Section: Anaesthesiology

Original Research Article

THE EFFECT OF LOW DOSE INTRAVENOUS KETAMINE COMPARED TO PLACEBO TO ATTENUATE HYPOTENSION AFTER SPINAL ANAESTHESIA DURING CAESAREAN SECTION – A RANDOMIZED PLACEBO CONTROLLED DOUBLE BLINDED TRIAL

Dhayanithy M[1], Yumnam Arunkumar Singh[2], Ningri Sengul[1], Takhelmayum Hemjit Singh[2], Gojendra Rajkumar[3], Lalan Singam[4]

[1]Senior Resident, Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India
[2]Associate Professor, Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[3]Professor, Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[4]PGT, Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India.

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Corresponding Author:
Dr. Takhelmayum Hemjit Singh,
Email: takhelhem@yahoo.com

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Abstract

Background: Spinal anaesthesia is the most preferred technique for caesarean section with hypotension as its most common side effect. There is no single measure that reduces the incidence of post spinal hypotension in caesarean section to a clinical satisfactory level. However, recent studies has pointed out the role of prophylactic low doses ketamine by stimulating the cardiovascular system with increase in blood pressure, heart rate and cardiac output. The objective is to determine the effect of low dose intravenous ketamine in attenuation of spinal anaesthesia induced hypotension during caesarean section. **Materials and Methods:** A randomized, placebo controlled, double blinded study was conducted in the Department of Anaesthesiology, at a Tertiary care centre, Imphal, Manipur, in a period of two years, among parturients, aged 18-40 years, undergoing elective caesarean section delivery under subarachnoid block. 108 consented parturients were randomized into two groups- Group K (intervention group) and Group S to receive 0.5mg/kg body weight dose of intravenous ketamine or saline respectively as 5ml volume, 5 minutes before lumbar puncture for spinal anaesthesia. The haemodynamic parameter, vasopressor dose requirements, sedation scores and side effects were recorded at different time points. **Result:** There was significantly greater fall in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) in group S than group K ($p<0.05$). at 5min, 10min ,15 min and 20 min ($p<0.05$). The Heart rate (HR) also fall more in group S than group K eventhough it was significat only at 10 min. There were more requirements of rescue phenylephrine dose in control group (Group S) with 120.37±78.62 (micrograms) as compared with ketamine group (Group K) 25.93 ± 38.54 micrograms with $p<0.05$. The incidence of nausea was also higher in group S than group K (33.33% vs 22.2% respectively). Higher Ramsay sedation score (RSS scores) indicates better sedation and were recorded statistically significantly [p-value <0.0001]in the ketamine group. **Conclusion:** The use of low dose intravenous ketamine of 0.5mg/kg body weight attenuated the fall in blood pressure following spinal anaesthesia with less vasopressor consumption.

INTRODUCTION

Spinal anaesthesia is the most widely used and preferred technique for caesarean section due to its low rate of airway complications, facilitating postoperative analgesia, less neonatal exposure to anaesthetic drugs; and mother can witness the child birth thus establishes maternal- infant bonding and breastfeeding.[1] Hypotension, with incidence from 7.4% to 74.1%.[2] is the most common side effects of spinal anaesthesia due to preganglionic sympathetic blockade, leading to vasodilation. A decreased

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systolic pressure can affect blood flow to the uterus and foetal circulation, thereby causing hypoxia and acidosis in the foetus leading to dangerous maternal and foetal effects. Some of the measures to prevent hypotension are pre-loading with crystalloid and the use of lateral uterine displacement, drugs like ephedrine, phenylephrine and norepinephrine.[3,4] The above measures are not without its limitation, such as lack of clinically relevant positive effect on neonatal outcome with prophylactic ephedrine use. The high incidence of post spinal hypotension with most of the pharmacological and non-pharmacological methods suggests the need for multimodal protocols for prevention and management of this problem.[5] There is no single measure that reduces the incidence of hypotension in caesarean section under spinal anaesthesia to a clinically satisfactory level.[5,6] Ketamine is a non-competitive antagonist at the N Methyl – D – Aspartic acid (NMDA) receptor,[7] and acts by stimulating cardiovascular system with high blood pressure, heart rate and cardiac output which is due to the centrally mediated sympathetic response.[8] These changes are not related to the sub-anaesthetic dose of ketamine.[9] The current study aims to identify the effect of low dose intravenous ketamine to attenuate hypotension due to spinal anaesthesia during caesarean section.

MATERIALS AND METHODS

The study was a randomized, placebo controlled, double blinded one conducted in the Department of Anaesthesiology, at a tertiary care centre, Imphal, Manipur for two years period from January 2021 to October 2022. 108 parturients, aged 18-40 years with American Society of Anaesthesiology (ASA) I & II, undergoing elective caesarean delivery under subarachnoid block were enrolled for the study after taking written informed consent. Parturients allergy to the study drug, chronic hypertension and pregnancy induced hypertension, coagulopathy (bleeding disorder), local site infections, patients with cardiac disease, respiratory disease, kidney disease, neurological deficit, spinal deformity, obese and patients on selective serotonin reuptake inhibitors or serotonin related migraine medications were excluded from the study.

Preoperative assessment were done a day before the scheduled day of surgery. Injection pantoprazole 40mg and injection metoclopramide were given, 2 hours before the operative procedure. All 108 patients were randomized to one of the 2 groups using a computer-generated random table: Group K were to receive 0.5 mg/kg body weight dose of intravenous ketamine, 5 minutes before lumbar puncture for spinal anaesthesia and Group S (control group) were to receive 5 ml of normal saline in the same way and at the same time. On arrival to the pre-operative room, intravenous (i.v) access were established with an 18-gauge peripheral intravenous cannula and pre-hydrated with 500 ml lactated ringer solution in all the patients. Inside the operation theatre before spinal anaesthesia, routine monitoring - heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry (SPO2), and electrocardiogram (ECG) were applied, and the baseline values of the above-mentioned parameters were recorded. The study drug or saline were prepared by an anaesthesiologist blinded to the group allocation and marked only with a coded label. The syringes containing the study drugs were identical to each other and made to contain the same volume of 5 ml. Lumbar puncture for spinal anaesthesia were performed with the patient in the left lateral position with a 25-gauge spinal needle through L3-4 or L4-5 intervertebral space under strict sterile conditions. 2 ml (10 mg) of hyperbaric bupivacaine (0.5%) were injected into the subarachnoid space in both groups when free-flowing cerebrospinal fluid were observed. Thereafter all patients were placed in a supine position with a left lateral tilt by placing a pillow under the left hip. 2-3 litres per minute of oxygen were administered via a venturi mask until the delivery of the baby. All the patients in both groups received 2mg of Midazolam intravenously after the delivery of the fetus. After obtaining a sensory block higher than the T6 dermatome, the surgical procedure was proceeded. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were recorded every 5 minutes up to 20 minutes then every 15 minutes until skin closure. Hypotension, defined as a fall in the systolic blood pressure (SBP) less than 80 mmHg or less than 20% of baseline was treated by infusion of 100 ml of crystalloids and with intravenous phenylephrine 50 micrograms bolus as and when required. A heart rate lower than 60 beats per minute will be defined as bradycardia and were treated with an injection of atropine 0.5 mg intravenously. The incidence of hypotension (defined as administration of at least one dose of phenylephrine), cumulative episodes of hypotension (the mean number of cumulative hypotension episodes), total phenylephrine consumption, and adverse effects such as hypertension, nausea, vomiting, and incidence of bradycardia were recorded throughout the study. APGAR score at 1 and 5 minutes were also recorded. Ramsay sedation score was used to evaluate the sedation effect in both groups at different time points. At the end of the surgery, all patients were shifted to the post-anaesthetic care unit for routine follow-up care.

The sample size of 54 parturients for each group was determined based on the study of Salah et al10 with power of 80% and α value of 0.05. Datas collected were entered in the licensed version 2016 of the Microsoft excel spreadsheet. The Statistical analysis of the data obtained were done using a Windows-based statistical package for social sciences [SPSS] Version 21.0 (Armonk, NY: IBM Corp). Descriptive statistics like age, weight, height, duration of surgery, APGAR score, Ramsay sedation score, heart rate

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(HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were expressed in mean and standard deviation. Independent t-test were used to compare outcome variables like hemodynamic parameters and Ramsay sedation score between the two groups. The level of significance[α] was 5% i.e., p-value <0.05 is considered statistically significant.

Ethical Considerations: The study was proceeded after the due clearance of protocol from Research Ethics Board, RIMS (Ref.No. A/206/REB-Comm(SP)/RIMS/2015/659/01/2020) and after due registration with Clinical Trial Registry of India. Confidentiality was maintained by concealing name of the patients with case number and datas were kept under lock and key in the department and can be accessed only by the investigators.

RESULTS

Study protocol were completed in all the enrolled patients. The demographic parameters such as age, weight, height, ASA and duration of Surgery were comparable in both the groups and statistically not significant (P>0.05), as shown in [Table 1].

The systolic and diastolic blood pressure fall significantly from the baseline value in all the time points in the control group as compared with the ketamine group. The increase in heart rate was more in the ketamine group at different time points eventhough it was significant only at 10 minutes, as shown in [Table 2].

Table 1: showing the distribution and comparison of demographic parameters and duration of surgery in the two groups.

Sl no	Parameters	Group K (n=54)	Group S (n=54)	P value
1	Age in years (Mean±SD)	29.28 ± 5.73	27.85 ± 5.41	0.19
2	Weight in kilograms (Mean±SD)	69.89 ± 8.59	67.89 ± 10.61	0.59
3	Height in centimetres (Mean±SD)	161.78 ± 9.00	164.57 ± 8.89	0.11
4	ASA I/II	51/3	50/4	1.00
5	Duration of Surgery in minutes (Mean±SD)	50.61 ± 7.88	50.39 ± 10.844	0.90

P<0.05 is significant

Table 2: showing the distribution and comparison of haemodynamic parameters in the two groups.

Time (mins)	Study group	Mean SBP (mmHg) Mean±SD	p-value	Mean DBP (mmHg) Mean±SD	p-value	Mean HR (Rate/minutes) Mean±SD	p-value
Baseline	S	116.83±6.40	0.08	78.94±7.17	0.40	92.67±12.73	0.22
	K	119.15±7.18		80.06±7.28		89.76±11.81	
5	S	101.39±7.76	<0.0001	65.35±10.37	<0.0001	90.56±13.93	0.659
	K	107.96±9.48		75.44±9.12		89.39±13.48	
10	S	98.48±6.81	<0.0001	62.20±9.49	<0.0001	83.54±12.94	0.024
	K	114.33±9.91		75.56±10.02		89.39±11.83	
15	S	103.39±7.61	<0.0001	65.33±8.27	<0.0001	83.31±14.67	0.113
	K	118.81±6.30		78.57±8.26		87.50±12.43	
20	S	107.22±7.37	<0.0001	67.20±11.10	<0.0001	84.48±14.48	0.507
	K	118.87±7.42		79.96±9.67		86.20±12.32	
35	S	110.87±6.27	<0.0001	71.78±7.89	<0.0001	84.54±11.48	0.507
	K	118.43±7.16		78.69±10.06		86.39±11.83	
45	S	111.65±6.09	<0.0001	71.65±6.39	<0.0001	83.22±12.28	0.093
	K	117.65±6.08		78.33±8.81		87.20±12.09	

* p< 0.05 is significant

Table 3: showing the distribution and comparison of Ramsay Sedation Score in the two groups.

Sl. no	Ramsay Sedation Score [RSS]	Intervention: Ketamine	Control: Normal Saline	p-value*
		Mean ± SD		
1	RSS score at 5 minutes	1.09 ± 0.29	1.00 ± 00	0.024
2	RSS score at 10 minutes	1.39 ± 0.49	1.11 ± 0.31	0.001
3	RSS score at 15 minutes	1.56 ± 0.51	1.06 ± 0.23	<0.0001
4	RSS score at 30 minutes	1.65 ± 0.25	1.13 ± 0.39	<0.0001
5	RSS score at 45 minutes	1.85 ± 0.56	1.11 ± 0.37	<0.0001
6	RSS score at endline	1.89 ± 0.53	1.02 ± 0.13	<0.0001

*p-value <0.05 is significant.

Table 4: showing the distribution and comparison of rescue doses of Phenylephrine required in the two groups.

Rescue dose	Mean± SD (micrograms)	p-value
Group S (n=54)	120.37 ± 78.62	0.00
Group K (n=54)	25.93 ± 38.54	

P<0.05 is significant

Table 5: showing the distribution of Incidence of adverse events in the two groups.

Adverse events	Group		Total
	K	S	
None	33	22	55

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Bradycardia	5	7	12
Chills	1	4	5
Giddiness	1	0	1
Nausea	12	18	30
Vomiting	2	3	5
Total	54	54	108

[Table 3] demonstrate the Ramsay Sedation Score [RSS] among the two groups. Higher RSS scores indicates better sedation. All along the progression of the time from 5 minutes post-intervention to endline, the sedation was better among the intervention group compared to the control group. The difference in the sedation between the groups was statistically significant. [p-value <0.0001]

[Table 4] shows that Group S required a higher phenylephrine dose than Group K which was significant, p <0.05 by independent t-test.

The adverse effects, as shown in table 5, are comparatively more in the control group eventhough it is statistically not significant (p>0.05). The APGAR scores of the foetus in the two groups at 1 and 5 minutes were comparable thus indicating that low dose ketamine did not have any effect on the foetus.

DISCUSSION

Regional anaesthesia in caesarean section is gradually increasing, spinal anaesthesia being the most preferred method. The rate of spinal anaesthesia has increased from 84.9% in 2010 to 93.3% in 2017.[11] One of the most important drawbacks of spinal anaesthesia is Spinal-induced hypotension (SIH). SIH may cause maternal nausea and vomiting, fetal acidosis and even cardiovascular collapse if not managed quickly and effectively.[12] The incidence of spinal anaesthesia induced hypotension (SIH) varied as 33% in non-obstetric cases and as high as 90% in obstetrics cases.[13] A decrease in systolic blood pressure can affect blood flow to the uterus and fetal circulation, thereby causing hypoxia and acidosis in the fetus. Maintaining systemic vascular resistance, venous capacitance and splanchnic venous tone are likely to prevent decrease in cardiac output. Techniques to decrease the incidence of hypotension includes- uterine displacement, lower legs compression, administration of crystalloids and/or colloids, patient's position and use of vasopressors or ondansetron and ketamine.[10,14] The use of intravenous fluids as the sole prophylactic method may be unsatisfactory for many anaesthesiologists. Although phenylephrine causes less fetal acidosis than ephedrine, there is no evidence to support phenylephrine for a better overall neonatal outcome. There is no single measure that reduces the incidence of hypotension in caesarean section to a clinically satisfactory level.[5,6]

Ketamine is a non-competitive antagonist at the N Methyl – D – Aspartic Acid (NMDA) receptor,[7] and acts by stimulating the cardiovascular system thereby increasing the high blood pressure, heart rate, and cardiac output. These changes are not related to the dose of ketamine.[9] The mechanism by which ketamine stimulates the cardiovascular system seems to be the central rather than peripheral. Ketamine attenuates the baroreceptor effect by blocking the NMDA receptor in the nucleus tracts solitaries.[8]

Our study showed comparable values of demographic parameters such as age, weight, height, ASA and duration of Surgery in both the groups and similar findings were reported in most of the studies as with Bhiwal et al,[15] Hassanein et al,[16] Salah et al,[10] and Shakya et al.[17]

There were significantly greater fall in SBP, DBP and MAP in group S than group K, p<0.05, at 5min, 10min,15 min and 20 min. Greater fall in HR in group S than group K were recorded at all the time points and significant at 10 min, p<0.05. There were more requirements of rescue phenylephrine dose used in control group (Group S) with 120.37±78.62 (micrograms) and p-value of 0.00; whereas in ketamine group (Group K) the phenylephrine dose used was 25.93±38.54 (micrograms). Comparable haemodynamic findings with our study were reported by Hazarika et al,[18] Salah et al,[10] Kim et al,[19] and Hassanein et al.[16] There were more incidence of hypotensive events and use of rescue vasopressors noted in control group(S) when compared with ketamine group (K) [p-value = 0.00] and the same has been reported in all the above studies.

The incidence of nausea was higher in group S than group K (33.33% vs 22.2% respectively) eventhough it was not significant [p = 0.2]. All other side effects are comparable in both the groups and statistically not significant [p>0.05]. The sedation was better among the intervention group (Group K) compared to the control group and statistically significant. [p-value <0.0001]. Hassanein et al16 has come across a result that was in line with our study results. Salah et al10 in their study used RSS score to assess the sedation among the participants. Sedation score was significantly more in ketamine group than the control group. However, the average score in their study was higher than the present study indicating the deeper sedation in their study compared to ours and this may be due to the administration of larger dose of midazolam 2mg as against 1mg with our study.

Limitations of the study

The study need to be extrapolated to non parturients and further studies are also required to find the optimal minimal dose.

CONCLUSION

The use of low dose intravenous ketamine of 0.5mg/kg body weight attenuated the fall in blood

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pressure following spinal anaesthesia and also reduced the incidence of hypotensive events and vasopressor consumption.

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