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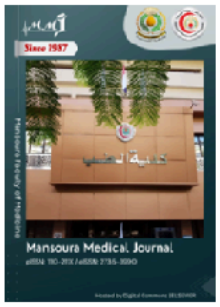

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ORIGINAL STUDY

Coload Effect on Cardiac Output Measurement Using Transthoracic Echocardiography in Preeclamptic Patients Undergoing Cesarean Delivery

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Abstract

Background: **During cesarean delivery (CD) for preeclamptic patients under spinal anesthesia (SA), much intravenous fluids are avoided. Through transthoracic echocardiography, study conducted to assess the hypothesis that colloid plus crystalloid coload will maintain the cardiac output (CO) than crystalloid fluid alone.**

Methods: **Thirty-four preeclamptic patients, scheduled for elective CD, under SA, were allocated according to the fluid coloading into two groups; Crystalloid group (group I); in which the patients received Ringer's acetate or Crystalloid-colloid group (group II); in which the patients received 6% Hydroxyethyl starch and Ringer's acetate. The primary outcome was CO while, left ventricular end-diastolic diameter, heart rate, systolic blood pressure and output of urine were secondary outcomes.**

Results: **Study groups had no statistical difference as regard CO systolic blood pressure, and heart rate. Both left ventricular end diastolic diameter and Velocity time integral demonstrated statistical increase in group II in comparison to the group I immediately postdelivery, 1 and 2 h after induction of SA.**

Conclusion: **Coloading with 500 ml colloid added to 500 ml crystalloid has the same influence as 1000 ml of crystalloid fluid regarding CO measurement in preeclamptic patients underwent CD under SA.**

Keywords: Cardiac output, Colloid, Coload, Crystalloid, Left ventricular end diastolic diameter, Preeclampsia, Spinal anesthesia

1. Introduction

Preeclampsia (PE), a pregnancy-induced hypertension disorder defined by American College of Obstetricians and Gynecologists clinical practice bulletin, is affecting 2−8% of pregnancies after 20 weeks' gestation resulting in serious maternal and foetal morbimortality (American College of Obstetrician and Gynecologists, 2020).

PE symbolizes an acute pressure overload situation that could prompt significant alterations in the left ventricle (LV) function or structure (Novelli et al., 2003; Simmons et al., 2002).

During cesarean delivery (CD) for preeclamptic patients; spinal anesthesia (SA) is a common anesthetic technique as it reduces the maternal plasma catecholamines and help in blood pressure (BP) (Henke et al., 2013). However, its sympathetic blockade leads to hypotension (Nikooseresht et al., 2016). Severe hypotension can complicate the pre-existing uteroplacental hypoperfusion so, furtherly compromise the fetus (Higgins et al., 2018).

As the plasma colloid oncotic pressure is reduced approximately to 14 mm Hg in preeclamptic patients; increased fluid administration during CD could induce systemic and pulmonary edema so, colloid fluid is theoretically superior to crystalloid (Mazda et al., 2018).

This study was conducted to assess the hypothesis that, during CD for preeclamptic patients, adding

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colloid to the crystalloid fluid coload would maintain the cardiac output (CO) compared with crystalloid alone.

The primary outcome was CO measured 1 h post-SA. While, left ventricle end-diastolic diameter (LVEDD) measurement besides, heart rate (HR), systolic blood pressure (SBP) and urine output (UOP) were the secondary outcomes.

2. Patient and method

This prospective randomized controlled double-blinded study was done at Mansoura University hospitals after obtaining informed written consent from each patient. The study was registered at ClinicalTrials.gov (NCT05435573), approved from Institutional Research Board Faculty of Medicine (code number: MS.22.08.2084) before starting and conducted in consistent with principles of ethics set by Declaration of Helsinki and good clinical practice (Stockhausen, 2000).

Preeclamptic patients with a singleton pregnancy greater than or equal to 34 weeks' gestational age, aged 19–40 years, American Society of Anesthesiologists status (ASA) II or III, arranged for CD under SA were enrolled in this study.

Cases with body mass index greater than or equal to 40 kg/m^2, had any urgent delivery situations, conditions associated with fetal threat, or not candidates for SA (coagulopathy, increased intracranial pressure, or infection at injection site) were excluded. Also, patients with hemoglobin less than 10 g/dl, serum creatinine level equal to or more than 1.1 mg/dl, sever cardiovascular, and cerebrovascular disorders, or on current administration of vasoactive drugs were not enrolled.

2.1. Sample size

Power Analysis and Sample Size software program (PASS) version 15.0.5 for windows (2017); sample size was calculated with the CO difference as the primary outcome. Based on the result of a pilot study held in Mansoura University, the mean CO value at 1 h after induction of SA was 7.4 ± 1.2 l/min in the crystalloid group versus 8.88 ± 1.15 l/min in the crystalloid colloid group. 30 patients sample size was needed to attain 90% power using a two-sided hypothesis test with a significance level stated at 0.05. As dropout (10%) was considered, so 34 patients were enrolled (17 per group) in this study.

Preoperative assessment was done for all patients, and they fasted 6 h for solid food, but clear fluid was allowed up to 2 h before surgery.

In the theater, the patient laid supine with 15° left lateral table tilt for 5 min; an intravenous (IV) 18-gauge cannula was established. All patients were attached to the monitor to display; electrocardiogram (ECG), HR, peripheral oxygen saturation, and noninvasive BP. All the basal parameters were reported.

Transthoracic echocardiographic (TTE) measurement of baseline LVEDD and CO was done using a transducer (s2-4 MHz) (ClearVue 350; Philips, Bothell, WA) after obtaining two successive measurements for each reading and then record its mean.

To obtain LVEDD; parasternal long axis view was used at the peak of the R wave on ECG or first video frame at end-diastole to measure the LV chamber dimension linearly immediately after mitral valve (MV) leaflet closure. The chamber should be revealed in the image along its center axis for maximum dimension without the appearance of the papillary muscles. An electronic caliper was situated at the borderline between a line that extend perpendicular to the LV long axis to the internal border of both the compacted myocardium of the posterior wall and myocardium of the interventricular septum just underneath the MV leaflet tips.

Also, through parasternal long axis, left ventricular outflow tract (LVOT) was inspected. A validated image was definite where the aortic valve could be visualized as a tubular structure. To get the diameter of the aortic valve; in systole during quiet breathing, a zoomed two-dimensions was recorded. Then the diameter was halved to obtain the radius (r). After that, aortic CSA was obtained based on by the equation $CSA = \pi r^2$.

Velocity time integral (VTI) was recorded using the apical five chamber (A5C) view, by Doppler incorporation angle less than 20° to the blood flow. The best image was evaluated by a vertical long axis, maximal MV opening size, and maximal chamber size. Pulsed wave Doppler was applied with a 3 mm sample volume located within the LVOT almost half cm near the aortic valve. Three successive beats were measured, and the mean was recorded.

After that, the stroke volume (SV) was obtained by multiplying the CSA of LVOT by VTI. Finally, CO was measured using the formula CO=SV × HR.

Via a computer-generated random number of codes in sealed envelopes; 34 preeclamptic patients were randomly assigned according to the used fluid coloading into two groups (each of 17). Crystalloid group (group I); in which the patients received Ringer's acetate 250 ml over 5 min subsequently,

500 ml over 55 min then, 250 ml over the next 60 min. While, in Crystalloid-colloid group (group II); patients received 250 ml of 6% Hydroxyethyl starch (HES) 130/0.4 in 0.9% sodium chloride (Voluven; Fresenius Kabi, Bad Homburg, Germany) over 5 min then Ringer's acetate (500 ml) over 55 min followed by 250 ml of 6% HES over the next 60 min. The fluid bottles were put inside a pressure infusion bag, which was covered from outside, by the anesthetist who was responsible for opening the envelope and administration of the study fluid along its specific duration without being involved in data collection.

Under complete aseptic technique, SA was performed by a senior anesthesiologist at L4-L5 or L3-L4 interspace. All patients received 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine and 20 μg fentanyl using a 25 G spinal needle. Once, the cerebrospinal fluid was identified; IV coload was started, according to the group.

After the patients were adjusted in supine position with left lateral table tilt, urinary Foley's catheter was inserted.

The surgery was initiated once the spinal sensory level reached T6 or more (assessed using pinprick test) with recording of the maximum level of sensory block after 20 min from intrathecal (IT) injection. If the level did not reach T6 after 20 min; the case would be out of the study.

Measurements of LVEDD and CO were repeated in the same way at other four-time points; 5 min after induction of SA, immediately after delivery, at 1 h and 2 h after induction of SA. HR and SBP were monitored and recorded with the CO measurements. IV atropine 0.5 mg was given if bradycardia occurred (HR <50 beats/min) and repeated as needed. Hypotension is SBP less than 20% of basal then IV 5 mg ephedrine was used.

Immediately after delivery of the fetus, in both groups, 10 units of oxytocin diluted in 50 ml ringer acetate was infused over 30 min. Once surgery was completed; rectal misoprostol 400 μg was administered.

UOP was measured and recorded at 1 and 2 h after SA was initiated.

The duration from induction of SA to umbilical cord clamping (spinal-to-delivery time) and the duration from induction of SA to the end of skin closure (spinal-to-skin closure time) were recorded. Apgar score was evaluated at 1 and 5 min after delivery for neonates. After the surgery, all cases were moved to PostAnesthesia Care Unit. The occurrence of nausea and/or vomiting was recorded intraoperatively till 2 h postoperatively and treated with IV metoclopramide 10 mg.

2.2. Statistical analysis

Statistical analyses were done by IBM SPSS for Windows, version 27 (IBM SPSS Inc., Chicago, Illinois, USA). Data were assessed for normality via Shapiro–Wilk test. Normally distributed continuous data were examined via the Student's t-test. Abnormal distributed continuous and ordinal data were analyzed using Mann–Whitney U test. Categorical data were examined by Chi square test. The results were presented as mean ± SD, median (minimum – maximum) or number as appropriate. P value less than 0.05 was considered significant.

3. Results

A prospective randomized controlled double-blinded study was performed on preeclamptic patients, aged 19–40 years old, ASA II and III prepared for elective CD under SA. Fifty patients were assessed for eligibility. Sixteen patients were excluded (eleven didn't fulfill inclusion criteria and five patients were <34 weeks' gestational age). Thirty-four participants were included and randomly allocated into group I: crystalloid group or group II: crystalloid-colloid group as shown in Fig. 1.

There was no statistically significant difference between both groups as regard demographic, clinical, and anesthetic characteristics (Tables 1 and 2) Without any case of failed SA.

Both groups had no statistically significant difference as regard CO (Table 3). Comparison with the basal CO value within the same group; statistically significant increase immediately post-delivery was detected in group II ($P = 0.001$) while, significant decrease at 1, 2 h following induction of SA in group I ($P = 0.012$ and < 0.001).

Regarding the VTI, no statistically significant difference was detected in both groups at baseline and 5 min after starting spinal induction. However, there was statistically significant increase in Group II compared with group I immediately post-delivery, 1 h, 2 h following induction of SA (Table 3). Comparing the basal VTI value within the same group; statistically significant increase immediately post-delivery was detected in both group ($P < 0.001$) as well as in group II at 5 min, 1 and 2 h after induction of SA ($P = 0.002$,<0.001, and <0.001).

Preoperative mean aortic valve diameter (cm) measurements were 2.07 ± 0.17 and 2.02 ± 0.13 ($P = 0.351$) while aortic cross-sectional area (cm^2) was 3.38 ± 0.55 and 3.21 ± 0.39 ($P = 0.304$) in group I and group II.

A statistically significant increase in LVEDD values was noticed in group II compared with group

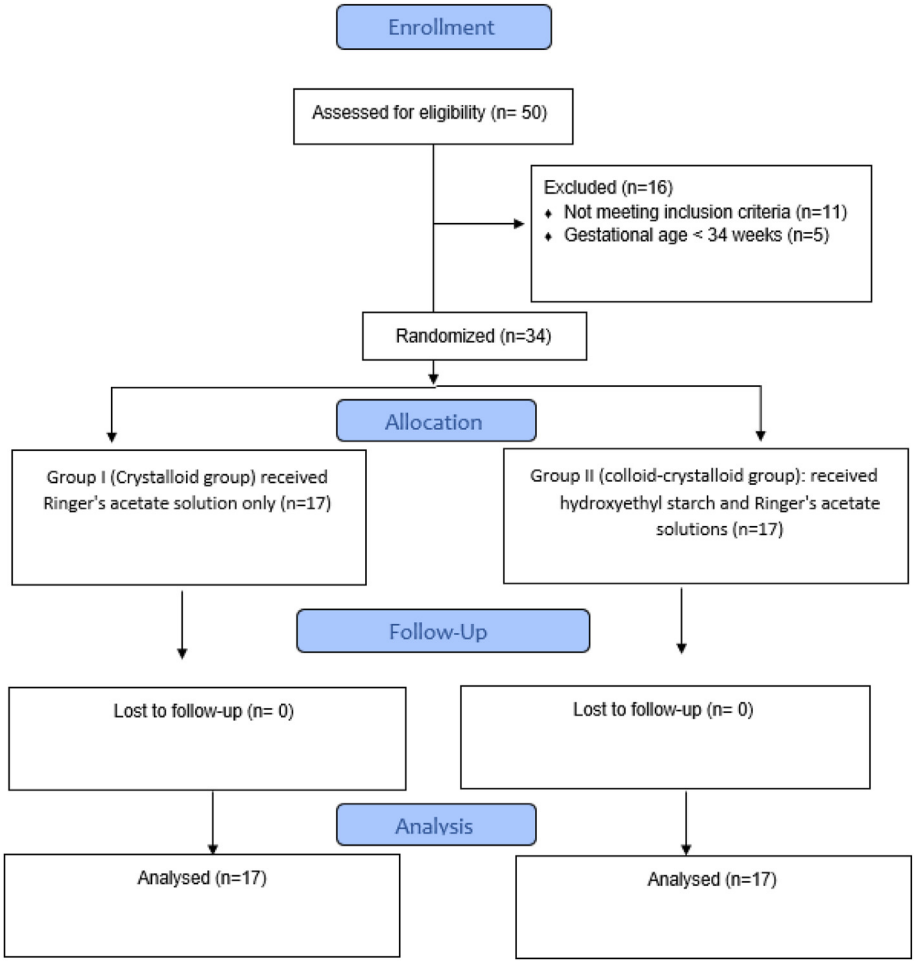

Fig. 1. CONSORT flow chart showing study design.

I immediately postdelivery, 1 h, 2 h following induction of SA as shown in Table 4. Comparison with the basal value in the same group revealed statistically significant increase immediately postdelivery and 2 h following induction of SA in both group and at 1 h following induction of SA in group II (all *P* values were <0.001 except at 2 h following induction of SA; it was 0.032 in group I).

The SBP in Fig. 2 and HR in Table 3 were not significantly different between both groups. HR showed a significant decrease 1 and 2 h after induction of spinal in group I ($P = 0.003$ and < 0.001, respectively) and after 2 h in group II ($P = 0.014$) when compared with basal values.

The use of ephedrine, atropine, and metoclopramide was not significantly different between groups.

Table 1. Demographic and clinical characteristics of the studied groups.

Variables	Group I ($N = 17$)	Group II ($N = 17$)	*P* value
Age (years)	29.06 ± 7.28	28.35 ± 5.42	0.750
Gestational age (weeks)	36.12 ± 1.83	36.18 ± 1.59	0.921
Parity	2 (0–3)	1 (0–3)	0.164
Height (cm)	163.41 ± 5.14	162.82 ± 4.86	0.734
Weight (kg)	84.06 ± 8.44	82.82 ± 9.11	0.684
BMI (kg/m^2)	31.43 ± 2.09	31.17 ± 2.29	0.731

Data are described as mean ± standard deviation or median (minimum– maximum).
Group I: Crystalloid group; Group II: Crystalloid-colloid group; BMI: Body mass index.

Table 2. Spinal anesthetic characteristics.

	Group I ($N = 17$)	Group II ($N = 17$)	*P* value
Maximum level of sensory blockade, *n* (%)			
T4	7 (41.2)	10 (58.8)	0.303
T6	10 (58.8)	7 (41.2)	
Spinal-to-delivery time (min)	14.29 ± 3.70	14.35 ± 3.69	0.963
Spinal-to-skin closure time (min)	63.35 ± 15.78	67.35 ± 14.89	0.453

Data are described as mean ± standard deviation or number (percentage).
Group I: Crystalloid group; Group II: Crystalloid-colloid group.

Table 3. Velocity time integral (cm), Heart rate (beat/minute) and cardiac output (l/min) of the studied groups.

	Velocity time integral (cm)		*P* value	Heart rate (beat/min)		P value	Cardiac output (l/min)		*P* value
	Group I (N = 17)	Group II (N = 17)		Group I (N = 17)	Group II (N = 17)		Group I (N = 17)	Group II (N = 17)	
Baseline (Preoperative)	20.31 ± 1.84	20.70 ± 2.58	0.617	93.06 ± 14.27	96.41 ± 17.13	0.540	6.39 ± 1.74	6.35 ± 1.44	0.950
5 min postspinal anesthesia	20.35 ± 1.82	21.58 ± 2.45[b]	0.106	90.18 ± 17.40	98.12 ± 14.14	0.154	6.13 ± 1.53	6.72 ± 0.99	0.194
Immediate postdelivery	21.74 ± 1.87[b]	23.76 ± 2.28[b]	0.008[a]	90.88 ± 13.83	97.71 ± 8.85	0.096	6.54 ± 1.53	7.37 ± 0.85[b]	0.060
1 h after induction spinal anesthesia	20.85 ± 1.67	22.38 ± 2.39[b]	0.039[a]	83.47 ± 13.64[b]	88.29 ± 13.16	0.302	5.81 ± 1.28[b]	6.29 ± 1.19	0.264
2 h after induction of spinal anesthesia	20.58 ± 1.55	22.39 ± 2.37[b]	0.013[a]	79.88 ± 12.39[b]	85.94 ± 11.24[b]	0.145	5.52 ± 1.36[b]	6.17 ± 1.46	0.189

Data are described as mean ± standard deviation.
Group I: Crystalloid group; Group II: Crystalloid-colloid group.
[a] Statistically significant difference ($P < 0.05$) between the two groups.
[b] Statistically significant difference ($P < 0.05$) with baseline value within the same group.

Table 4. Left ventricular end diastolic diameter (LVEDD) (cm).

	Group I (*N* = 17)	Group II (*N* = 17)	*P* value
Baseline (Preoperative)	4.30 ± 0.33	4.50 ± 0.29	0.075
Five minutes after induction of spinal anesthesia	4.38 ± 0.42	4.54 ± 0.31	0.214
Immediate post delivery	4.73 ± 0.60[b]	5.20 ± 0.32[b]	0.008[a]
One hour after induction of spinal anesthesia	4.39 ± 0.52	4.90 ± 0.36[b]	0.002[a]
Two hours after induction of spinal anesthesia	4.43 ± 0.39[b]	4.85 ± 0.31[b]	0.002[a]

Data are described as mean ± standard deviation. Group I: Crystalloid group; Group II: Crystalloid-colloid group.
[a] Statistically significant difference ($P < 0.05$) between the two groups.
[b] Statistically significant difference ($P < 0.05$) with baseline value within the same group.

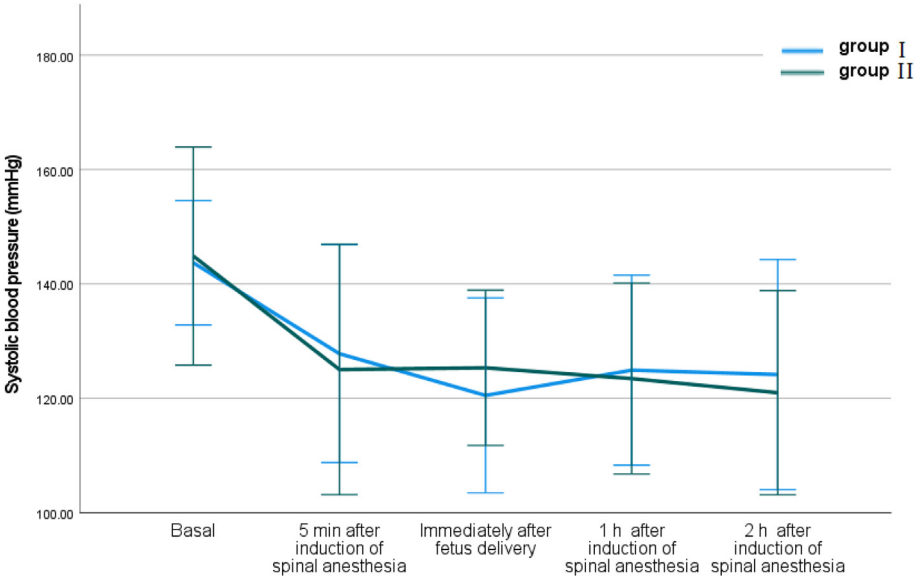

Fig. 2. Comparison of systolic blood pressure (mmHg) between studied groups. Data are described as mean ± standard deviation.

Additionally, UOP at 1, 2 h following induction of SA shows no statistically significant difference between groups (Table 5).

In both groups, the median (minimum–maximum) APGAR score of neonates was 7 (5–7) at 1 min and 10 (7–10) at 5 min postdelivery ($P = 0.112$ and 0.909, respectively).

4. Discussion

This study, conducted on 34 preeclamptic patients underwent CD under SA, did not determine a significant variance in CO when administrate coload of 500 ml 6% HES and 500 ml Ringer's acetate compared with Ringer's acetate (1 l).

Table 5. The incidence of occurrence of hypotension, bradycardia, nausea and/or vomiting besides, the urine output (UOP) and total ephedrine consumption used.

	Group I ($N = 17$) [n (%)]	Group II ($N = 17$) [n (%)]	P value
Number of patients developed bradycardia and required atropine	1 (5.9)	0	0.310
Number of patients developed hypotension	9 (52.9)	4 (23.5)	0.078
Total ephedrine consumption (mg)	5 (0–10)	0 (0–10)	0.099
Number of patients developed nausea and/or vomiting requiring metoclopramide	8 (47.1)	7 (41.2)	0.730
UOP 1 h after induction of spinal anesthesia (ml)	91.76 ± 42.61	93.53 ± 34.08	0.895
UOP 2 h after induction of spinal anesthesia (ml)	244.12 ± 52.69	255.88 ± 74.75	0.599

Data are described as mean ± standard deviation or number (percentage).
Group I: Crystalloid group; Group II: Crystalloid-colloid group.

In the current study, coload fluids were used during CD of preeclamptic patients. The maximum volume expansion occurred at the time of fluid administration (Timing of infusion is possibly a basic key in preventing hypotension) (Oh et al., 2014). So, before SA, large volume of fluid preload is not requested in preeclamptic patients (Pretorius et al., 2018).

In study groups, proper perfusing CO was maintained as there was no statistically significant difference between both groups' measurement at the five points of measurement. Comparing the CO values within the same group; there was increase immediately postdelivery in both group (statistically nonsignificant in group I and significant in group II). This could be due to blood autotransfusion occurred after delivery (Datta et al., 2010).

Furthermore, comparison within the same group, there was significant decrease in CO values at 1 and 2 h after induction of SA in group I which could be explained as crystalloids T1/2 is generally 20–40 min so, its intravascular persistence is short (Hahn and Lyons, 2016).

A recent study by Elsakka and his colleagues on 44 preeclamptic patients scheduled for CD was in agreement with the current study. After SA with 2 ml bupivacaine (10 mg) and 0.5 ml (25 μg) fentanyl, their patients received 500 ml coload over 30 min of either ringer acetate (group R) or voluven (group V). They found that CO had no statistical significance between the two groups in baseline and after 30 min so that, both fluids could maintain proper perfusing CO (Elsakka et al., 2022).

In the same line, McDonald and his colleagues conducted a study on 66 healthy parturients divided into two groups; the crystalloid group (1 l of Hartmann solution) and colloid group (1 l of HES) started at the time of intrathecal injection (of hyperbaric bupivacaine 0.5% 12 mg with fentanyl 15 μg). CO was studied by Cardiac Function Monitor applied before and at 5 min intervals for 20 min after induction of SA. There was no statistically significant difference between two groups in terms of CO and SV (McDonald et al., 2011).

Zhao and colleagues conducted a study on 10 preeclamptic participants who received 2.4 ml intrathecal injection of 0.5% ropivacaine. Immediately after that, 250 ml of IV crystalloid fluid was rapidly initiated. CO measurements showed slight non-significant increase started 4 min after intrathecal anesthetic administration resulted from increased SV rather than HR (Zhao et al., 2020). On contrary to group I in the current study; CO 5 min after induction of SA was nonsignificantly decreased (VTI at 5 min after SA mostly did not differ from basal). The explanation could be that intrathecal bupivacaine induces more reduction in systemic vascular resistance and SV than ropivacaine (Khalil et al., 2024).

Immediately postdelivery; VTI showed a significant increase compared with its basal value in both groups. This can be explained by the increase in blood volume that occurred by uterine contractions during labor, which squeeze blood from the intervillous space into the maternal systemic circulation besides termination of placental circulation resulting in an autotransfusion of almost 500 ml of blood (Datta et al., 2010).

While subsequent significant increase in VTI at 1, 2 h following induction of SA in group II in comparison to its basal value can be explained by the larger molecular weight of colloids preventing it from crossing into the interstitial fluid easily. So, colloid remains in the intravascular space for an extended time compared with crystalloids, promoting more intravascular volume expansion (Gousheh et al., 2018).

LV preload is the tension on the myocardium of LV at the termination of the diastolic phase (end-diastolic wall stress). In clinical practice, it is known as LV end-diastolic pressure or LV end diastolic volume. Routinely, LVEDD could be used for

assessing LV preload (Blanco and Sasai, 2015). In our study, LVEDD demonstrated a statistical increase in group II compared with group I immediately postdelivery, 1 h, 2 h following induction of SA. This is attained by the lengthier stay of colloid in the intervascular space so, permitting greater intravascular volume expansion beside increased osmotic pressure (Gousheh et al., 2018).

Our study found that there was no statistically significant difference between the two groups in terms of HR, SBP, and total amount of consumed ephedrine.

Two studies agreed with this. First, Elsakka and colleagues' study (used 0.5 l of ringer acetate vs. 0.5 l of voluven coload) showed no statistical difference between two studied groups of preeclamptic patients as regard SBP and HR (Elsakka et al., 2022). Similarly, McDonald and his colleagues (used 1 l of Hartmann solution vs. 1 l of HES) documented maintained SBP in two groups besides, no significant change was detected in total phenylephrine consumption or in patients required additional doses (McDonald et al., 2011).

In contrast, a study by Kaufner and colleagues was conducted on 345 healthy pregnant parturients (crystalloid group = 193 vs. colloid group = 152). The dose of bupivacaine was correlated to the patients' height and ranged from 8 to 10 mg of isobaric bupivacaine plus 5 μg sufentanil. Coloading was done with 1000 ml balanced HES or 1 l balanced crystalloid solution. After coloading, patients received an infusion of half liter crystalloid solution up to surgery end of both groups. Their crystalloid group showed greater drop in BP and significantly more incidence of hypotension [93.3% vs. 83.6%] (Kaufner et al., 2019). Their higher incidence of hypotension (although larger coload volume) could be due to that healthy parturients without hypertensive disorders are almost six times more liable to develop hypotension after SA than parturients with hypertensive diseases (Aya et al., 2003).

Sivanna performed a randomized study on 60 healthy parturients underwent elective CD under SA. At the start of spinal injection, participants received 15 ml/kg coload of either 3.5% Haemaccel (colloid group) or lactated ringer (crystalloid group). Hypotension incidence, ephedrine amount was significantly greater in group of crystalloid related to group taking colloid. So, the study recommended that colloid coloading has more efficacy and superiority over crystalloid coloading in preventing maternal hypotension during CD (Sivanna, 2017).

One limitation of the current study is that it did not assess renal function in the postoperative period. Our recommendation is to apply TTE monitoring of LV diastolic function in further research on preeclamptic patients.

4.1. Conclusion

Coloading with 500 ml colloid added to 500 ml crystalloid has the same influence as 1000 ml of crystalloid fluid regarding CO measurement using TTE in cases with PE underwent CD under SA.

Funding

Research didn't receive any fund or grant.

Registration

The study was registered at ClinicalTrials.gov (NCT05435573), approved from Institutional Research Board Faculty of Medicine (code number: MS.22.08.2084).

Conflict of interest

There are no conflicts of interest.

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