

ORIGINAL RESEARCH

REGIONAL ANESTHESIA

Crystalloids versus colloids versus hypertonic saline co-load during spinal anesthesia: which is more effective?

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Abstract

Background: Spinal anesthesia is very commonly accompanied by hypotension due to sympathetic blockade, which leads to vasodilation. There is an ongoing debate concerning pre-load versus co-load and also the best suitable type of fluid to be given, including hypertonic saline (HS). We conducted this study to compare the efficacy of the three solutions, crystalloids vs. colloids vs. hypertonic saline co-load during spinal anesthesia.

Methodology: 120 adult patients were randomly allocated into one of the three groups, each consisting of 40 patients; Group A: received crystalloids (normal saline 0.9% 15 ml/kg), Group B: received colloids (hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride 5 ml/kg) and Group C: received hypertonic saline 3% (3 ml/kg). Serum sodium level, osmolarity, number and doses of ephedrine required, mean arterial pressure (MAP), stroke volume (SV), systemic vascular resistance index (SVRI) and cardiac index (CI) were measured.

Results: MAP, SVRI, CI and SV values were comparable throughout the study time in all the three groups. The need for ephedrine and total doses were statistically significant for the Group B ($p < HS$ group) ($p = 0.02$ and < 0.005 respectively). The changes in serum sodium and osmolarity were significant ($p = 0.005$) but remaining within the normal levels.

Conclusion: The use of hypertonic saline as a co-loading fluid may maintain hemodynamics after spinal anesthesia without the need of infusing large fluid volume making it a good alternative for the use in fluid restricted patients.

Key words: Spinal anesthesia; Hypertonic saline; Colloids

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1. Introduction

Spinal anesthesia (subarachnoid block), a commonly used regional blockade is a good alternative to general anesthesia (GA) for surgeries below the umbilicus for patients in whom GA is contraindicated, or in cases of patient fears or refusal of explained risks.¹ But it is commonly accompanied by hypotension due to vasodilation that follows sympathetic blockade and decreased systemic vascular resistance.¹ Prevention of hypotension is usually achieved through administration of fluids and vasopressors.^{2,3} Fluids are

either administered before initiation of spinal anesthesia which is defined as fluid pre-loading or at the time of initiation of spinal anesthesia which is defined as fluid co-loading.⁴

There is an ongoing debate concerning the proper fluid timing, e.g., pre-load vs. co-load, as well as fluid type to be used, e.g., crystalloids vs. colloids.² Fluid preloading with colloids appears to have superior effect to that of crystalloids, as the later shows a shorter intravascular half-life. While both colloid and crystalloid co-loading show comparable results.^{2,3,5}

Although crystalloid preloading has been the traditional regimen for long time, it failed to reduce the incidence of hypotension. This is because crystalloids rapidly distribute out of the intravascular compartment to the interstitial space.⁶ Superiority of fluid co-loading might be explained by decrease of the extravascular crystalloid redistribution secondary to the simultaneous vasodilatation response to sympathetic block.⁷

Infusion of large volumes of fluids to manage spinal induced hypotension (SIH) can lead to undesirable fluid overload especially in elderly and critically ill patients. Infusion of smaller amounts of hypertonic saline (1.8-7.5%) can maintain the intravascular volume.⁸ Hypertonic saline (HtS) has a higher sodium concentration than isotonic saline. It can help maintaining the intravascular volume through withdrawing fluid from the interstitial space, by increasing intravascular osmolality.^{9,10}

1.1 Objective of Study

This study aimed for comparing the effectiveness of co-loading of crystalloids vs. colloids vs. hypertonic saline 3% on blood pressure changes induced by spinal anesthesia.

2. Methodology

The study was approved by the Institutional Review Board of the National Cancer Institute, Cairo University (IRB No. 201617029.2P) and registered at clinicaltrials.gov (NCT03676699). A written informed consent was taken from all of the patients enrolled in the study. All patients were explained about the technique of spinal anesthesia, the expected hazards and complications including hypotension and how we manage it. Also, the study design, different types of fluids used for resuscitation and the technique of randomization into the 3 studied groups was described. The study was done from March 2018 to August 2018.

2.1 Inclusion criteria

One hundred and twenty adult cancer patients ASA II and III, aged between 18 and 65 y referred to the anesthesia clinic in National Cancer Institute planned for pelvic or lower limb surgeries. Patients were randomized using permuted random blocks method into 3 study groups, each consisting of 40 patients. Group A: received crystalloids (normal saline 0.9% 15

ml/kg) over 15-20 min, Group B: received colloids (hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride 5 ml/kg) over 15-20 min and Group C: received hypertonic saline 3% (3 ml/kg) over 30 min.

2.2 Exclusion criteria

Exclusion criteria were patients with coagulation defects, abnormal kidney or liver functions, local infection at site of injection, uncontrolled hypertension, bone metastases, cardiac disease and elevated baseline serum sodium level > 145 mEq/L.

All patients had routine preoperative assessment conducted as standard (CBC, Liver and kidney function tests, coagulation profile and chest x-ray). Upon arrival to the preoperative area, all the patients were monitored by standard monitoring (ECG, pulse oximetry and non-invasive automated arterial blood pressure). Patients were pre-medicated with midazolam (3-5 mg IV) after fixation of 18 G cannula. In the operating room patients were positioned laterally and under complete aseptic technique a 25 G spinal needle was introduced at the level of L3-4 or L4-5 intervertebral space using a midline approach. Upon identification of the cerebrospinal fluid (CSF), 3.5 ml of heavy bupivacaine 0.5% were injected. Intravenous fluids were started rapidly at its maximum rate according to the designed group. After administration of the bolus study fluid, patients received maintenance fluid using ringer acetate at a rate of 10 ml/kg/h for the 3 studied groups.

If hypotension occurred (defined as a decrease in mean arterial pressure (MAP) \geq 20% of baseline or MAP < 60 mmHg), vasopressor (ephedrine hydrochloride) was given in boluses (6 mg/bolus) and repeated as needed. MAP was measured at baseline then every 5 min and recorded every 15 min in the 1st h then every 30 min for 2 h then by the end of the operation.

Stroke volume (SV), systemic vascular resistance index (SVRI) and cardiac index (CI) were measured and recorded at baseline then every 15 min in the 1st h then every 30 min for 2 h, and by the end of the operation using the non-invasive hemodynamics (Electrical cardiometry™ ICON; Osypka Medical, GmbH. Albert-Einstein-Strasse 3. 12489 Berlin, Germany). Serum sodium, potassium, chloride levels and serum osmolality were measured at baseline (30 min before the spinal), 30, 60 min and after the end of operation. The total blood loss and timing of surgical

onset after spinal anesthesia were kept almost the same to avoid any influences on the BP and in case of severe bleeding patients were excluded from the study (Figure 1).

2.3 Statistical analysis

Based on a previous paper by Lotfy et al.¹¹ the incidence of hypotension among crystalloid group was 50% and among colloid group was 20%. Using power 80% and 5% significance level, 38 patients are required in each group. We used an uncorrected chi-squared statistic to evaluate this null hypothesis. The sample size was calculated by PS program. Data were analyzed using IBM® SPSS® Statistics version 23 (IBM® Corp., Armonk, NY, USA). Data were summarized as a mean and standard deviation or frequency and percentage for categorical data. The comparisons between quantitative variables were made using the unpaired t-test or the Mann-Whitney test. For comparison of the serial measurements within each group, ANOVA for repeated measures or the Friedman test were used. Comparisons of categorical data were made using the Chi-square test or Fisher's exact test as appropriate. All tests were two-tailed. $p < 0.05$ was considered significant.

3. Results

One sixty three patients were recruited into this study, 27 patients were primarily excluded (12 patients refused, 5 patients were converted to GA, 10 patients didn't meet the inclusion criteria) finally 136 patients were randomly allocated into 3 groups. In HS group 46 patients were included (3 were shifted to G.A, 2 developed severe surgical bleeding required massive blood transfusion and 2 had failed spinal block). In NS and colloid groups, 45 patients were included (2, 1 shifted to GA, 2, 2 developed severe surgical bleeding required massive blood transfusion and 1, 2 had failed spinal block respectively) (Figure 1).

Demographic data were comparable for the three studied groups; there was no statistically significant difference between the studied groups in duration of anesthesia, sensory level of the block. The need for ephedrine and total ephedrine consumption were statistically significant to the HS group as compared to NS and colloid groups ($p = 0.02$ and < 0.005 respectively) (Table 1).

Hemodynamic response to spinal anesthesia was assessed by monitoring the changes in MAP (mean arterial blood pressure), SV (stroke volume), SVRI (systemic vascular resistance index) and CI (cardiac index). Hemodynamic responses of each group were compared to their baseline values at different time interval then between the 3 groups at each specific time interval. MAP values were comparable through the study time in the NS, colloid and HS groups except for the HS group who showed statistical significant increase in their values at 45 and 120 min. Comparing the MAP values between the 3 groups, the HS group showed statistical significant difference to NS group at 15 min and to the colloid group at 90 min (Table 2).

SV values were comparable for each group and between the 3 groups throughout the study time (table 2). Regarding SVRI, the 3 studied groups showed a statistically significant decrease in the values when compared to their baseline with no significant difference between the 3 groups, however by the end of study; SVRI values regained to their normal value range (Table 4).

Measurements of CI were comparable to baseline values in NS group, the colloid group showed significant increase in CI values at 15 min compared to baseline while the HS group had increased values at 15 and 30 min. CI values were also statistically significant higher for the HS group compared to the colloid group at 60 min and to the NS group at 150 min (Table 5).

Serum electrolytes (Na^+ , K^+ , Cl^-) and serum osmolarity, were measured and compared for the 3 studied groups at baseline, after 30, 60 min and at end of surgery. Changes in serum Na levels were statistically significant in HS group starting at 30 min and remained till the end of surgery when compared to baseline values, similarly there was a statistical significance after 30 min till the end of surgery between the 3 groups, and these changes were explained by the changes in the HS group when compared to other groups. Regarding serum K^+ and CL levels, values were comparable to baseline in the 3 groups. There was a statistically significant difference in serum K^+ at baseline, 30 and by end of surgery between all groups, while for the CL levels there was a significant change at 30, 60 and by the end of surgery between the 3 studied groups.

Finally, measurements of the serum osmolarity showed statistically significant changes between the 3

groups at 30 min while there was an increase for HS group at 30 and 60 min when compared to baseline. (Table 6).

Figure 1: Consort flow diagram

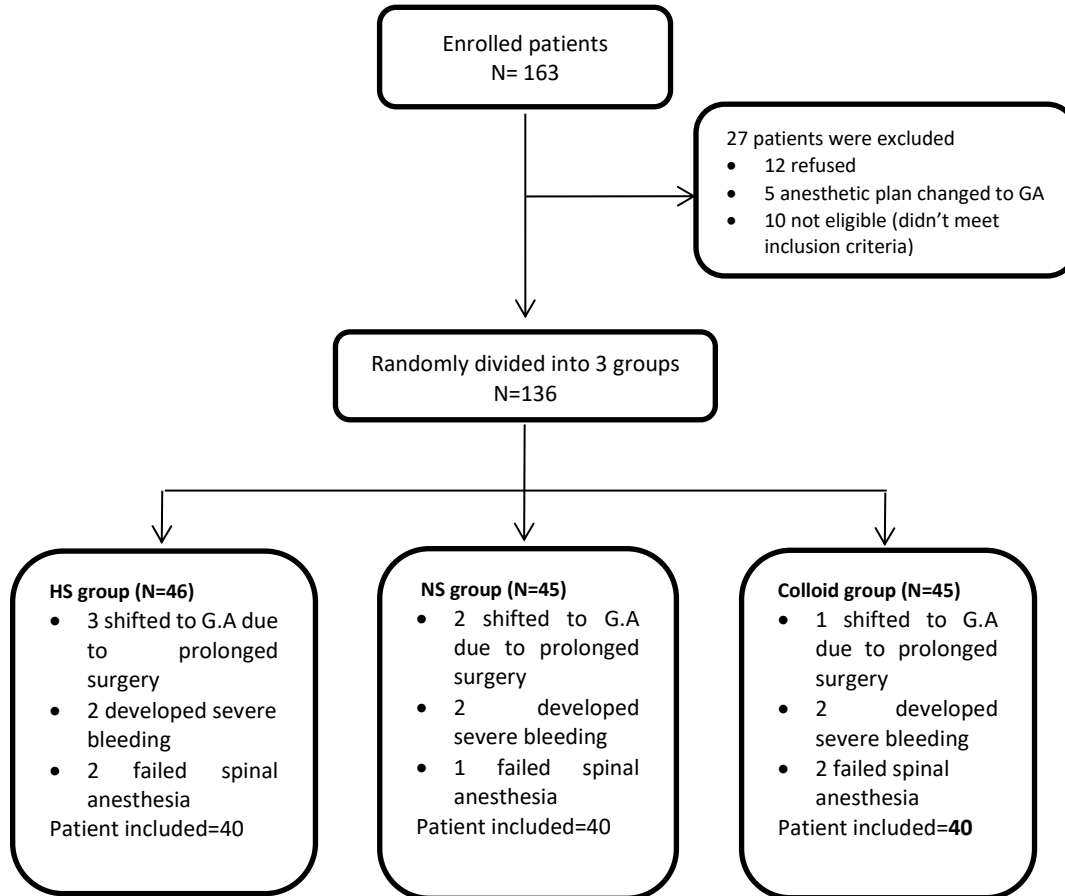


Table 1: Demographic data

Group	NS (n=40)	Colloid (n=40)	HS (n=40)	p value
Age (y)	53 ± 7	54 ± 8	53 ± 4	0.73
Sex (F/M)	18/22	21/19	23/17	0.53
Height (cm)	162 ± 8	159 ± 10	158 ± 12	0.18
Weight (kg)	82 ± 16	75 ± 20	83 ± 15	0.08
Duration of anesthesia (min)	153 ± 30	150 ± 41	156 ± 38	0.76
Sensory level of anesthesia	T6 (T4 - T10)	T7 (T5 - T10)	T6 (T5 - T11)	
Need for ephedrine (n)	17	14	6	0.02
Total dose ephedrine	156 ± 7	134 ± 8	58 ± 7	0.001

p value is considered statistically significant if ≤ 0.05; F (Female), M (Male)

Table 2: Mean arterial blood pressure (MAP) changes over different time intervals

Time	MAP (mmHg)						
	NS	p value*	Colloid	p value*	HS	p value*	p**
0	94 ± 13		95 ± 15		98 ± 7		0.31
15	92 ± 15	0.53	97 ± 13	0.53	100 ± 4	0.12	0.01*
30	93 ± 11	0.71	94 ± 11	0.73	96 ± 6	0.17	0.37
45	92 ± 6	0.38	95 ± 8	1	94 ± 2	0.001*	0.07
60	97 ± 11	0.27	96 ± 7	0.71	97 ± 7	0.52	0.83
90	97 ± 9	0.24	94 ± 7	0.71	99 ± 8	0.55	0.02*
120	95 ± 3	0.63	94 ± 7	0.70	93 ± 4	0.002*	0.2
150	96 ± 8	0.41	95 ± 8	1	98 ± 8	1	0.27
End	95 ± 12	0.72	94 ± 11	0.73	96 ± 7	0.21	0.68

$p \leq 0.05$ is considered statistically significant

p value* for the comparison between the baseline with different time points in the same group.

P**= p value for the comparison among the three groups at different time points.

Table 3: Mean stroke volume (SV) changes over different time intervals

Time	SV (ml)						
	NS	p value*	Colloid	p value*	HS	p value*	p**
0	85 ± 18		86 ± 12		84 ± 14		0.83
15	83 ± 16	0.6	84 ± 11	0.44	83 ± 13	0.74	0.07
30	84 ± 13	0.78	82 ± 9	0.09	84 ± 13	1	0.68
45	83 ± 14	0.58	85 ± 11	0.69	82 ± 16	0.55	0.61
60	84 ± 16	0.79	87 ± 9	0.67	85 ± 12	0.73	0.56
90	82 ± 19	0.47	86 ± 11	1	84 ± 12	1	0.47
120	85 ± 17	1	85 ± 14	0.73	85 ± 11	0.72	1
150	86 ± 16	0.79	84 ± 13	0.48	83 ± 15	0.76	0.65
end	84 ± 17	0.79	85 ± 13	0.72	85 ± 14	0.75	0.94

$p \leq 0.05$ is considered statistically significant

p value* for the comparison between the baseline with different time points in the same group.

P**= p value for the comparison among the three groups at different time points.

Table 4: Systemic vascular resistance index (SVRI) over different time intervals

Time	SVRI (dyn s cm-5 m-2)						
	NS	p value*	Colloid	p value*	HS	p value*	p**
0	2050 ± 215		2030 ± 220		2020 ± 210		0.81
15	1670 ± 184	≤ 0.001*	1735 ± 186	≤ 0.001*	1720 ± 182	≤ 0.001*	0.26
30	1720 ± 195	≤ 0.001*	1690 ± 194	≤ 0.001*	1700 ± 196	≤ 0.001*	0.78
45	1850 ± 180	≤ 0.001*	1805 ± 180	≤ 0.001*	1875 ± 182	0.001*	0.22
60	1810 ± 193	≤ 0.001*	1795 ± 194	≤ 0.001*	1800 ± 195	≤ 0.001*	0.94
90	1730 ± 188	≤ 0.001*	1760 ± 185	≤ 0.001*	1770 ± 186	≤ 0.001*	0.61
120	1870 ± 186	≤ 0.001*	1830 ± 184	≤ 0.001*	1880 ± 183	0.002*	0.44
150	1910 ± 190	0.002*	1905 ± 192	0.008*	1900 ± 194	0.009*	0.97
End	2010 ± 195	0.38	2015 ± 197	0.75	2005 ± 196	0.74	0.97

$p \leq 0.05$ is considered statistically significant

p value* for the comparison between the baseline with different time points in the same group.

p**= p value for the comparison among the three groups at different time points.

Table 5: Cardiac index over different time intervals

Time	CI (L min-1 m-2)						
	NS	p value*	Colloid	p value*	HS	p value*	p**
0	2.80 ± 0.55		2.74 ± 0.62		2.78 ± 0.64		0.9
15	3.02 ± 0.61	0.09	3.01 ± 0.53	0.04*	3.11 ± 0.65	0.02*	0.71
30	2.94 ± 0.56	0.26	2.86 ± 0.61	0.38	3.08 ± 0.58	0.03*	0.24
45	2.86 ± 0.52	0.62	2.76 ± 0.58	0.88	3.01 ± 0.61	0.1	0.15
60	2.78 ± 0.64	0.88	2.72 ± 0.48	0.87	3.03 ± 0.62	0.08	0.05*
90	2.68 ± 0.72	0.41	2.71 ± 0.52	0.82	2.98 ± 0.67	0.17	0.08
120	2.73 ± 0.62	0.59	2.74 ± 0.58	1	3.01 ± 0.62	0.11	0.06
150	2.70 ± 0.63	0.45	2.71 ± 0.54	0.82	3.03 ± 0.64	0.08	0.03*
End	2.74 ± 0.55	0.63	2.76 ± 0.58	0.88	2.94 ± 0.61	0.25	0.24

$p \leq 0.05$ is considered statistically significant

p value* for the comparison between the baseline with different time points in the same group.

p**= p value for the comparison among the three groups at different time points.

Table 6: Serum sodium, osmolality, chloride and K+ levels over different time intervals

Parameter	Time	NS	p value*	Colloid	p value*	HS	p value*	p**
Serum Na+ (mmol/L)	0	134 ± 3		135 ± 2		134 ± 2		0.09
	30	133 ± 2	0.08	135 ± 1	1	143 ± 3	< 0.001*	< 0.001*
	60	134 ± 1	1	134 ± 3	0.08	141 ± 3	< 0.001*	< 0.001*
	End	133 ± 3	0.14	134 ± 4	0.16	139 ± 1	< 0.001*	< 0.001*
Serum Osmolality (mmol/Kg)	0	291 ± 4		290 ± 7		288 ± 6		0.07
	30	290 ± 7	0.43	288 ± 5	0.15	292 ± 4	< 0.001*	0.006*
	60	292 ± 5	0.33	289 ± 6	0.49	291 ± 6	0.03*	0.06
	End	291 ± 5	1	288 ± 7	0.21	290 ± 7	0.17	0.11
Serum CL- (mmol/L)	0	107 ± 3		106 ± 2		107 ± 4		0.26
	30	106 ± 4	0.21	107 ± 3	0.08	108 ± 2	0.16	0.02*
	60	107 ± 2	1	106 ± 4	1	108 ± 3	0.21	0.02*
	End	106 ± 4	0.21	105 ± 5	0.25	108 ± 3	0.21	0.05*
Serum K+ (mmol/L)	0	3.8 ± 0.2		3.6 ± 0.4		3.7 ± 0.3		0.02*
	30	3.7 ± 0.3	0.08	3.7 ± 0.4	0.27	3.7 ± 0.2	1	0.02*
	60	3.7 ± 0.4	0.16	3.6 ± 0.5	1	3.7 ± 0.3	1	1
	End	3.8 ± 0.4	1	3.5 ± 0.1	0.13	3.6 ± 0.4	0.21	< 0.001*

$p \leq 0.05$ is considered statistically significant

p value* for the comparison between the baseline with different time points in the same group.

p**= p value for the comparison among the three groups at different time points.

4. Discussion

Spinal anesthesia is preferred whenever possible in lower limb and pelvic surgeries, as it decreases blood loss, with subsequent decrease in rate of blood transfusion in addition to reduction in the incidence of thromboembolism;¹² additionally in our patient population who suffers from cancer it is assumed that regional analgesia may offer benefits over GA and usage of systemic opioids in decreasing cancer recurrence rate.¹³⁻¹⁶

On the other hand, spinal anesthesia results in preganglionic sympathetic blockade followed by drop in the systemic vascular resistance (SVR) and reduction in blood pressure and cardiac output.¹⁷ The incidence of hypotension following spinal anesthesia ranges from 25% up to 75%.¹⁸ In order to overcome hypotension following spinal anesthesia infusion of fluids either by preloading or co-loading as well as administration of vasopressors is adopted. There is still

an ongoing debate about the ideal fluid for co-pre hydration.¹⁹ Crystalloids are widely used for prevention of hypotension associated with spinal anesthesia, with the co-loading timing being preferred than the preloading one.^{20,21} When crystalloid is used, large volume is needed to be infused and this results in large amount of excess free extracellular water.²² Although colloids offers a good alternative to crystalloids with less extracellular excess free water but concerns about their high cost, possibility of inducing coagulopathy and allergic reactions still limit their use.²³

Crystalloid and colloid co-loading can effectively prevent hypotension following spinal anesthesia, decrease the need for vasopressors and reduce the incidence of nausea and vomiting.¹¹ A good alternative to crystalloids and colloids is using hypertonic saline. Hypertonic saline is used in variable concentrations starting from 1.8% to 7.5 %, ²² infusion of HS results in withdrawal of extracellular water to the intravascular

space secondary to its high osmolarity thus improving hemodynamics, it has been used in different conditions including hypovolemic, cardiogenic and hemorrhagic shocks.²⁴⁻²⁷

In the current study authors compared the co-loading of crystalloids, colloids and hypertonic saline effect in prevention of hypotension and their effect on hemodynamics following spinal anesthesia for cancer patients undergoing pelvic or lower limb surgeries. It was found that using crystalloids and colloids as well as hypertonic saline (HS) 3% have comparable results.

Mean arterial blood pressure was one of the hemodynamic measures used to assess and compare HS to NS and colloid co-loading. The recorded measures were comparable between the 3 groups except for the HS group which showed elevated MAP values at 15 and 90 min, thus HS is as effective as crystalloids and colloids with lesser infused fluid volume. This is in agreement with Järvelä et al.,²⁸ who compared the effect of hypertonic saline 7.5% versus normal saline as preloading solutions for spinal anesthesia. They reported that hypertonic saline is a good alternative to normal saline for prophylaxis of hemodynamic instability sequelae of spinal anesthesia. This was followed by another study done by Järvelä in 2001²² concluding that the use of hypertonic saline 7.5% may be more beneficial in maintaining hemodynamic stability than normal saline in cases where excess free water is undesirable. Wang et al.,²⁹ compared pre-loading lactated ringer solution with hypertonic saline 3% for patients undergoing spinal anesthesia; they stated that hypotension associated with spinal anesthesia could be prevented by small amount of hypertonic saline with no increase in excess body water. Talaat et al.,³⁰ compared the efficacy of hypertonic saline versus normal saline and colloids preload in preventing hypotension following spinal anesthesia in patients undergoing cesarean section. They reported that hypertonic saline is effective and safe in prevention of hypotension associated with spinal anesthesia especially in patients whom excess free water is not desired. When comparing isotonic solutions to colloid solutions and hypertonic solutions for perioperative use and trauma patients resuscitation, Kramer³¹ stated that using hypertonic solutions in small volumes effectively expand the intravascular volume secondary to their ability to mobilize extravascular water and expanding the blood volume

this is superior to the effect of isotonic solution where only small volume of it remains in the circulation, whereas using colloids expands the intravascular volume only in a volume equivalent to the infused quantity.

There was no change in SV measurements for the studied groups with comparable values. Although there was a comparable decrease in SVRI for the 3 groups secondary to sympathetic blockade following spinal anesthesia, but the CI was maintained with statistically significant difference in CI between the 3 groups at 60 and 150 min and this may be attributed to intravascular volume expansion after fluid co-loading especially with colloids and HS. These results were supported by study done by McAlister and colleagues⁹ who reviewed 15 randomized controlled trials including 614 patients comparing peri-operative hypertonic saline (HS) administration versus isotonic saline (IS). They stated that patients who received HS had lesser volume of fluid administered intra-operatively than the normal saline group patients with no difference in diuresis. They reported increase in the intraoperative cardiac index for HS group with no increase in intraoperative pulmonary capillary wedge pressure. This is in agreement with Azoubel and colleagues,³² who reviewed 30 studies which investigated the use of hypertonic saline in different operative settings including cardiac surgeries, repair of aortic aneurysm, neurosurgery, abdominal hysterectomy as well as minor operations. They concluded that using hypertonic saline resulted in an increase in the cardiac index, decrease in the systemic vascular resistance as well as reduction of positive fluid balance.

An increase in serum Na⁺ level was observed after 30 min till the end of surgery for the HS group. Although there was a statistically significant difference between all groups being higher for the HS group but serum sodium remained within its normal accepted plasma level range. Same was reported in McAlister and colleagues⁹ review and Wang et al.,²⁹ who stated transient increase in serum sodium level after using HS for patients undergoing spinal anesthesia. Furthermore, McAlister and colleagues⁹ reported that the infusion of hypertonic saline can result in an increase in serum osmolarity similarly in this study, there was a transient rise in serum osmolarity for HS group that was normalized by the end of surgery.

5. Conclusion

The use of hypertonic saline as a co-loading fluid can maintain hemodynamics in patients under spinal anesthesia without the need of infusing large fluid load making it a promising tool that can be used in patients with congestive heart failure, chronic kidney disease or in any fluid restricted patients. The results of this study can be used for further large multi-centric trials including such varieties of patients to determine the safety of hypertonic saline in this context and to identify the maximum allowed volume that can be given in such critical conditions requiring spinal anesthesia.

6. Conflict of interest

None declared by the authors.

7. Authors' Contribution

EH: Concept, data collection statistical analysis and manuscript editing.

WY: help in data collection, manuscript writing and patients' explanation

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