Comparative Study between Volume Preload versus Ephedrine Infusion for Prevention of Hypotension Due to Spinal Anesthesia for Caesarean Section

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Abstract: A caesarean section (C-section), is a form of childbirth in which a surgical incision is made through a mother's abdomen (laparotomy) and uterus (hysterotomy) to deliver one or more babies. It is usually performed when a vaginal delivery would lead to medical complications. The anesthetic plan for cesarean delivery should take into account the well-being of two patients: the mother and the fetus. Regional anesthesia is the most common method of anesthesia for delivery because it allows the mother to be awake and immediately interact with her baby. It is also safer for the mother than general anesthesia. Regional anesthesia is used for 95 percent of planned cesarean deliveries in the United States. The aim of this study is to evaluate the efficacy of ephedrine infusion versus preload crystalloid administration in reducing the incidence of hypotension during spinal anaesthesia. This study was conducted in the obstetric department of Al Matarya Teaching Hospital on fifty parturient undergoing elective caesarean section after the approval of the ethical medical committee. A written consent was taken from all patients who were either class II according to the classification of the American society of Anesthesiologists ASA II. This study was a prospective double blind randomized controlled study where the patients were allocated into 2 equal groups 25 patients each. We concluded that prophylactic IV Ephedrine infusion is more effective than fluid preload in prevention of hypotension due to spinal anesthesia for cesarean section without causing significant tachycardia or hypertension.

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1. Introduction

A caesarean section (C-section), is a form of childbirth in which a surgical incision is made through a mother's abdomen (laparotomy) and uterus (hysterotomy) to deliver one or more babies. It is usually performed when a vaginal delivery would lead to medical complications. The anesthetic plan for cesarean delivery should take into account the well-being of two patients: the mother and the fetus. Regional anesthesia is the most common method of anesthesia for delivery because it allows the mother to be awake and immediately interact with her baby. It is also safer for the mother than general anesthesia. (1)

Spinal anesthesia is often used for genital, urinary tract, or lower body procedures. A successful regional anaesthesia effectively suppresses many of the pain mediated stress responses to surgery such as rise in blood pressure, heart rate and increase in plasma concentrations of catecholamines, cortisol and glucose. Spinal block is also associated with lesser amount of surgical haemorrhage. (2)

Spinal anaesthesia produces few adverse effects on the respiratory system as long as unduly high blocks are avoided. (3) As control of the airway is not compromised, there is a reduced risk of airway obstruction or the aspiration of gastric contents. post-operative deep vein thrombosis and pulmonary emboli are less common following spinal anesthesia. (4)

Hypotension is the most common complication of spinal anaesthesia for cesarean section. It can cause significant morbidity and mortality. It could be associated with severe nausea and vomiting and serious risk to the mother (unconsciousness and pulmonary aspiration) and baby (hypoxia, acidosis, and neurological injuries). (5)

Hypotension is due to sympathetic nervous system blockade which result to decreased systemic vascular resistance and peripheral pooling of blood with decreases cardiac output. Aortocaval compression (ACC) can result in haemodynamic disturbances and uteroplacental hypoperfusion in parturients. The incidence of hypotension and high spinal anaesthesia is higher in cesarean sections (6).

Various attempts have been made to reduce the incidence and severity of hypotension including expansion of intravascular volume with up to 2liters of fluids. The use of lateral uterine displacement is a routine procedure to prevent hypotension. intravenous fluid preload has been shown to reduce the risk of hypotension but doesn't eliminate it and many patients

still need vasopressor treatment to correct hypotension. parenteral ephedrine may be an effective alternative. [7]

Ephedrine is a non-catecholamine sympathomimetic agent that stimulates alpha and beta adrenergic receptors directly and predominantly indirectly, producing its effects by releasing norepinephrine from nerve endings in the autonomous nervous system. Traditionally it is the vasopressor of choice in spinal anesthesia despite the lack of confirmation of its superiority over other vasopressors. [8]

Aim of the Work

The aim of this study is to evaluate the efficacy of intravenous ephedrine versus preload crystalloid administration in reducing the incidence of hypotension during spinal anaesthesia.

2. Patients and Method:

This study was conducted in the obstetric department of Al Matarya Teaching Hospital on fifty parturient undergoing elective caesarean section after the approval of the ethical medical committee.

A written consent was taken from all patients who were either class I or II according to the classification of the American society of Anesthesiologists ASA I, II.

This study was a prospective double blind randomized controlled study where the patients were allocated into two equal groups twenty five patients each: Group F & Group E (by closed envelope method):

- **Group F:** those who received crystalloid preloading.
- **Group E:** those who received prophylactic ephedrine intravenously after spinal anesthesia.

Inclusion criteria:

- The patient selected according to ASA status (ASA I, II).
- prime gravida
- Normal coagulation profile.
- Age range between 20 till 45 years old.
- BMI not more than 35
- Height 160 to 170 cm.

Exclusion criteria:

- Patient refusal.
- Hypertensive and Diabetic patients.
- Pre-eclampsia and eclampsia.
- Patients having any coagulopathy disorder or receiving any anticoagulant drugs.
- Patients with signs suggesting cardiac or respiratory system failure.
- Infection at site of the injection.
- Patients with known history of allergy to local anaesthetics' drugs.
- Any pre-existing neurological or psychological disease.

Statistical Analysis

A prospective power study showed that a sample size of 25 per study group will have 80% power at the 5%signficance level to detect a difference of 50%in the incidence of hypotension in the E group compared with F group assuming a baseline incidence of 80% as reported by a published study of a similar patient group.

Statistical analysis will be done with mixed ANOVA design to compare inter-groupal & intra-groupal results.

Obtained data will be presented as mean ± standard deviation or median, interquartile range (IQR) or count & percentage as appropriate.

Comparisons will be performed using student t-test, Chi square test, or analysis of variance according to type of variance data.

Data will be analyzed using computer package SPSS (version 20, 2012) and Microsoft Excel 2013.

P value $\leq$ 0.05 will be considered statistically significant.

3. Results

Fifty patients were recruited for this study and randomly allocated into 2 groups, F group (fluid) and E group (ephedrine).

1) Demographic Data:

They showed no significant differences as regard age, BMI, height and parity (table 1).

Table (1): Demographic Data of patients included in the study

	F Group	E Group	*P* value
Age	27 (20-39)	27 (20-40)	0.21
BMI	35.2±1.7	35.3±1.7	0.40
Height	162.7±2.9	163.3±3.7	0.24
Parity	2 (0-4)	1(0-5)	0.44

Data represented as Mean ± *SD* or Median (Range)

2) Blood Pressure:

SBP was generally higher in E group when compared to F group, however the results were statistically unsignificant except at 4 and 22 min. post spinal. (Table 2. Incidence of hypotension was

significantly lower in E group 6/25 (24%) when compared to F group12/25 (12%), P value (0.03).

3) Heart rate:

The heart rate was generally higher in E group when compared to F group, In (F Group) mean pulse rate changed from baseline of 90.1 ± 8.5 to a maximum of 92.6 ± 11.7 at 28 minute. In (E Group) mean pulse rate increased from baseline of 92.5 ± 5 to maximum of 95.6 ± 8 at 7 minute after spinal block, however it was not statistically significant (table 3) (figure 5).

Table (2): Systolic BP

	F Group	**E Group**	***P* value**
Baseline	122.6±7.8	119 ±9.9	0.09
1 min	116.3±12.3	116.4±12.3	0.48
4 min	103.9±8.8	110.2±15.5	0.04*
7 min	110.6±12.8	111.7±13.7	0.4
10 min	111.7±10.1	112.4±13.2	0.4
13min	108.7±6.6	110.4±12.0	0.3
16 min	111.4±10.2	115.6±10.9	0.08
19 min	111.9±10.9	113.7±13.5	0.3
22 min	112.1±11.8	117.8±10.8	0.04*
25 min	113.3±8.6	116.4±9.7	0.1
28 min	113.3±12.5	117.5±11.9	0.08
31 min	114.3±8.3	118.1±9.7	0.0
36 min	112.4±9.7	116±9	0.0
41 min	115.1±6.1	116.2±6.0	0.3
46 min	113.4±6.8	116.4±9.8	0.1
51 min	117.0±5.4	118±6.7	0.3
56 min	119.1±9	119.7±6.2	0.4
61 min	122.5±6.2	122.9±5.2	0.4
90 min	120.5±6.5	121.4±7.59	0.3

Data represented as Mean ± SD; *= P value ≤ 0.05

Table (3): Heart Rate trends.

	F Group	**E Group**	***P* value**
Baseline	90.1±8.5	92.5 ±5	0.1
1 min	92.7±13.4	93.9±7.4	0.35
4 min	90.5±16.5	92.2±9.1	0.32
7 min	91.9±13	95.6±8	0.11
10 min	92±10.6	94.7±9.5	0.17
13min	91.5±11.3	94.7±10.6	0.15
16 min	91.6±8.8	95±10.4	0.11
19 min	90±10.5	93.2±8.4	0.11
22 min	87.9±13.6	91.6±7.5	0.11
25 min	90.6±14.2	92.6±9.2	0.27
28 min	92.6±11.7	94.2±9.6	0.3
31 min	91.2±9.4	94.5±8.9	0.10
36 min	91±10.9	93.4±8.4	0.2
41 min	90.7±12	91.2±6.5	0.42
46 min	88.7±10.9	91.4±7.2	0.10
51 min	88.4±9.4	91.4±7.2	0.10
56 min	87.9±8.7	90.5±5.6	0.10
61 min	88.3±9	91±5.9	0.10
90 min	85.6±9.5	87.7±6.3	0.17

Data represented as Mean ± *SD*

4) Incidence of complications:

Regarding incidence of complications; incidence of hypotension was significantly higher in F group when compared to E group, incidence of nausea and vomiting was higher in F group when compared to E group but it was not statistically significant, and there was no chest symptoms in both groups (table 4) (figure 6).

Table (4): Incidence of Complications:

	F Group	E Group	*P* value
Hypotension	12/25(48%)	6/25(24%)	0.03 *
Nausea & Vomiting	5/25(20%)	3/25(12%)	0.23
Chest symptoms	0/25(0%)	0/25(0%)	0

Data represented as Number of positive cases /total number of patients (%)
*= *P* value ≤ 0.05

5) Number of ephedrine boluses:

Number of boluses of ephedrine required to correct hypotension were significantly lower in ephedrine group when compared to fluid group (f group) 0.6±0.8 and (E group) 0.3±0.54 with a p value 0.046 (table 5) (figure 7).

Table (5): Number of ephedrine boluses required to correct hypotension:

	F Group	E Group	*P* value
Number of boluses	0.6±0.8	0.3±0.54	0.046*

Data represented as Mean ± *SD*
*= *P* value ≤ 0.05

6) Oxygen saturation:

Regarding oxygen saturation there was no significant differences between the 2 groups (table 6).

Table (6): Oxygen saturation:

	F Group	E Group	*P* value
Baseline	98.5±0.8	98.3±0.7	0.23
30 min	99.7±0.5	99.8±0.4	0.26
60 min	99.8±0.4	99.8±0.4	0.5
90 min (Post)	98.9±0.5	98.7±0.6	0.11

Data represented as Mean ± *SD*

4. Discussion

Spinal anaesthesia is considered to be safe as compared to general anaesthesia for caesarean section. General anesthesia is associated with higher mortality rate in comparison to regional anesthesia. However spinal anesthesia is not without risk, Hypotension during caesarean section under spinal anaesthesia is very frequent and if not prevented, it can induce complication for the mother and/ or the fetus [9].

Untreated, severe hypotension can pose serious risks to both mother (unconsciousness, pulmonary aspiration, apnoea or even cardiac arrest) and baby (impaired placental perfusion leading to hypoxia, fetal acidosis and neurological injury). Even mild hypotension can reduce the uteroplacental blood flow and can contribute to fetal acidosis [10].

Intravenous preloading is the most popular non-pharmacological method. Early studies had impressive results and it became established as an accepted standard of care. However, more recent controlled studies have questioned the efficacy of preloading. Some had shown that it reduced the severity of hypotension, and some showed that preloading have minimal effect on the incidence of hypotension [11].

Vercauteren et al. (2000) stated that ephedrine is the vasopressor of choice for hypotension associated with spinal anesthesia in the parturient because of its ability to maintain uteroplacental blood flow since Ephedrine's action is considered to be mainly indirect, via stimulating release of norepinephrine from sympathetic nerve terminals; and the uteroplacental circulation is largely devoid of direct sympathetic innervation, so it is relatively resistant to the vasoconstrictive effects of ephedrine. The appropriate route and dose of ephedrine that should be used to prevent hypotension after spinal anaesthesia during caesarean section still remains controversial. [12]

In this study we compared the efficacy of fluid preloading with 15ml/Kg ringer (F group) versus prophylactic IV ephedrine infusion without fluid

preload (E group) for prevention of hypotension after spinal anesthesia for cesarean section.

The changes in blood pressure are related to the level of block, and the risk of hypotension increase with height of block due to higher level of sympathetic block. [13] In this study, there was no significant difference in the distributions by dermatome levels for patients of both groups ranged between T4 – T5 upper sensory level block, so patients treated was having similar degrees of sympathetic block. Therefore, the differences in the incidence of hypotension observed between the two groups to were due to presence or absence of preventive measures only.

Our findings showed that SBP was generally higher in ephedrine group when compared to fluid group and it was high statistically significant difference found between two groups from 4min till 28min post spinal, statistically significant difference found between two groups from 33min till 38min post spinal. The heart rate was generally higher in E group when compared to F group, In (F Group) mean pulse rate changed from baseline 89.68 ± 0.48to a maximum of 92.64 ± 1.21at 16 minute. In (E Group) mean pulse rate increased from baseline of 92.40 ± 0.71to maximum of 95.12 ± 1.33at 7 minute after spinal block. Number of boluses of ephedrine required to correct hypotension were significantly lower in ephedrine group (E group) 1.60±0.71 when compared to fluid group (f group) 2.20±0.96 and with a p value 0.015.

Also the incidence of nausea and vomiting was lower in the E group when compared with F group.

Gajraj et al. (1993) [14] compared the efficacy of an ephedrine infusion with crystalloid administration for reducing the incidence of hypotension during spinal anesthesia for patients scheduled for postpartum tubal ligations under spinal anesthesia, the patients were randomly allocated to receive either 15 mL/kg of crystalloid (crystalloid group) or ephedrine infusion (infusion group). Spinal anesthesia was performed using 70-90 mg of hyperbaric 5% lidocaine. Patients in the infusion group immediately thereafter received an ephedrine infusion at the same rate as in our study. He found that the incidence of hypotension was significantly higher in the crystalloid group compared to the infusion group ($P < 0.05$). There was no significant difference between the groups in relation to the level of anesthesia or maximal heart rate, and hypertension did not occur in either group which is similar to our results but there was no difference in the incidence of nausea and vomiting in contrast with our study, which may be due different type of patient (pregnant versus non pregnant) and different type of surgical procedure (cesarean section versus postpartum tubal ligation).

Bhovi et al. (2014) [15]**,** studied the efficacy of ephedrine for preventing hypotension in patients undergoing caesarean section under spinal anesthesia. The patients were randomly allocated to receive either ephedrine infusion 50mg in 500ml of Ringer's Lactate immediately after administration of spinal anesthesia at rate of 50ml/min for first 2 minutes, and 10ml/min for next 18 min. or 20ml/kg of Ringer's Lactate solution as preloading solution prior to subarachnoid block. The study revealed that the incidence of hypotension was significantly higher in the patient group who received fluid preload (60%) compared with (12%) in the patients group who received ephedrine infusion. The incidence of hypotension in the ephedrine group in this study was (12%) in comparison with our study the incidence of hypotension in the ephedrine group was (24%), this difference may be due to different doses of ephedrine used and different volume of infusion.

In contrast to this study; ***Thiangtham et al. (2009)*** [16] performed a concealed randomized study, 96 parturients were divided into two groups, the study group received ephedrine 18 mg (3 ml) added to 100 ml normal saline, while the control group received 3 ml of normal saline instead of ephedrine given by intravenous continuous infusion over 10 minutes. All patients had preloading fluid with lactated Ringer's solution 20 ml/kg 10 minutes before spinal block was done with 0.5% hyperbaric bupivacaine mixed with preservative free morphine. He found that there was no statistically significant difference in the incidence of hypotension between the two groups, the incidence of hypotension was 93.8% in the control group and 85.4% in the study group, this may be due to the small dose of ephedrine used and different infusion rate.

In contrast to this study; ***Iclal et al. (2009)*** [17] designed a randomized, double-blinded study to determine the efficacy and safety of 0.5 mg/kg intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery, and its effect on neonatal outcome and umblical artery PH. Patients were randomly allocated into two groups: ephedrine group and control group. All patients received preloading with 15ml/kg lactated ringer before spinal block, patients of the ephedrine group were injected with 0.5mg/kg ephedrine intravenously over 60 seconds while patients of control group were injected with saline. He found that there were significant lower incidences of hypotension and nausea and vomiting in the ephedrine group compared with the control group.

In consistence with our results, **Minj et al. (2018)** [18] comparing the incidence of hypotension and the need for vasopressors in patients submitted to caesarean section under spinal anaesthesia following preload crystalloid with vasopressors conclude that

the combined use of volume preloading to compensate for vasodilatation and vasopressor to counteract arterial dilatation is a very effective method in reducing the incidence, severity and duration of spiral hypotension. The combination group with decreased volume of preload and reduced dose of vasoconstrictor provides better haemodynamic stability when compared to preloading of vasoconstrictors alone. It differ from our study by different method (combined preload and vasopressor group and preloading of vasoconstrictors alone group)

Limitations in our study; the umbilical artery PH and neonatal APGAR score were not measured to demonstrate the effect of ephedrine on acid base status of the fetus and whether it is clinically significant or not.

Recommendations for further studies; to compare neonatal APGAR score and fetal acid base status in both groups ephedrine and phenylephrine.

Conclusion

We concluded that prophylactic IV Ephedrine infusion is more effective than fluid preload in prevention of hypotension due to spinal anesthesia for cesarean section without causing significant tachycardia or hypertension.

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