USE OF KETAMINE PLUS MIDAZOLAM VERSUS KETAMINE ALONE IN PREVENTION OF SHIVERING DURING SPINAL ANAESTHESIA: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

OBJECTIVE: To compare the efficacy of combination of ketamine plus midazolam with that of ketamine alone in the prevention of shivering during spinal anaesthesia

METHODOLOGY. This double blinded randomized controlled clinical trial was carried out at institute of kidney diseases Hayatabad, Peshawar from 16 October 2012 to 15 April 2013. Two hundred patients, classified by American Society of Anesthesiologists (ASA) physical status category I-II, listed for urologic surgery were randomized by card method in two groups of 100 patients each. Subarachnoid (spinal) anaesthesia was performed in all patients with bupivacaine 15 mg. The patients were randomly allocated to receive ketamine 0.25 mg/kg plus midazolam 37.5 μg/kg (Group A) or ketamine 0.5 mg/kg (Group B). During surgery, a shivering score was recorded at 5 min intervals. If 15 minutes after spinal anaesthesia and concomitant administration of a prophylactic dose of one of the study drugs, grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective and pethidine 25 mg intravenously was administered.

RESULTS: After 15 min, the incidences of shivering in groups A and B were 4% and 25% (P= <0.0001). Mean shivering score was 0.05±0.26112 and 0.43±0.87911 in group A and group B respectively. The number of patients with a shivering score of ≥3 was significantly higher in group B compared with groups A (4 vs. 0, respectively, P=0.0434).

CONCLUSION: Prophylactic use of ketamine (0.25 mg/kg) plus midazolam (37.5 μg/kg) intravenously was more effective than ketamine (0.5 mg/kg) intravenous alone in preventing shivering developed during spinal anaesthesia.

KEYWORDS: spinal anaesthesia, ketamine, midazolam; temperature regulation, shivering.

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INTRODUCTION

Spinal anaesthesia is a safe and popular anaesthetic technique for various surgeries. Around 40-60% of the patients under spinal anaesthesia develop shivering.[1] Shivering can be very unpleasant and physiologically stressful for the patients after enjoying the comforts of modern anaesthesia. Mild shivering increases oxygen consumption to a level that is produced by light exercise, whereas severe shivering increases metabolic rate and oxygen consumption up to 100-600%. It may induce arterial hypoxemia, lactic acidosis, increased intraocular pressure and intracranial pressure and interferes with ECG monitoring, pulse rate, B.P.[2] Shivering may be detrimental to the patients with low cardio respiratory reserves.[3] Spinal anesthesia significantly impairs thermoregulation and predisposes patients to hypothermia, which reduces the threshold for vasoconstriction and shivering. Various pharmacological therapies such as pethidine[4], ketamine,[5,6] clonidine[7] and tramadol[8-10] have been used to prevent shivering, because shivering may affect the cardiovascular system and induce hypertension and tachycardia; ultimately increasing oxygen consumption by 400-500%.[11]

Although both Ketamine and Midazolam have been used alone to prevent shivering during anaesthesia; to the best of my knowledge, there is only one study regarding the use of Midazolam-Ketamine combination as a prophylactic agent against intra- postoperative or postoperative shivering during regional anaesthesia in Egypt.[12] This study was conducted to see the effect of combination of ketamine and midazolam in decreasing the incidence of shivering compared to ketamine alone in local population.

METHODOLOGY

It was a double blind randomized clinical trial. This study was performed in Institute of Kidney Diseases, Hayatabad, Peshawar. After obtaining institutional approval and written informed consent from all patients; 200 patients classified by American Society of Anesthesiologists (ASA) physical status category I-II, both male and female between the ages of 45-85 years who were undergoing different urological procedures under spinal anaesthesia were enrolled in the study. Patients with hypothyroidism or hyperthyroidism, cardiopulmonary disease, psychological disorders, a need for blood transfusion during surgery, an initial body temperature >38.0°C or <36°C, a known history of alcohol or substance abuse, or receiving vasodilators, or medications likely to alter thermoregulation were excluded from the study.

Patients were randomized through unrestricted randomization by a card shuffling method. Patients did not receive any premedication. In the operating theatre, an 18 gauge venous cannula was inserted in the largest apparent vein on the dorsum of hand. Lactated Ringer's solution was infused at 10 ml kg^{-1} h^{-1} over 30 min before spinal anaesthesia. The infusion rate was then reduced to 6 ml kg^{-1} h^{-1}.

Subarachnoid anaesthesia was instituted at either L3/4 or L4/5 interspaces. Hyperbaric bupivacaine, 7.5 mg ml^{-1}, 15 mg was injected using a 25 G spinal needle. The patients were randomly allocated to receive ketamine 0.25 mg/kg plus midazolam 37.5 μg/kg (Group A) or ketamine 0.5 mg/kg (Group B). Just after intrathecal injection, all drugs were given as an i.v. bolus. The treatment drugs were diluted to a volume of 4 ml and presented as coded syringes by an anaesthesiologist who was blinded to the group allocation. Supplemental oxygen (5 liters min^{-1}) was delivered via a facemask during the operation. All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation.

The presence of shivering was observed by an observer blinded to the study drug administered. Shivering was graded using a scale used by Crossley AWA et al[13] and validated by Tsai YC et al[14] (Table 1).

During surgery, a shivering score was recorded at 5 min intervals. If 15 min after spinal anaesthesia and concomitant administration of a prophylactic dose of one of the study drugs, Grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective and pethidine 25 mg intravenously was administered.

Statistical analyses were performed using SPSS (Statistical Package for So-cial Sciences) windows version 17. Quantitative variables were expressed as mean ± SD, while qualitative variables were expressed as percentage. Age and weight were analyzed by using student t-test, while gender, frequency of shivering and use of rescue antiemetic were analyzed by using chi-square test. P-value less than 0.05 were considered significant.

RESULTS

There were no statistically significant differences among the groups regarding age, weight and sex (Table II). Age and weight were analyzed by student t test entering means and standard deviations. While gender was analyzed by using chi-square in 2x2 contingency table.

In Group A after spinal anaesthesia and concomitant administration of ketamine 0.25 mg/kg plus midazolam 37.5 μg/kg, shivering after 15 min was observed in

TABLE I: SHIVERING GRADES USED BY CROSSLEY AWA ET AL[13] AND TSAI YC ET AL[14]

Grade 0	No shivering
Grade 1	Piloerection or peripheral vasoconstriction but no visible shivering
Grade 2	Muscular activity in only one muscle group
Grade 3	Muscular activity in more than one muscle group but not generalized
Grade 4	Shivering involving the whole body.

TABLE II: DEMOGRAPHIC DATA

Variable	Group A (n=100)	Group B (n=100)	P-value
Age (years)	64.59 ± 10.82	66.46 ± 10.19	0.2098
Sex (M:F)	78 : 22	82 : 18	0.596
Weight (Kg)	76.13 ± 05.86	77.43 ± 06.54	0.4795

TABLE III: NUMBER (%) OF PATIENTS WITH DIFFERENT GRADES OF SHIVERING AFTER 15 MINUTES OF SPINAL ANAESTHESIA

Shivering grade	Group A (n=100)	Group B (n=100)	P-value
0	96 (96%)	75 (75%)	<0.0001
1	03 (03%)	13 (13%)	
2	01 (01%)	08 (08%)	
3	0 (0.0%)	02 (02%)	
4	0 (0.0%)	02 (02%)	

four patient and it was sig-nificantly lower when compared with Groups B where shivering was observed in twenty five patients, P= <0.0001. (Table III). Mean shivering score was 0.05 ± 0.26112 and 0.43 ± 0.87911 in group A and group B respectively.

The number of patients with a shivering score of ≥3 was significantly higher in Group B compared with Groups A (4 vs. 0, respectively, P=0.0434.

Four patients in group B had to be given pethidine 25 mg intravenously, as grade 3 or 4 shivering was noted after administration of a prophylactic dose and the prophylaxis was regarded as ineffective. No patients in group A had shivering of grade 3 or 4 and did not need any rescue drug.

DISCUSSION

Hypothermia during regional anaesthesia is common[15] and can be nearly as severe as that observed during general anaesthesia.[16] There are three principal reasons for hypothermia under spinal anaesthesia. First, spinal anaesthesia leads to an internal redistribution of heat from the core to the peripheral compartment.[17] Secondly, with loss of thermoregulatory vasoconstriction below the level of the spinal block; there is increased heat loss from body surfaces. Lastly, there is altered thermoregulation under spinal anaesthesia characterized by a 0.5°C decrease in vasoconstriction and shivering thresholds.[18]

Ketamine, which is a competitive receptor antagonist of N-methyl-D-aspartic acid (NMDA), has a role in thermoregulation at various levels. In rats, application of NMDA agonist increases the firing rate of neurones in the preoptic-anterior hypothalamus. Moreover, NMDA receptors act by modulating the noradrenergic and serotoninergic neurones in the locus ceroleus. Serotonin, as a neuromodulator, enhances the effects of the NMDA receptor in the dorsal raphe nucleus. Finally, NMDA receptors modulate ascending nociceptive transmission at the dorsal horn of the spinal cord.[19] Additionally, ketamine has many other pharmacological properties such as blocking amine uptake in the descending inhibitory monoaminergic pain pathways, interacting with muscarinic receptors, having a local anaesthetic action, and being a K opioid agonist. Ketamine probably controls shivering by non-shivering thermogenesis either by action on the hypothalamus or by the b-adrenergic effect of norepinephrine.[20]

Ketamine causes sympathetic stimulation and vasoconstriction in patients at risk of hypothermia. This effect of ketamine is in contrast to that of midazolam which reduces core-body temperature by inhibiting tonic thermoregulatory vasoconstriction.[21]

Kurz, et al. studied the effect of midazolam on thermoregulation and found that reduction in heat production after administration of midazolam is less than that after induction of anesthesia with clinical doses of volatile anesthetics, propofol and opioids. They also reported that midazolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control.[22] This explains the lower incidence of shivering observed in our patients receiving midazolam. However, in another study by Grover et al, showed that administration of midazolam towards the end of the anesthetic procedure doesn't prevent shivering but it subsides earlier in the postoperative period.[21]

It is clear from our data that the combination of ketamine and midazolam prevents the hypothermia that is often seen with premedication with midazolam alone. It is probable that ketamine prevented the arteriovenous shunt vasodilation normally induced by midazolam. Since these shunts are under sympathetic control,[23] it seems that ketamine acts centrally to inhibit the effect of midazolam.

It is clear from the present study that adding midazolam to ketamine enhanced its anti-shivering effect. This suggests that Ketamine has a synergistic anti-shivering effect when combined with midazolam. So, further studies are needed to find out the exact mechanism of interaction.

Our results are comparable to another study done in Egypt where incidence of shivering was 5% in patients who were given ketamine plus midazolam for prophylaxis.[12]

CONCLUSION

The present study demonstrated the combination of ketamine plus midazolam is superior to ketamine alone in preventing shivering developed during spinal anaesthesia.

REFERENCES

1. De Whitte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. Anaesthesiology 2002; 96(2): 467-84.
2. Katyal S, Tewari A,Sood D, Narula N, Garg S, Kaul TK. Shivering: Anesthetic considerations. J Anaesth Clin Pharmacol 2002; 18(4): 363-76.
3. Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering- A new look at Tramadol. Anaesthesia 2002; 57: 387-403.
4. Hong JY, Leel H. Comparison of the effects of spinal morphine and pethidine on shivering after Caesarean delivery under combined-spinal epidural anaesthesia. Anaesthesia 2005; 60(12): 1168-72.
5. Nasreen L, Muhammad NK, Namika N, Shahid K. Prevention of postoperative

shivering by prophylactic ketamine in patients undergoing major surgeries under General Anesthesia. Ann Pak Inst Med Sci 2006; 2(3): 163-6.

6. Kose EA, Dal D, Akinci SB, Saricaoglu F, Aypar U. The efficacy of ketamine for the treatment of postoperative shivering. Anesth Analg 2008; 106(1): 120-2.
7. Weant KA, Martin JE, Humphries RL, Cook AM. Pharmacologic options for reducing the shivering response to therapeutic hypothermia Pharmacotherapy 2010; 30(8): 830-41.
8. Mohta M, Kumari N, Tyagi A, Sethi AK, Agarwal D, Singh M. Tramadol for prevention of postanaesthetic shivering: a randomized double-blind comparison with pethidine. Anaesthesia 2009; 64: 141-6.
9. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth 2011; 55(3): 242-6.
10. Fatemeh J, Reza A, Kaveh BA, Alireza O, Mehrdad S. Effects of Tramadol on shivering, post spinal anesthesia in elective cesarean section. Pak J Med Sci 2009; 25(1): 12-7.
11. Yi JW, Lee BJ, Han JH. Effects of spinal meperidine on prevention of shivering during spinal anesthesia for herniorrhaphy. Korean J Anesthesiol 2005; 49: 484-9.
12. Abdelrahman RS. Prevention of shivering during regional anaesthesia: Comparison of Midazolam, Midazolam plus ketamine, Tramadol, and Tramadol plus Ketamine. Life Sci J 2012; 9(2): 132-9.
13. Crossley AWA, Mahajan RP. The intensity of postoperative shivering is unrelated to axillary temperature. Anaesthesia 1994; 49: 205-7.
14. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. Anesth Analg 2001; 93: 1288-92.
15. Hendolin H, Lansimies E. Skin and central temperatures during continuous epidural analgesia and general anaesthesia in patients subjected to open prostatectomy. Ann Clin Res 1982; 14: 181-6.
16. Frank SM, Beattie C, Chritopherson R, Norris EJ, Rock P, Parker S, et al. Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. Anesthesiol 1992; 77: 252-7.
17. Matsukawa T, Sessler DI, Christensen R,Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia. Anesthesiol 1995; 83: 961-7.
18. Ozaki M, Kurz A, Sessler DI, Lenhardt R, Schroeder M, Moayeri A et al. Thermoregulatory thresholds during spinal and epidural anesthesia. Anesthesiol 1994; 81: 282-8.
19. Dal D, Kose A, Honca M, Akinci B, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. Br J Anaesth 2005; 95: 189-92.
20. Sharma DR, Thakur JR. Ketamine and shivering. Anaesthesia 1990; 45: 252-3.
21. Grover VK, Mahajan R, Yaddanapudi LN, Sudarshana HG, Gill KD. Efficacy of midazolam in preventing postoperative shivering. Int J Clin Pharmacol Ther 2002; 40: 534-6.
22. Kurz A, Sessler DI, Annadata R, Dechert M, Christensen R, Bjorksten AR. Midazolam minimally impairs thermoregulatory control. Anesth Analg 1995; 81(2): 393-8.
23. Hales JRS. Skin arteriovenous anastomoses, their control and role in thermoregulation. In: Cardiovascular Shunts: Phylogenetic, Ontogenetic and Clinical Aspects—Johansen K, Burggren W, eds. (1985) Copenhagen, Denmark: Munksgaard. 433-51.

AUTHOR'S CONTRIBUTION

The sole author has made substantial contributions to the manuscript regarding conception and design; acquisition, analysis and interpretation of data acquisition of data; drafting the manuscript & final approval of the version to be published. Author agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Author declares no conflict of interest

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