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Research Article

Prophylactic Ketamine for Prevention of Post-Spinal Shivering: Randomised Controlled Trial

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Abstract

Background: Post spinal anaesthesia shivering is a common complication and a leading cause of discomfort to patients under spinal anaesthesia. It follows a decrease in sympathetic tone which results in vasodilatation and redistribution of heat from core to peripheral part of the body. The physiological consequences of shivering include increase in cardiac and systemic energy expenditure, oxygen consumption and carbon dioxide production.

Objective: The aim of this study was to compare prophylactic low dose intravenous ketamine with placebo for prevention of post spinal anaesthesia shivering.

Methods: Following Institutional Ethical Review committee approval, this randomized, double blind study was conducted on eighty two patients aged ranged 16 to 50 years and ASA I and II who had repair of vesicio-vaginal fistula under spinal anaesthesia. Immediately after the spinal anaesthesia was established; Groups K and S received iv ketamine 0.25 mg/kg diluted to 5 mls and iv normal saline 5mls respectively. Incidence of shivering, haemodynamic parameters and side effects were assessed as primary outcome measures.

Results: The incidence of shivering in groups S and K was 46.3% vs 7.3% in Group S compared to Group K respectively. Two (4.8%) patients had hallucination and 1 (2.4%) patient vomited among the group K patients. Similarly, mean arterial blood pressure, heart rates at 5 and 10 minutes after the spinal anaesthesia Group K were significantly higher.

Conclusion: The use of prophylactic low dose ketamine significantly reduced spinal anaesthesia-induced shivering.

Keywords: Ketamine; Spinal anaesthesia; Shivering

1. Introduction

Shivering is an involuntary, repetitive activity of skeletal muscles [1, 2]. Post-anaesthetic shivering is one of the leading causes of discomfort for patients after spinal anaesthesia [1]. The main cause for intra and post-operative shivering during regional anaesthesia is decrease sympathetic tone which results in vasodilatation and there is redistribution of heat from core to peripheral tissues from the trunk (below the level of the block) [3, 4]. These two effects predispose patients to hypothermia and shivering. Shivering is associated with various undesirable physiological changes such increases cardiac and systemic energy expenditure, resulting in increased oxygen consumption, carbon dioxide and lactic acid productions. There is also associated increase metabolic rate by up to 400%, which result in hypoxia and hypercapnia [4, 5]. These may cause problems in patients with low cardiopulmonary reserve. Intra- and post-operative prevention of shivering can be done by controlling the ambient operating room temperature, use of warmed IV and irrigation fluids where applicable, external heating using forced air warming and pharmacological interventions. Although different groups of drugs like 5-hydroxytryptamine receptor (5-HT) antagonists and Tramadol has been used with mixed results, however, only intravenous (IV) pethidine have shown promising result [5-7]. However, in limited resource setting pethidine is not readily available, the use of drugs that are readily available even in limited resource settings such as ketamine is a NMDA receptor antagonist and have a wide safety margin, may serve as an alternative in both preventing and management of shivering after spinal anaesthesia and result in reduce morbidity and discomfort associated with post spinal shivering. The aim of this study is to determine the effectiveness of prophylactic intravenous ketamine in prevention of shivering after spinal anaesthesia compared to placebo.

2. Methodology

Following institutional ethical committee approval, consent for study was obtained. This is prospective randomized single blinded study of eighty two American society of Anesthesiologists (ASA) status I and II patients scheduled for vesico-vaginal fistula (pool effort) repair at women and children hospital in north western Nigeria over two weeks (2-13May 2016). Patients with hypertension and hypertensive heart diseases, Patient refusal and Patients with fever were excluded from the study. All patients had pre anaesthetic review done 3 days before the schedule surgery, consent for spinal anaesthesia and surgery was obtained, routine electrolyte and urea, pack cell volume and urinalysis was also done. Demographic variables recorded were age, ASA, weight, height. All patients received 10mg of diazepam as pre-medication. On arrival to the operating theatre, all patients had a size 18G venous cannula inserted. IV Ringer's lactate solution were infused at a rate of 15 ml\Kg over 30 minutes before spinal anesthesia, the rate was reduced to 10 ml\Kg\h. fluids were kept at room temperature. Baseline non-invasive blood pressure, oxygen saturation and non- invasive tympanic membrane temperature was recorded. The ambient temperature was

maintained at 24-25^{o}C. All patients had spinal anesthesia with 15 mg hyperbaric Bupivacaine 0.5% injected at either L3/L4 or L4/L5 using a 25 G quincke spinal needle under aseptic conditions.

Patients were randomly divided into two groups. Group K, received 0.25 mg/kg of ketamine diluted to 5 ml with saline and was given as bolus immediately 10 minutes after spinal anaesthesia. Group S were given 5 mls of normal saline. This was done by an assistant who was not involved in the data collection or intra-operative monitoring of the patients. Patients were covered with one layer of surgical drapes. Five minutes after intrathecal injection, sensory and motor block was assessed. When spinal anesthesia was established, presence of shivering was recorded using study data collection preforma as graded by using Tsai and Chu validated shivering scale by the attending anaesthetist who is not aware of the patient group: 0- No shivering. 1- Piloerection or peripheral vasoconstriction, but no visible shivering. 2- Muscular activity in only one muscle group. 3- Muscular activity in more than one muscle group, but not generalized. 4- Shivering all over the body If shivering grade 3 and 4 occurred was considered as severe shivering and a rescue treatment in the form of intravenous pethidine 25 mg and humidified oxygen via nasal prong at 5 L/minutes was given.

Heart rate, respiratory rate, non-invasive blood pressure, peripheral oxygen saturation (SpO_2) and non- invasive tympanic membrane temperature were recorded using standard non-invasive monitors every 5 minutes during the procedure. The level of sedation was assessed according to Ramsey sedation score as 1: agitated, 2: Tranquil and calm, 3: Sleeping but responds to verbal, 4: sleeping, but brisk responds to glabella tap, 5: sleeping with sluggish respond to glabella tap or loud auditory stimulus, 6: Asleep not responding to glabella tap or loud auditory stimulus. Any other side effects was recorded and treated as appropriate. Data collected was analysed with Statistical Package for Social Sciences (SPSS) version 25, Continuous variables were presented as mean and standard deviation while categorical variables as the frequency and percentages were presented using relevant tables and figures.

3. Results

Total of eighty two patients were enrolled in the study, forty one patients in group K and 41 for group S respectively.

Variables	**Groups**	
	K (Mean ± SD) **N=41**	**S (Mean ± SD)** **N=41**
Age (years)	16.84 ± 2.57	16.61 ± 2.52
ASA I/II	36/5	40/1
Duration of Surgery (minute)	32.52 ± 3.10	33.48 ± 4.21
BMI (Kg/m^2)	17.8 ± 0.50	17.6 ± 0.81

Pulse rate (bpm)		
Base line	65.72 ± 8.06	66.15 ± 7.09
Intra-operative	79.88 ± 11.12	71.29 ± 6.85
Systolic blood pressure (mmHg)		
Base line	104.43 ± 7.90	106.10 ± 8.09
Intra-operative	115.82 ± 9.78	99.34 ± 7.48
Temperature (^{0}C)		
Base line	36.60 ± 0.03	36.42 ± 0.01
Intra-operative	36.51 ± 0.01	36.48 ± 0.10

Table 1: Intraoperative hemodynamic parameters.

Table 1 showed the mean age of the study participant for Ketamine group was 16.84 ± 2.57 and the Saline group was 16.61 ± 2.52, majority are ASA I patients, duration of surgery was relatively longer 33.48 ± 4.21 and all the patients in both groups were underweight BMI < 18.5 Kg/m^2. The mean intra operative pulse rate and systolic blood pressure were higher 79.88 ± 11.12 and 115 ± 9.78 and among the ketamine than saline group 71.29 ± 6.85 and 99 ± 7.48 respectively. Core temperature among the ketamine study population was found to be more relatively preserved 36.5 ± 0.01 in comparison with baseline than saline group 36.48 ± 0.01.

Variables	**Group**	
Label of block	**Group K**	**Group S**
T8	10 (24.4%)	8 (19.5%)
T7	26 (63.4%)	27 (65.9%)
T6	5 (12.2%)	5 (12.2%)

Table 2: Level of sensory Block.

Table 2 showed majority 63.4% and 65.9% the patients had a satisfactory block at T7 for ketamine group and saline respectively, while both groups was found to have equal number of patients 12.2% with T6 respectively.

Variables	**Group**	
	Group K	**Group S**
O	23 (56.1%)	10(24.4%)
I	5 (12.2%)	4 (17.1%)
II	10 (24.4%)	5 (12.2%

III	3(7.3%)	17 (41.5%)
IV	0	2 (4.8%)

Table 3: Grade of shivering among the study groups.

Table 3 showed incidence of grade III shivering was higher 41.5% among the groups saline compared to 7.3% among the ketamine group. Similarly, 4.8% of patients in the saline group was found to have a grade IV shivering while none of the patients in ketamine group had grade IV shivering. The overall incidence of shivering grade (III and IV) among the ketamine group was 7.3%, while for saline group was 46.3%.

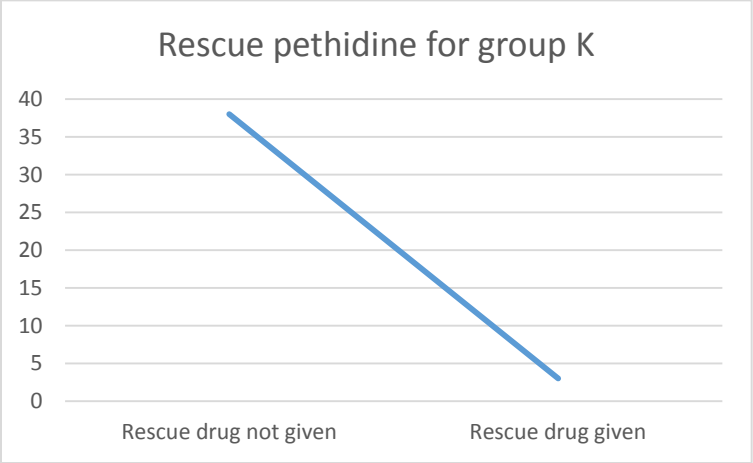

Figure 1: Showed Rescue pethidine was not administer among the majority 38 (92.68%) of the patients in group K due lower incidence of shivering among the group.

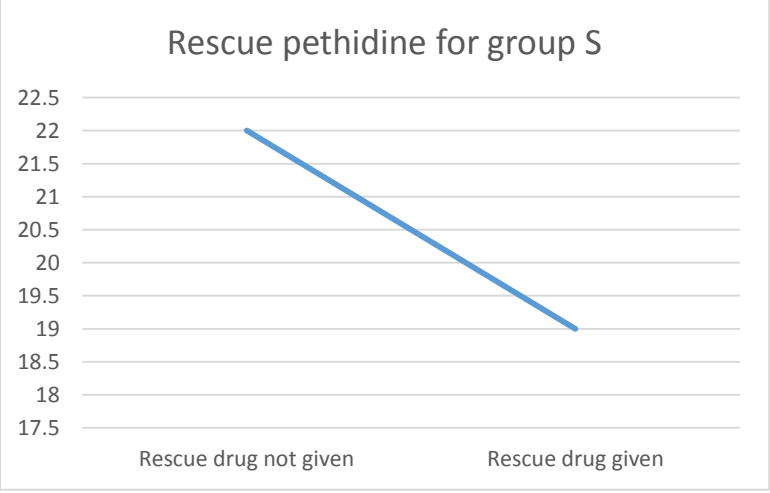

Figure 2: Showed 19 (46.34%) of patients received rescue intravenous pethidine 25 mg in group S indicating significant incidence of shivering within the group.

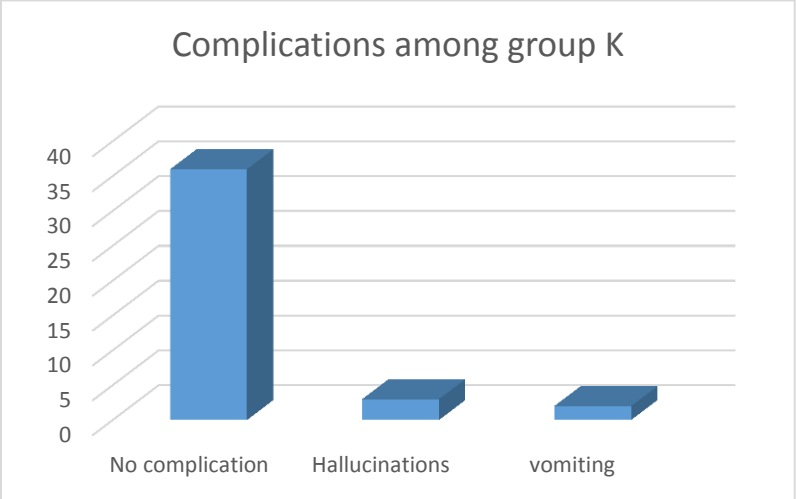

Figure 3: There was more incidence of hallucinations 3 (7.32%) than vomiting 2 (4.88%) among group K.

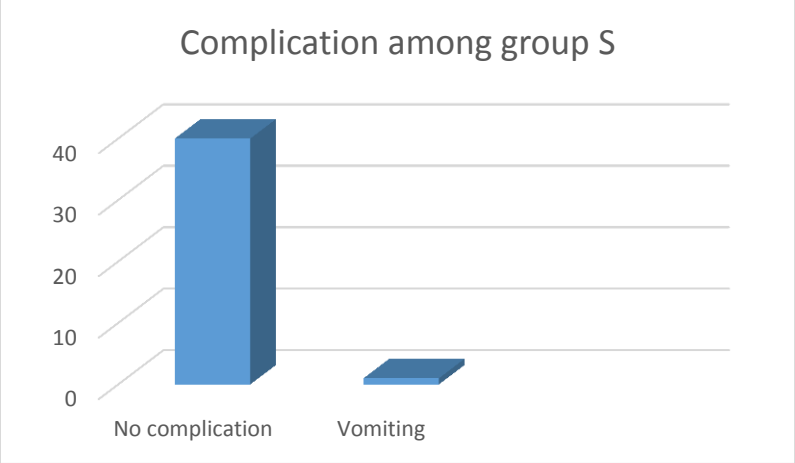

Figure 4: There is only one (2.45%) incidence of vomiting recorded as complication in group S.

4. Discussion

The results of our study showed that post spinal anaesthesia shivering was less among the patients that received prophylactic ketamine compared to those that received placebo. Ketamine, a competitive N-methyl-D-Aspartate (NMDA) receptor antagonist, also inhibits postoperative shivering, it is likely due to the fact that, NMDA receptor antagonists modulate thermoregulation at several levels in the brain. Furthermore, NMDA receptors modulate thermogenesis through noradrenergic and serotoninergic neurones in the locus coeruleus, dorsal raphe nucleus and serotonin acts as a neuromodulator to enhance the effects of NMDA receptors [6]. Therefore being a competitive NMDA receptor antagonist it probably controls shivering through non-shivering thermogenesis either by action on

the hypothalamus or by the B-adrenergic effect of norepinephrine [6-8]. Our study revealed a decrease incidence of shivering among the patients that received prophylactic ketamine by three fold when compared with those that received saline as placebo. Two patients had a shivering grade IV among the placebo group and none was recorded among the ketamine group, this may explain that prophylactic dose of ketamine may also reduce the severity of shivering.

In this study, shivering was graded using a scale that was validated by Tsai and Chu [9]. The prophylactic ketamine was considered ineffective if the patient shivered to grade 3 and 4. Pethidine 25 mg IV was administered to control the shivering and humidified oxygen 4l/minute. Only 3 (7.31) received rescue pethidine among group K compared to19 (46.34%) in the control group. Pethidine was found to be effective among those three patients, this may be due to different mechanisms of action compared to ketamine. Another explanation could be that this dose of ketamine was not optimum. We chose a dose of 0.5 mg kg_1 because the only other report with ketamine had used this dose effectively to treat shivering in the postoperative period [10]. This findings is consistent with results of previous studies by Sagir et al. [10] and Kose et al. [8]. Sagir et al. [10] in their study used same protocol. In our study, the incidence of shivering was 42.50% in the control group. In the study by Sagir et al. [10] the shivering rate was 55% in the control group. Shivering was observed in 36% in Kose et al. study [7]. In the study done by Dal et al. [8] shivering rate was 57% in the control group. In our study, tablet diazepam 10mg was used as premedication. Similarly Kose et al. [7] also administered10 mg of diazepam as premedication. However, in the study of Sagir and Dal, no premedication was used. The relatively low incidence of shivering in the control group in our study and the study by Kose et al. [7] may be attributable to diazepam which has anti shivering property In that study, involving 30 patients for different types of surgery under spinal, epidural or general anaesthesia in which halothane was used as one of the anaesthetics, ketamine was reported to be quite useful in spinal and epidural anaesthesia, where it provided sedation and analgesia but two patients developed hallucinations and four developed delirium [11]. In our study 3 patients had hallucinations and 2 vomited among the ketamine group, while only one patient vomited in the saline group. The vomiting observed among the study population may be related to episodes of hypotension after the spinal anaesthesia. Gecaj-Gashi A.et al. [11] 2010 found that Ketamine 0.5-0.75 mg/kg is more rapid than meperidine (25 mg) for the reduction of postoperative shivering, but the side effect profile may limit its usefulness. Ketamine produces undesirable psychological reactions termed emergence phenomenon. The common manifestations are vivid dreaming, sense of loating out of body, visual and auditory illusions. However, the higher incidence of side effect in their study can be attributed to the dose 0.5-0.75 mg/kg when compared to the current study 0.25 mg/kg was used, the incidence of hallucinations in patients that received ketamine was lower 7.3% compared to study conducted by Gecaj-Gashi A et al. [11]. Tramadol/Ketamine group, 10% and 5% in group Midazolam/Ketamine respectively. This can be explained by the use of low dose of ketamine in the present, similar findings were reported by Honarmand et al. [12], and Sagir et al. [10] where dose of 0.25 mg/Kg of ketamine was used with no incidence of hallucinations.

Median level of sensory block after 15 minutes of spinal anaesthesia was comparable (up to T6) in the study groups. All the patients in the two group showed hemodynamic stability, however there was increased in both pulse rate and

systolic blood pressure among the ketamine group. Ketamine has several other pharmacological properties such as blocking amine uptake in the descending inhibitory mono aminergic pain pathways resulting in indirect sympathomimetic effect, Imrie et al. [2] and Alfonsi et al. [5] also reported there was no significant difference among the groups regarding hemodynamic values, Similar finding was reported by Reda SA et al. [13] that MAP and heart rate values were not significantly different between the control, midazolam/ketamine and Tramadol/ketamine groups at any time of the post anesthesia period. Although Reda et al. [13, 14] combine ketamine with midazolam and Tramadol while in our study only ketamine was used no significant difference in haemodynamic changes was observed.

In our study, tympanic temperature was measured using non-invasive Braun thermoscan thermometer. Tympanic temperature is one of the most reliable site for measurement of core temperature and correlates well with brain temperature. This study found decrease in mean tympanic temperature following spinal anaesthesia among the groups with respect to their baseline values. This is expected because hypothermia may occurs after spinal anaesthesia as a results of internal redistribution of body heat, heat loss to environment and inhibition of centrally mediated thermoregulatory control [2]. In this study, the temperature was preserved in ketamine group with respect to control group. This relative preservation of temperature may be due to vasoconstrictive action of ketamine, the difference in mean tympanic temperature in both saline groups and ketamine group was not significant. Dal et al. [8] reported similar finding, in their study there were no significant difference in tympanic temperature among the pethidine and ketamine groups. The tympanic temperatures of the patients were >36^{o}C and there was no need for active warming. Although in their study pethidine and ketamine was used, both drugs can preserved temperature and inhibit shivering after spinal by different mechanism while in our study the control group received Saline as placebo. In contrast to our findings Sagir et al. [10], reported a decrease of core temperature among the control group were significantly more than patients that received ketamine and granisteron from the 10th minutes ($p<0.001$). The prophylactic use of IV ketamine 0.25 mg/kg significantly reduced the frequency and the intensity of perioperative shivering associated with spinal anaesthesia but also exhibited some side effects of the drug. Lower doses of prophylactic ketamine should be studied using large sample size.

5. Conclusion

The use of prophylactic ketamine significantly reduced spinal anaesthesia-induced shivering, for these reasons ketamine can be an alternative prophylaxis against postoperative shivering. Future studies may find the optimal dose of ketamine for this purpose with minimal or no side effect.

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