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CO-ADMINISTRATION OF PHENYLEPHRINE TO OFFSET OXYTOCIN-INDUCED HYPOTENSION IN LOWER SEGMENT CAESAREAN SECTION (LSCS): A PROSPECTIVE RANDOMISED DOUBLE-BLINDED STUDY

Anaesthesiology

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ABSTRACT

Introduction- Spinal induced hypotension has been recorded in 85 percent of parturients following LSCS and is the most common consequence, offering a significant treatment challenge. The purpose of this study is to assess the effect of co-administration of 100mcg phenylephrine and 5IU oxytocin as a bolus on oxytocin-induced hypotension during LSCS under SAB. **Methodology-** Patients were randomly assigned to receive phenylephrine (P100) [GROUP-A] or saline (P0) [GROUP-B] in this prospective randomised double-blinded research. During the LSCS technique, theincidence of hypotension, comprising various vital signs and sequelae, was evaluated and compared during intra-operative procedures. **Results-** All the demographical parameters were comparable in both groups. The majority of Group-A patients had zero number of episodes of hypotension [n=30(81.08%] followed by one [n=6(16.22%] and two [n=1(2.70%], respectively. Whereas, the majority of Group-B patients had two number of episodes of hypotension [n=27(72.97%] followed by one [n=4(10.81%] and three [n=4(10.81%], respectively and a statistically significant difference was found between them (P<0.0001*). **Conclusion-** Co-administration of oxytocin 5 IU and phenylephrine 100 mcg during caesarean delivery under spinal anaesthesia significantly lowers the incidence of oxytocin-induced hypotension compared to oxytocin alone.

KEYWORDS

Phenylephrine, Oxytocin-induced hypotension, Lower segment caesarean section

INTRODUCTION

Spinal anesthesia is a commonly utilized approach for caesarean delivery because it avoids the hazards associated with general anesthesia, such as difficult intubation and aspiration of gastric contents. **[1]** In 1898, German Surgeon Karl August Bier introduced spinal anesthesia into clinical practice. Over the last several decades, there has been a global movement in obstetric anesthetic practice toward regional anesthesia, with spinal anesthesia being the most prevalent. Today, it is one of the most often used techniques for surgeries involving the lower limbs and abdomen, including caesarean section. Subarachnoid block is the preferred technique of anesthesia for LSCS since it is associated with decreased maternal mortality and improved neonatal prognosis. **[2]** Spinal induced hypotension in parturients undergoing LSCS has been reported in 85% of the patients and is the most prevalent complication, posing a considerable therapeutic challenge. **[3]** Postpartum haemorrhage (PPH) is a leading cause of maternal death, with uterine atony accounting for around 50% of cases. It can be minimised with the proper use of uterotonic medications, oxytocin being the most frequently used.

Oxytocin increases uterine muscle tone and is used to induce delivery at term, decrease and avoid uterine atony, hence reducing postpartum haemorrhage. Routine prophylactic usage of oxytocin lowers PPH incidence by 40%. **[4]** However, oxytocin has the undesirable consequence of hypotension and reflex tachycardia, as oxytocin receptors are also found in the heart and major arteries. **[5]** Pregnant patients at term are more likely to suffer hypotension due to aortocaval compression by the foetus and enhanced sympathetic blockade caused by increased local anaesthetic distribution in the CSF. Post spinal hypotension persists despite numerous attempts to lower its severity. **[6]** A decrease in systemic blood pressure occurs due to systemic vasodilation consequent to sympathetic blocking caused by intrathecal local anaesthetic injection. Hypotension can be hazardous to both mother and infant during spinal anaesthesia for caesarean delivery. The foetal adverse effects include decreased uteroplacental blood flow, impaired placental perfusion resulting in hypoxia, foetal acidosis, neurological injury, detrimental impact on uterine blood flow, and ultimately adverse neonatal outcomes as measured by umbilical artery pH and APGAR score. **[7]** Maternal consequences of untreated severe hypotension are nausea, vomiting, dyspnoea and cardio-vascular collapse. As a result, all efforts are made for preventing and manage hypotension during obstetric anaesthesia. Various measures like careful positioning and volume preloading have been used in order to avoid it. Rapid infusion of high volumes of crystalloids increases the risk of pulmonary oedema and postoperative urine retention. Moreover, they alone are insufficient measures, **[8-9]** and a vasopressor is necessary to rectify/prevent hypotension rapidly. Numerous vasopressors have been used to prevent oxytocin-induced hypotension, including ephedrine, mephentermine, and phenylephrine. Ephedrine, frequently administered during caesarean surgeries, acts, directly and indirectly, stimulating mainly β-receptors (β1 and β2), increasing cardiac output, heart rate, systolic and diastolic blood pressure. **[10]** However, it has been shown to worsen maternal tachycardia and precipitate arrhythmia. In the treatment of hypotension, phenylephrine, a selective alpha-1 adrenergic agonist, is as effective as ephedrine. It causes an increase in the pH of the umbilical artery and a decrease in fetal acidosis. **[11]** Hypotension and reflex tachycardia caused by oxytocin can be treated with phenylephrine, a rapid onset vasopressor with minimal placental transit. Combining phenylephrine and oxytocin has been shown to decrease oxytocin-induced hypotension after Caesarean section under spinal anesthesia, while greater doses may cause reflex bradycardia. The purpose of this study is to determine the effect of co-administration of phenylephrine (100mcg) with 5IU of oxytocin as a bolus on oxytocin-induced hypotension during LSCS under SAB.

MATERIAL AND METHOD

This prospective randomised double-blinded study was carried out at the Department of Anaesthesiology, Era's Lucknow Medical College and Hospital, Lucknow. During 2020-2021. After obtaining clearance from Institutional Ethical Committee and informed consent, 74 parturient of ASA Grade 1 and 2 posted for LSCS under Spinal Anaesthesia in 20 - 40 yrs of age with an uncomplicated singleton pregnancy was enrolled. However, Patients with bradycardia,

hypertension, placenta previa, prolonged labour, abnormal presentation, multiple gestations, short stature (height < 150 cm), spine deformity. And patients with a history of respiratory, cardiac or hepato-renal disorder, severe anaemia and bleeding diathesis and allergy to the drug used or severe neurological deficit were excluded. Patients were randomly allocated into two groups of 37 each to receive phenylephrine (P100) [GROUP-A] and saline (P0) [GROUP-B].

All participants received oral pantoprazole (40 mg) the night before and morning of the day of surgery with a sip of water, and IV metoclopramide (10 mg) was given. Two Intravenous access with 18 G cannula, one for fluids and the other for drugs, was established**.** IV injection of ondansetron 0.1mg/kg was administered**.** Preloading with 10 ml/Kg of Lactated Ringer's solution was given. Allocation concealment was done by snooze's method and opened by anaesthesiologists just before administration of subarachnoid block. Parturients were randomly allocated into two groups of 37 each to receive saline (P0) and phenylephrine (P100). Pulse rate, NIBP, EKG, SpO2 was recorded till the end of surgery. Another anaesthesiologist who was not involved in the study prepared the control and test drug according to the randomisation group: Oxytocin 5 IU and phenylephrine 100 mcg diluted up to 10 ml in NS and Control Drug - Oxytocin 5 IU diluted up to 10 ml in NS.

Parturient and principal anaesthesiologists were blinded to the group assignment. The SAB was performed at L3-L4/L4-L5 interspace using 25G Quincke Babcock needle in sitting position and bupivacaine hyperbaric (0.5%) 12.5 mg were used to attain T6 dermatome block height. Immediately after the SAB, the patient was repositioned supine with a 15° wedge below the right buttock to achieve the left uterine tilt. Lactated Ringer's solution was transfused @ 10 ml/kg/hr. Intraoperatively pulse rate, electrocardiogram, pulse oximetry were monitored continuously NIBP was monitored every minute for the first 10 minutes and every 5 min after that till the end of surgery.

Hypotension was defined as a fall in MAP > 20% from baseline and treated with a 200 ml IV fluid bolus. Patients who were non-responsive to fluid bolus were excluded from the study, and a rescue dose of phenylephrine 100 µg IV was given. Phenylephrine IV was repeated every 2 min until the MAP increased to 20% of baseline. After delivery of the fetus, test drug solutions were administered based on group allocation given over 1 min. Oxytocin infusion at 10 IU/h was continued up to 4 hrs. A maximum of 4 doses of phenylephrine was administered, after which rescue vasopressor was changed to ephedrine 6 mg IV. In the control group, after delivery of fetus mephentermine 6mg was given to overcome the hypotension whenever needed, and a number of doses were noted. Bradycardia was defined as heart rate <60 beats/min and treated with atropine qs. During the intraoperative period, adverse effects such as desaturation, nausea, vomiting, headache, bronchospasm, and dysrhythmias, if any, was noted and treated accordingly. The patient was monitored in the postoperative care unit for 6 hrs for any complications.

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows program (21.0 version). When required, the continuous variables were evaluated by mean (Standard deviation) or range value. The dichotomous variables were presented in number/frequency. To compare the means between the two groups, analysis by Student t-test, ANOVA (one way) with 95% confidence interval was used. The correlation was done using Spearman correlation analysis. A p-value of < 0.05 or 0.001 was regarded as significant.

RESULT

The mean age of Group-A and Group-B patients were 22.4±3.5 and 22.9±2.6, respectively, and the mean difference was statistically insignificant (P=0.4877) [Table-1]. Further, the mean height of Group-A and Group-B patients were 154.86±4.55 and 155.44±4.13, respectively, and the mean difference was statistically insignificant (P=0.5677). Furthermore, the mean weight of Group-A and Group-B patients were 69.05±6.59 and 69.71±4.77, respectively, and the mean difference was statistically insignificant (P=0.6232). The sensory block in Group-A and Group-B patients were T6-T8 in both groups. The mean duration of surgery in Group-A and Group-B patients were 78.5±3.04 and 79.09±3.91, respectively, and the mean difference was statistically insignificant (P=0.4962) [Table-1]. The incidence of hypotension after subarachnoid block (T1) in Group-A and Group-B [86.49% vs. 81.08%] patients were comparable, and the mean difference was statistically insignificant (P=0.5382). Whereas, after delivery of the baby (T7), Group-B patients showed the majority (P=0.0004*) of hypotension as compared to Group-A [18.92% vs. 10.81%]. The majority of Group-A patients had zero number of episodes of hypotension [n=30(81.08%] followed by one [n=6(16.22%] and two [n=1(2.70%], respectively [Table-2]. Whereas, the majority of Group-B patients had two number of episodes of hypotension [n=27(72.97%] followed by one [n=4(10.81%] and three [n=4(10.81%], respectively and a statistically significant difference was found between them (P<0.0001*) [Table-3]. The mean heart rate of preoperative patients of Group-I and Group-II were 98.19 ±5.06 and 99.65± 5.19, respectively, and the mean difference was statistically insignificant [Figure-1]. After giving SAB (subarachnoid block), group-A and Group-B patients' mean heart rate was comparable (T0-T6), and a statistically insignificant difference was found between them. After delivery of baby, the mean heart rate of Group-A patients was lower (T6-T25) than Group-B, and a statistically significant difference was found between them. Afterwards (T25-T80), group-A and Group-B patients' mean heart rate was again comparable, and a statistically insignificant difference was found between them. The Systolic blood pressure (SBP) of preoperative patients of Group-A and Group-B were 127.62±7.70 and 126.25± 5.60, respectively, and the mean difference was statistically insignificant. After giving SAB (subarachnoid block), the mean SBP of Group-A and Group-B patients were comparable (T0-T6), and a statistically insignificant difference was found between them [Figure-2]. After delivery of baby, the mean SBP of Group-A patients was higher (T6-T25) than Group-B, and a statistically significant difference was found between them. Afterwards (T25-T80), the mean SBP of group-A and Group-B patients showed a statistically insignificant difference. The diastolic blood pressure (DBP) of preoperative patients of Group-A and Group-B were 88.95± 3.38 and 89.58±2.30, respectively, and the mean difference was statistically insignificant. After giving SAB (subarachnoid block), the mean DBP of group-A and Group-B patients were comparable (T0-T6). After delivery of baby, the mean DBP of Group-A patients as higher (T6-T25) than Group-B, and a statistically significant difference was found between them. Afterwards (T25-T80), the mean DBP of group-A and Group-B patients were comparable [Figure-3]. The mean arterial pressure (MAP) of preoperative patients of Group-A and Group-B were 101.84±5.54 and 102.26± 3.95, respectively, and the mean difference was statistically insignificant. After giving SAB (subarachnoid block), the mean MAP of group-A and Group-B patients were comparable (T0-T6). However, a statistically insignificant difference was found between them. After delivery of baby, the mean MAP of Group-A patients was higher (T6-T25) as compared to Group-B, and a statistically significant difference was found between them [Figure-4]. Afterwards (T25-T80), the mean MAP of group-A and Group-B patients were comparable, and a statistically insignificant difference was found between them. The mean SPO2 of preoperative patients of Group-A and Group-B were 99.49 ±0.5 and 99.68±0.58, respectively, and the mean difference was statistically insignificant. After giving SAB (subarachnoid block), the mean SPO2 of group-A and Group-B patients were comparable (T0-T6). However, a statistically insignificant difference was found between them. After delivery of the baby, the mean SPO2 of group-A and Group-B patients were comparable (T7-T80), and a statistically insignificant difference was found between them [Figure-5].

DISCUSSION

Despite fluid preloading, lateral uterine displacement, and the use of vasopressors, the incidence of hypotension during spinal anaesthesia for Caesarean delivery is reported to be as high as 80%. Maternal hypotension is associated with uncomfortable symptoms such as dizziness, nausea, and vomiting, and may also cause complications during the surgical operation. While fluid preloading is still routinely utilised, its role in the therapy of hypotension caused by spinal anaesthesia has been called into question. The preferred treatment method for this common complication is to administer intravenous (i.v.) vasopressors as needed. In the present prospective randomised double-blinded research, a total of 74 parturients undergoing LSCS were assigned to one of the two groups at random. Parturient were randomly allocated into two groups of 37 each to receive phenylephrine (P100) [GROUP-A] and saline (P0) [GROUP-B]. In the present study, no demographical differences were observed. Duration of surgery and incidence of hypotension after sub arachnoid block (T1) was also comparable. However, the incidence [After delivery of baby (T7)] and the number of episodes of hypotension were

significantly reduced in Group-A compared to Group-B. The mean SBP, DBP, MAP was maintained and significantly at a higher side in Group-A compared to Group-B after baby delivery. However, the mean HR was much elevated in Group-B as compared to Group-A after delivery. Blood loss during surgery was comparable in both groups, and Ephedrine was not needed to manage hypotension in Group-A. Gangadharaiah et al. 2017[13] observed that co-administration of 75 mcg phenylephrine with oxytocin decreased the incidence and number of episodes of oxytocin-induced hypotension, whereas 50mcg of phenylephrine did not reduce the incidence of hypotension but decreased the number of episodes of hypotension and rescue vasopressor requirement when compared to control. The present study also showed significantly less episode of hypotension in Group-A patients treated with 100 mcg phenylephrine. Endogenous oxytocin is a 9–amino acid polypeptide that is synthesised in the posterior pituitary.[13] Because oxytocin's uterotonic effect is critical for reducing blood loss from the site of placental attachment and lowering the risk of postpartum haemorrhage, it is the preferred uterotonic choice.[13] Because oxytocin receptors are abundant in the heart and major veins, oxytocin has a negative effect on hypotension and reflex tachycardia. Because oxytocin appears to primarily influence SVR, a medication that raises SVR directly would neutralise oxytocin's effect.[5] Certain investigations have demonstrated that administering oxytocin at a slower rate significantly reduces the cardiovascular side effects of a bolus dose without impairing therapeutic advantages.[13] The dose of oxytocin administered to induce appropriate uterine contractions is not consistent. The usual use of 5 units oxytocin during elective caesarean delivery is no longer recommended, as appropriate uterine tone can be achieved with lower oxytocin dosages (0.5–3 units).[14] Dyer and Langesaester colleagues found that cardiac output and stroke volume increase a few minutes after spinal anaethesia. [15] It shows that arteriolar dilatation is the main cause responsible for hypotension after spinal anaesthesia. Thus, vasopressor drugs like Ephedrine and Phenylephrine may have a role in reducing incidence of hypotension.

Phenylephrine is a α1 adrenergic agonist, vasoconstrictor that may counteract the vasodilatation caused by spinal anaesthesia. Various studies have highlighted that continuous infusion of intra venous Phenylephrine (vasopressor) during cesarean section in spinal anaesthesia is preferred for prevention of maternal hypotension and foetal acidosis.[16] Several studies have examined the haemodynamic effects of oxytocin 3 U IV bolus over 15 seconds against 3 U infusion over 5 minutes in women undergoing caesarean section, concluding that 3 U infusion is superior than 3 U IV bolus.[17] Gangadharaiah et al. 2017[12] employed 3U oxytocin for 5 minutes and found that uterine contraction was adequate in all cases, without the requirement for further uterotonic agents. Few writers have reported that phenylephrine (100 mcg) was more effective in controlling blood pressure than mephentermine (6 mg) or ephedrine (6 mg). As a result, they found that phenylephrine is 80 times more powerful than ephedrine for equal maternal blood pressure regulation.[18] Our study supports these findings. Several studies investigated the efficacy of three different doses of phenylephrine, 100mcg, 125mcg, and 150mcg, in treating postspinal hypotension following elective caesarean section and determined that there was no statistically significant difference between the three groups.[19] Although, we had taken only single dose of phenylephrine (100mcg), and found substantial effect of it without any significant side effect. Intravenous phenylephrine 50 mcg administered immediately before 3U oxytocin did not prevent maternal hypotension or tachycardia during elective caesarean section, but co-administration of phenylephrine 80 mcg and 2.5 U oxytocin obtunded oxytocin induced decreases in SVR and increases in heart rate and cardiac output. Gangadharaiah et al. 2017[12] found that co-administration of phenylephrine 75 mcg with oxytocin 3U was more efficacious than co-administration of phenylephrine 50 mcg with oxytocin 3U and was associated with a low incidence of side events. Gangadharaiah et al. 2017[12] used the haemodynamic recordings just prior to baby extraction as a baseline to prevent confounding by SAB-induced hypotension, and found that they were equivalent. Gangadharaiah et al. 2017 [12] additionally eliminated parturients who developed hypotension prior to oxytocin injection in order to study the effect of phenylephrine on oxytocin-induced hypotension, assuming that hypotension generated by oxytocin would be attributable to oxytocin's influence. Similarly, we also excluded cases who developed hypotension prior to oxytocin treatment in the current study to avoid bias. Following the bolus dose, phenylephrine causes a considerable decrease in heart rate.[20] There was no evidence of bradycardia, which the infusion may explain rather than bolus delivery of phenylephrine. There is evidence that intraoperative phenylephrine infusion is the most effective technique of reducing maternal hypotension and nausea or vomiting during surgery.[21] Our finding relies upon study conducted by Ashutosh et al., 2019[22] that were administered Phenylephrine, Ephedrine, and normal saline intramuscularly immediately following spinal anaesthesia. Both Phenylephrine and Ephedrine were shown to considerably lower the incidence of hypotension. However Phenylephrine was found to be more effective than Ephedrine at reducing hypotension episodes. These findings are consistent with those of B.T. Ayorinde et al. [23], who found that when 4 mg Phenylephrine, 2 mg Phenylephrine, and 45 mg Ephedrine (via intramuscular route) were compared, the Phenylephrine 4 mg group demonstrated the substantial reductions in episodes of hypotension without recurrence of hypertension. The findings of less Ephedrine rescue dosage consumption in the Phenylephrine group than in the Ephedrine group are also compatible with the above study, in which the least amount of Ephedrine rescue dose was required in the Phenylephrine 4 mg group. The lower frequency of hypotension in the Phenylephrine group than the Ephedrine group may be due to Phenylephrine's stronger vasoconstrictor effect, whereas Ephedrine functions primarily via raising cardiac output and heart rate. However, the incidence of hypotension could not be fully reduced; this could be because the vasopressor agent was delivered following spinal anaesthesia, and the arrival of peak effect via the intramuscular route may take time. This could possibly be attributed to the lower dose of vasopressor medication utilised. Previous research has demonstrated that attempting to totally eradicate hypotensive events may increase hypertensive episodes. [24] The small sample size and the single centric study was the major limitation of the study. Furthermore, a single dose of Phenylephrine further restricted our findings. Due to the absence of estimation of intraoperative blood loss, the effect of phenylephrine co-administration on blood loss could not be examined. We have not performed pulse waveform analysis (perfusion index) or cardiac output monitoring in any of our instances, which is a potential drawback. Cardiac output is used to determine the amount of oxygen delivered to tissues. It is used to guide fluid resuscitation and the administration of vasoactive and inotropic medications, and so may require additional research. We recommended further multicentric studies to increase the reliability and generalizability of the present study findings.

CONCLUSION

We concluded that Co-administration of Oxytocin 5 IU and phenylephrine 100 mcg reduces the incidence of oxytocin-induced hypotension compared with oxytocin alone during caesarean section under spinal anaesthesia.

Table-1: Distribution of patients according to their clinic-demographical parameters

PARAMETER	Group-A [n=37]	Group-B [n=37]	P-VALUE
Age	22.4±3.5	22.9±2.6	t=0.6976 P=0.4877
Height	154.86±4.55	155.44±4.13	t=0.5741 p=0.5677
Weight	69.05±6.59	69.71±4.77	t=0.4935 p=0.6232
Sensory block	T6-T8	T6-T8	----
Duration of surgery	78.5±3.04	79.09±3.91	t=0.6843 p=0.4962

Student t-test

Table-2: Distribution of patients according to Outcome and Haemodynamics

Outcomes And Haemodynamics	Group-A [n=37]		Group-B [n=37]		P-value
	N	%	N	%	
Incidence of hypotension after sub arachnoid block (T1)	32	86.49%	30	81.08%	X=0.3978 p=0.5282
After delivery of baby (T7)	4	10.81%	27	18.92%	X=12.63 P=0.0004*

*Significant, Student t-test

Table-3: Distribution of patients according to number of episodes of hypotension

Number of episodes of hypotension	Group-A [n=37]		Group-B [n=37]		P-value
	N	%	N	%	
0	30	81.08%	2	5.41%	X=52.04
1	6	16.22%	4	10.81%	P<0.0001*
2	1	2.70%	27	72.97%	
3	0	0.00%	4	10.81%	

*Significant, Chi-square test

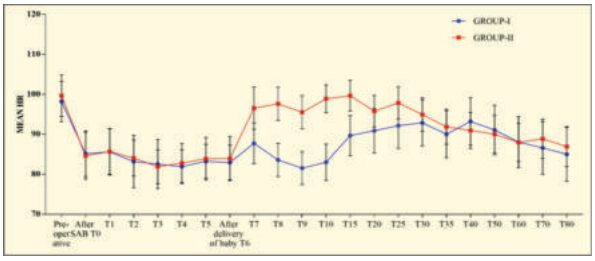

Figure-1: Distribution of patients according to mean heart rate

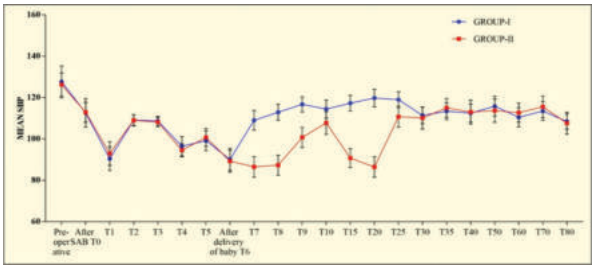

Figure-2: Distribution of patients according to mean Systolic blood pressure (SBP)

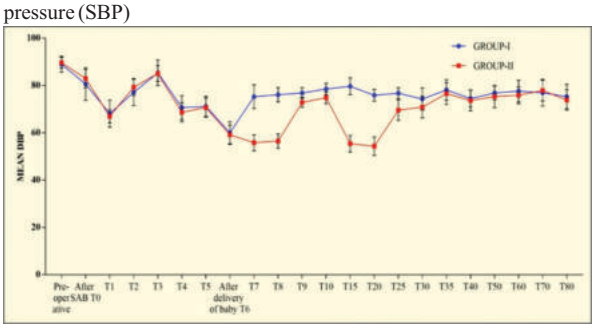

Figure-3: Distribution of patients according to mean diastolic blood pressure (DBP)

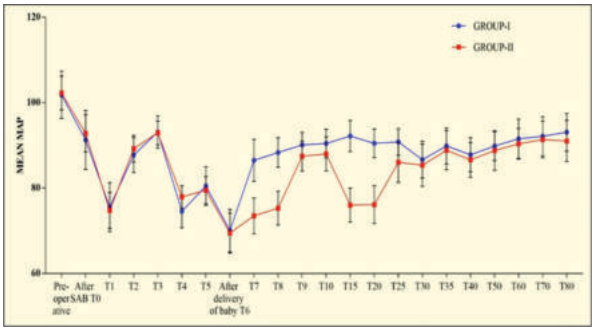

Figure-4: Distribution of patients according to mean arterial pressure (MAP)

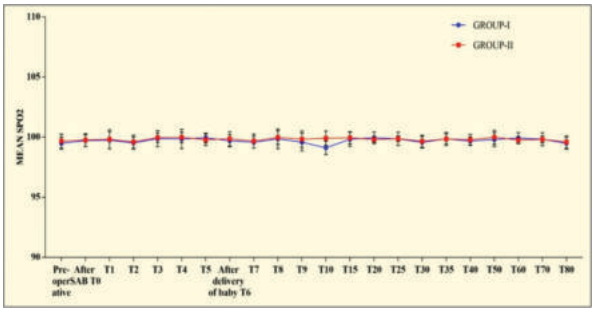

Figure-5: Distribution of patients according to mean SPO2

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