral fracture surgery under spinal anesthesia.

What is already known about this topic?

Co-loading with colloids can be an effective strategy to prevent hypotension by enhancing blood volume and CO in patients undergoing cesarean sections. However, there are currently no studies addressing other groups at risk of hypotension

following spinal anesthesia, such as older patients or those undergoing femur or hip surgery.

What does this study add?

The authors included patients who underwent hip and femur surgery under spinal anesthesia, and the results demonstrated that co-loading with colloids, compared to crystalloids, did not reduce the incidence of intraoperative hypotension.

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Conflicts of interest

The authors declare no conflicts of interest.

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