Original Article

Efficacy of Intravenous Midazolam & Ketamine Combination in the Treatment of Shivering after Spinal Anaesthesia – A Comparative Study with Intravenous Midazolam & Pethidine Alone

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Abstract

Background: *Post spinal shivering is very distressing for patients and may induce a variety of complications.[1] The principal reasons for hypothermia are - it leads to an internal redistribution of heat from the core to the peripheral compartment, loss of thermoregulatory vasoconstriction below the level of the spinal block and altered thermoregulation due to vasodilation and shivering thresholds[3,4,5,21]. Present study demonstrated that the combination of midazolam and ketamine treats the hypothermia that is often less effective with midazolam or pethidine alone.*

Objectives: *To assess the effectiveness of midazolam-ketamine combination over midazolam & pethidine alone in post spinal shivering.*

Methods: *This hospital based randomized double blind controlled study. One hundred fifty patients, classified by (ASA) physical status category I-II, were randomized by card method in three groups of 50 patients each. Subarachnoid (spinal) anaesthesia was performed . The patients were randomly allocated to receive 0.025 mg/kg midazolam + 0.25 mg/kg Ketamine (Group A), 0.035 mg/kg i/v midazolam (Group B), and 0.5 mg/kg i/v pethidine (Group C). After development of shivering, it graded and recorded. 1st dose of drugs given as coded in syringe A,B,C. If the grade 3 or 4 after 15 min from the administration of the study drug, the prophylaxis was regarded as ineffective and pethidine 25 mg intravenously was administered.*

Result: *Patients characteristics in respect of age, residence, others socio-demographic characteristics, ASA status and type of surgery were similar between the groups. Heart rate and mean arterial blood pressure values were less and close to base levels without requirement of any other rescue medication and remained stabilized throughout the intraoperative period in midazolam & ketamine (Group A) patient.*

Conclusion: *The most effective measures for prevention and treatment of post-spinal shivering are forced air warming, fluid warming with combating pharmacological agents e.g. midazolam, ketamine, morphine, fentanyl, and pethidine etc. In our study midazolam plus metamine is more effective than other had proven.*

Keywords: *Post spinal shivering, Spinalanesthesia, Midazolam, Ketamine, Pethidine, Thermoregulatory center.*

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Introduction :

Shivering- an involuntary, oscillatory muscular activity, is a physiological response to core hypothermia in an attempt to raise the metabolic heat production. It has been reported in 40 to 70% of patients undergoing surgery under regional anaesthesia.[2,3] Prolonged impairment of thermoregulatory autonomic control under anaesthesia along with the cold environment of operating rooms and cold infusion fluids, contributes to a fall in core body temperature, and hence shivering.[2,6] Other known causes of shivering include transfusion reactions, drug reactions, pre-existing high grade fever or bacteremia, or infusion of contaminated intravenous fluids (fungal growth in dextrose containing fluids.[6] Perioperative hypothermia is the most common cause of shivering, though the exact incidence of each is difficult to evaluate. It causes arterial hypoxemia due to 200–500% increase in oxygen consumption, a liner increase in carbon dioxide production lactic acidosis, increased intraocular pressure (IOP) and increased intracranial pressure (ICP); and interferes with pulse rate, blood pressure (BP) and electro-cardiographic (ECG) monitoring.[10-13] Thus in a patient with limited myocardial oxygen reserve or known coronary disease, shivering may further compromise myocardial function.[13] It may contribute to increased wound pain, delayed wound healing, and delayed discharge from post anesthetic care.[5] It is also very unpleasant, physiologically stressful for the patient undergoing surgery, and some patients find the accompanying cold sensation to be worse than the surgical pain. All these deleterious effects warrant prompt control on occurrence of shivering. A number of pharmacological interventions have been studied for the treatment and prophylaxis of shivering, including clonidine, ketamine, butorphanol, doxapram, tramadol, pethidine and other opioids , midazolam, ondansetron and other 5HT3 receptor antagonists[5,14-16].

All previous stydies doesn't compare midazolam, midazolam + ketamine, pethidine regarding their safety & efficacy in postspinal shivering.

Materials and methods:

After approval from the ethical review board this prospective randomized double blind comperative study was conducted in the department of anaesthesiology & ICU , Dhaka Medical College Hospital from 1st January 2015 to 30th June 2015.Patients ASA status I and II underwent surgical procedure under spinal anaesthesia and develop any grade of postspinal shivering were included in the study.

After arrival to the operating theatre, all patients ware inserted an 18 gauge venous cannula in the largest apparent vein on the dorsum of hand. Then all patients started lactated Ringer's solution, infused at 10ml/kg/h over 30 min before spinal anaesthesia. The infusion rate was then reduced to 6 ml/kg/h. The ambient temperature was maintained at 22-24 ^{0}C. After recording the baseline vital parameters, eg- pulse rate, blood pressure (NIBP) ,ECG (3 leads) , oxygen saturation (SpO_2), and axillary temperature , all patients was administered 0.5% bupivacaine heavy 10 mg intrathecally, at L2-L3 or L_3 - L_4 interspinous spaces, with 25G Quinke's spinal needle in sitting position. Immediately position was change to supine.

Supplemental oxygen (5 liters/min) 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 at 5 min interval by an attending anaesthetist. After development of shivering this patient was finally enrolled for this study and randomized by card method in three groups of 50 patients each. Attending anaesthesiologist graded and recorded. 1st dose of drugs given as coded in syringe A,B,C. Regular monitoring was done at 5 min interval. If the grade 3 or 4 after 15 min from the administration of the study drug, the treatment was regarded as ineffective and pethidine 25 mg intravenously was administered. The complications which were developed during the procedure was noted and managed accordingly. All collected information checked very carefully to identify the error in the data. Data processing work consist of registration schedules, editing computerization, preparation of dummy table, analyzing and matching of data. The presence of shivering was observed at 5 min interval by an observer blinded to the study drug administered. After development of shivering, it graded using a scale used by

Crossley AWA et al[39] and validated by Tsai YC et al[40] .1st dose of drugs given as coded in syringe A,B,C. Haemodynamic condition grade & complication was observed and recorded at 5 min interval. The patient received rescue drug was noted. The developed complication was recorded.

All collected data checked very carefully to identify the error in the data. Data processing work consist of registration schedules, editing computerization, preparation of dummy table, analyzing and matching of data.After collection of all information, these data were checked, verified for consistency and edited for finalized result. After editing and coding, the coded data directly entered into the computer by using SPSS version 6. Data cleaning validation and analysis was performed using the SPSS/PC software and graph and chart by MS excel.

Results

Table- 3.1 : *Demographic characteristics of the patients (n=150)*

Demographic variables	Group A (n=50)	Group B (n=50)	Group C (n=50)
Age (years)			
Mean ± SD	27.4 ±8.28	25.3 ±9.31	26.4 ±5.96

A total of 150 patients, 50 in each group, were evaluated. All groups were comparable with respect to the demographic and operational factors. No significant differences were found between groups with respect to age & gender.

Table- 3.2: *American Society of Anaesthesiologist (ASA) physical status (n=150)*

Status	Number of Patient			P
	Group A	Group B	Group C	value
ASA I	36(72%)	39(78%)	27(54%)	0.950
ASA II	14(28%)	11(22%)	23(46%)	

Patient distribution as regard to ASA status. There were no significant difference between the groups (p=0.950). Comparison was done by Chi-Square ($Ç^2$) test.

Table- 3.3: *Distribution of patients according to type of surgery (n=150)*

Types	Number of Patients			Total	P
	Group A	Group B	Group C		value
LUCS	34(68%)	30(60%)	28(56%)	92	0.726
Inguinal hernia opn.	9(18%)	12(24%)	14(28%)	35	
Orthopedic surgery	7(14%)	8(16%)	8(16%)	23	

No significant differences were found among groups with respect to type of surgery. The difference was statistically not significant (P>0.05).

Table- 3.4 : *Grade of shivering prior to medication (n=150)*

Shivering grade	Number of patients			P
	Group A	Group B	Group C	value
1-2	2(4%)	2(4%)	1(2%)	0.36
3-4	48(96%)	48(96%)	49(98%)	

145(96.66%) patients experienced shivering of grades 3 and 4 after spinal anesthesia. In case of groups A and B patients it was 48(96%) of patients respectively and In the Group C patients 49(98%) showed shivering score grade 3-4). The difference was statistically not significant (P>0.05).

Table- 3.5 : *Grade of shivering 5 minutes after medication (n=150)*

Shivering status	Number of patients			P
	Group A	Group B	Group C	value
Attenuation/ tempering	46(92%)	38(76%)	40(80%)	0.0001
1-2	2(4%)	4(8%)	6(12%)	
3-4	2(4%)	8(16%)	4(8%)	

After 5 min of medication, the incidences of shivering was 4(18%) in groups A, 12(24%) in groups B and 10(20%) in group C. The difference was statistically significant (P<0.05).

Table- 3.6 : *Changes of mean arterial blood pressure (n=150)*

State	Mean arterial blood pressure		
	Group A	Group B	Group C
Preanaesthesia	97.53	99.27	98.82
Prior medication	108.67	113.48	106.05
5 min after medication	84.24	92.84	87.16
At 15 min after medication	92.34	95.68	95.36

No significant difference was observed in the MAP before anaesthesia in all groups. After development of shivering blood pressure increased at the rate of 108.67, 113.48, 106.05 mmHg in group A, group B, and group C respectively. Heart rate and mean arterial blood pressure values were less and close to base levels in midazolam+ketamine (Group A) patient.

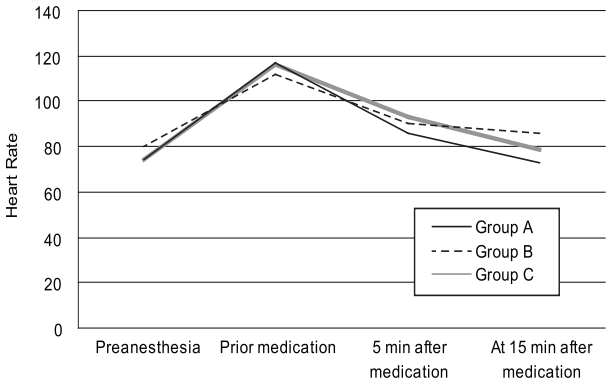

Fig.-1: *Comparison of heart rate (n=150)*

There was no significant difference in the preanaesthesia and prior of medication heart rate values in groups.). During shivering, it increased by 117, 112, 116 beats/min in group A,B,C respectively. 5 min later of medication, there was statistically significant attenuation of heart rate in groups A (86 beat/min) compared with group B (90 beat/min), and group C (93 beat/min).

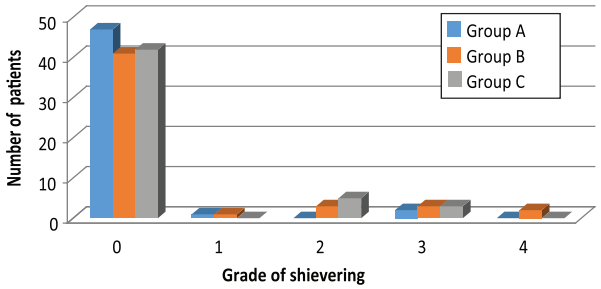

Figure- 3.2: Comparison of effectiveness of three drugs on controlling of shivering (n=150)

Shivering was controlled within 15 minute in 47(94%) patients given midazolam plus ketamine regime (group A). But in group B and group C it was 41(82%) and 42(84%) of patients respectively. Shivering grade 3 or 4 was existence mainly in patients of group B or C and more rescue drugs also had required in this group. Thus in this study suggest that regime of group A is superior to regime of group B,C in controlling the shivering immediately.

Discussion:

Patients characteristics in respect of age, residence, others socio-demographic characteristics and ASA status were similar amongst the groups. A total of 150 patients, 50 in each group, were evaluated. All groups were comparable with respect to the demographic and operational factors. Findings are consistent with result of others study in home and abroad. In a study in tertiary level hospital of Bangladesh[32] showed mean age were 31.46±11.27 years, in another study Karim KI[33] found that mean age 30.3±3.58. In a study published in Egyptian Journal of Anaesthesia described that among 226 patients, subject located to one of three groups, group N (n= 76) received nefopam, group K (n= 75) received ketamine plus midazolam and group S received saline 0.9% as placebo. All groups were similar with respect to demographic data, duration of surgery and anesthesia and baseline tympanic temperatures. ASA physical status were 40%-45% ASA I, 48%-51% ASA II, and 6%-9% ASA III. In patients treated with nefopam 0.2 mg/kg, 65 of 76 patients (85.5%) had no symptoms of shivering, 11 patients (14.5%) were shivering score grade 1, and no patient in this group showed score grade(2–4)[34].

In our study all 150 enrolled patients were randomized to one of the three medication treatment groups of 50 patients each. All patients were with ASA physical status I and II. Group A received midazolam plus ketamine, among them 36(72%) were ASA I and 14(28%) were ASA II. Group B received midazolam, among them 39(78%) were ASA I and 11(22%) were ASA II. Group C received pethidine, among them 27(54%) were ASA I and 23(46%) were ASA II.

No significant differences were found among groups with respect to type of surgery. Indication for spinal anaesthesia was LUCS 92(61.33%),

inguinal hernia repair 35(23.33%), and orthopedic surgery 23(15.33%). In this study no significant differences were found between groups with different operative procedure. In this study, some sort of risk factors elucidated in patients. Patient's history, clinical examination and analysis of previous investigation report elicit for find out of risk factors. Among the all risk factors UTI was the most common risk factor, present in 24% cases; next common risk factors are short stature 19%, previous history of abdominal pain 16%, obeses 17.33% and anemia 15.33% of patients.

We found 145(96.66%) patients experienced shivering score grade 3 and 4 after spinal anaesthesia. In patients groups A patients 2(4%) patients showed signs of muscular activity in only one muscle group (shivering score grade 2), and 48(96%) showed muscular activity in more than one muscle group to shivering all over the body (shivering score grade 3-4). In the group B patients only single patients showed piloerection or peripheral vasoconstriction (shivering score grade 1), and 48(96%) showed muscular activity in more than one muscle group to shivering all over the body (shivering score grade 3-4). In the Group C patients 49(98%) showed muscular activity in more than one muscle group to shivering all over the body (shivering score grade 3-4).

5 min after medication, the incidences of shivering was, 5(10%) in groups A (who receive 0.025 mg/kg midazolam + 0.25 mg/kg ketamine), followed by 12(24%) observed in groups B (who receive 0.035 mg/kg i/v midazolam), and 9(18%) in group C (who received 0.5 mg/kg i/v pethidine). The number of patients with a shivering score grade 2 was significantly higher in group B 8(16%) compared with groups A and C. Eight (16%) patients in group B had to be given pethidine 25 mg intravenously, as grade 3 or 4 shivering was noted after administration of a respective dose and the dose of medication was regarded as ineffective. In case of group C, 4(8%) cases considered as hopeless to respective primary dose (6% retained grade 3 and 2% grade 4 of shivering).

Almost incidence of shivering subsided at this time. At 15 min after medication, the incidences of shivering in groups A was observed only in three (6%) patient and it was significantly lower when compared with Groups B (18%) and Group C (16%). The number of patients with a shivering score of 3 or grade 4 was (2%) in group B and (4%) in group C. No patients in group A had shivering of grade 3 or 4. It was found in this study that use of 0.025 mg/kg midazolam + 0.25 mg/kg ketamine intravenously was more effective than midazolam or pethidine intravenous alone in preventing shivering developed during spinal anaesthesia.

All this result is correlates with other study in national and international university. A double blinded randomized controlled clinical trial revealed that, After 15 min, the incidences of shivering in groups A (who receive ketamine 0.25 mg/kg plus midazolam 37.5 μg/kg) and group B (receive ketamine 0.5 mg/kg) 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 grade 3 was significantly higher in group B compared with groups A (4 vs. 0, respectively, P=0.0434). Prophylactic use of ketamine (0.25 mg/kg) plus midazolam (0.025 mg/kg) intravenously was more effective than ketamine (0.5mg/kg) intravenous alone in preventing shivering developed during spinal anaesthesia[5]. Kamal MM et al reported in Egyptian Journal of Anaesthesia that. In the ketamine plus midazolam treated patients, 63 of 75 were symptom free (84%), 10 patients shivering score grade 1, and two patients reached shivering score grade 2 (3%) and no patient reached score grade 3 or score grade 4. In the placebo group 44 of 75 patients (59%) had no symptoms, nine patients showed score grade 1, and 13 patients scored grade 2 & 3 and 9 patient scored grade 4. Results showed that a significant reduction in the incidence of shivering in group N and group K in comparison to group S. There were no significant differences in hypotenion and bradycardia in all groups. Sedation was significant in group K in comparison with group N and S. Result showed that nefopam (0.2 mg/kg) is as effective as ketamine 0.25 mg plus midazolam 40 μg/kg in the prophylaxis of postspinal shivering and not accompanied by sedation or hemodynamic side effects[34].

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.[35] 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.[36]

Kurz, et al. reported that midazolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control.[37] 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.[36]

There was no significant difference in the preanaesthesia and prior of medication heart rate values in groups. Compared with (Group B) and (Group C), midazolam+ketamine group (Group A) showed slight but statistically significant decrease in heart rate after intravenously administration of medication. Maximum increase in heart rate from baseline was observed just before medication (during the onset of shivering). During shivering, it increased by 117, 112, 116 beats/min in group A,B,C respectively. 5 min later of medication, there was statistically significant attenuation of heart rate in groups A (86 beat/min) compared with group B (90 beat/min), and group C (93 beat/min). No significant difference was observed in the MAP before anaesthesia in all groups. After development of shivering blood pressure increased at the rate of 108.67, 113.48, 106.05 mmHg in group A, group B, and group C respectively. Then antishivering drugs were given accordingly. 5 min after medication, the attenuation of mean arterial blood pressure in group A was statistically significant as compared to group B, group C and remained stabilized during intraoperative period. At the 15 min time mean blood pressure was at the rate of 92.34, 95.68, 95.36 mmHg in group A, group B, and group C respectively. Heart rate and mean arterial blood pressure values were less and close to base levels without requirement of any other rescue medication and remained stabilized throughout the intraoperative period in midazolam+ketamine (Group A) patient.

Shivering was controlled within 15 minute in 47(94%) patients given midazolam plus ketamine regime (group A). But in group B and group C it was 41(82%) and 42(84%) of patients respectively. Shivering grade 3 or 4 was mainly in patients of group B or C. Thus in this study suggest that regime of group A is superior to regime of group B,C in controlling the shivering immediately.

By analyzing the shivering score, we found a significant higher grading in the Group C and Group B compared to Group A. The consumption of other medication was significantly lower in the A and B groups compared to group C. All findings are consistent with other study. A prospective randomized, comparative, placebo controlled study reported that, the One hundred ASA status I and II patients, group C (n=20) received saline as a control, group M (n=20) received midazolam 75 µg /kg, group MK(n=20) received midzolam 37.5µg/ kg plus ketamine 0.25 mg/kg ,group T(n=20) received tramadol 0.5mg/kg and group TK(n=20) received tramadol 0.25mg/kg plus ketamine 0.25mg/kg . The incidences of shivering in groups C,M,MK, T and TK were 55%,45%,5%,30% and 15% respectively. Group TK also showed a statistically significant lower incidence of shivering when compared to group and M, but when compared with group T, the difference was not statistically significant. The incidence of shivering in group T was less than its incidence in groups C and M but this was not statistically significant. The difference between groups C and M was not statistically significant[28].

No significant complication has occurred after use of medication with midazolam and ketamine combination in our study. Nausea, vomiting, sedation and headache were more common in the midazolam, pethidine group (group B.C). 2(4%) of group A developed hypotension after treatment. In addition the heart rate, respiratory rate and oxygen saturation were not significantly different after spinal anaesthesia, before treatment and 15 minutes after treatment. Shende SY et al demonstrated that disappearance of shivering

was significantly earlier in group C than in group T. Response rate to treatment in group C was higher (97.7%) than in group T (93.7%), but the difference was not significant. Nausea, vomiting and dizziness were found to be higher in group T s while the patients in group C were comparatively more sedated (sedation level, 2; group C, 33.3%). Result conclude that clonidine gives better thermodynamics than tramadol, with fewer side effects[8].

In this study we compared the efficacy of Midazolam plus ketamine to midazolam and pethidine for the treatment of shivering. The major finding was that didazolam plus ketamine significantly reduced the incidence of shivering as midazolam compared to pethidine. The relation between shivering and the effects of drugs on vasoconstriction means that it is possible to interpret our finding. The efficacy of the drug in the treatment of shivering is through its effect on patient shivering threshold and on the vasoconstriction threshold. Ketamine increases arterial pressure, heart rate and cardiac output because of direct sympathetic stimulation so it may be logical to use ketamine in patients who are at risk of hypothermia [38]. Kamal MM[34] and Sagir and colleagues [39] showed that ketamine 0.5 mg kg intravenously prevents postspinal shivering but patients may develop postoperative hallucinations and nausea or vomiting. In our study, we used midazolam + ketamine so patients didn't suffer from hallucinations postoperatively. So in this study it is suggested that use of ketamine + midazolam i.v. was more effective than use midazolam i.v. or pethidine alone in the treatment of postspinal shivering.

Conclusions:

The results of this study indicate that the combination of midazolam (0.025 mg/kg) and ketamine (0.25 mg/kg) is more effective than midazolam or pethidine, in the treatment of post spinal shivering. The response rate is better and time taken to control shivering shorter in the A group, then in the group B and C.

However, side effects like hypotension, hypertension, sedation, respiratory depression, nausea and vomiting, limit their use. Our study was designed to compare a combination dose of midazolam and ketamine, with that of midazolam, pethidine alone for control of shivering during spinal anaesthesia. Our study has limitations of small sample size, hence, further controlled large sample-sized studies with different doses of such drugs are required to confirm the optimal dose and the results of this study.

References :

1. Bhattacharya PK et al. Post Anaesthesia Shivering (PAS):A review. Indian J. Anaesth. 2003; 47 (2) : 88-93
2. Honarmand A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anaesthesia: a randomized double-blind placebo controlled trial. Br J Anaesth2008;101: 557–62
3. Hori T, Katafuchi T. Cell biology and the functions of thermosensitive neurons in the brain, Prog Brain Res 1998; 115: 9-23
4. De Whitte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. Anaesthesiology 2002; 96(2): 467-84.
5. Tariq MA. Use of Ketamine plus midazolam versus ketamine alone in prevention of shivering during spinal anaesthesia: A randomized controlled trial. Khyber Med Univ J 2014; 6(1): 5-8
6. Katyal S, Tewari A,Sood D, Narula N, Garg S, Kaul TK. Shivering: Anesthetic considerations. J Anaesth Clin Pharmacol 2002; 18(4): 363-76.
7. Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering- A new look at Tramadol. Anaesthesia 2002; 57: 387-403
8. Shende SY. A randomized controlled double blind study to compare efficacy, potency and safety of clonidine and tramadol for postspinalanaesthesia shivering in cesarean section. Volume 1 issue 7 2014 page no. 357-362
9. 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.
10. 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

11. Yu SC et al. Intrathecal meperidine and shivering in obstetric anesthesia response. Anesth Analg 2004;99:1272–3.
12. Kranke P, Roewer N, Tramer MR. Pharmacological treatment of post operative shivering. Anesth Analg 2002;94:453–60.
13. Bredahl C, Hindsholm KB, Frandsen PC. Changes in body heat during hip fracture surgery: a comparison of spinal analgesia and general anaesthesia, Acta Anaesthesiol Scand 1991; 35: 548-552.
14. Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia, Anaesthesiology 1995; 83: 961-967
15. De Whitte, Sessler DI. Perioperative shivering: Physiology and Pharmacology. Anaesthesiology 2002;96:467-84.
16. Sessler DI, Ponte J. Shivering during epidural anaesthesia. Anaesthesiology 1990;72:816-21
17. Bhatnagar S, Saxena A, Kannan TR, Punj J, Panigrahi M, Mishra S. Tramadol for postoperative shivering: A double blind comparison with Pethedine. Anaesth Intensive care 2001;29:149-54.
18. Katyal S, Tewari A. Shivering: Anesthetic Considerations.J Anaesth Clin Pharmacol 2002;18:363-76.
19. Alfonsi P. The effects of meperidine and sufentanil on the shivering threshold in postoperative patients. pascal.alfonsi@ apr.ap-hop-paris.fr. Anaesthesiology 1998;89(I):43–8.
20. Zhang Y, Wong KC. Anesthesia and postoperative shivering: itsetiology, treatment and prevention. Acta Anaesthesiologica Scand 1999;37:115–20.
21. De Witte J, Sessler DL. Perioperative shivering: physiology and pharmacology. Anaesthesiology 2002;9C:467–84.
22. Honarmand A, Safayi MR. Comparison of prophylactic use of midazolam, ketamine and ketamine plus midazolam for prevention of shivering during regional anesthesia: a randomized double-blind placebo controlled trial. Br J Anaesth 2008;101(4):557–62.
23. 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.
24. Adam RD, Victor M, Ropper AH. Motor paralysis. In: Adam RD, Victor M, Ropper AH, editors. Principles of neurology. New York: McGraw Hill, Inc.; 1997. p. 45–63.
25. Kranke P et al. Single-Dose Parenteral Pharmacological Interventions for the Prevention of Postoperative Shivering: A Quantitative Systematic Review of Randomized Controlled Trials. Anesth Analg 2004;99:718 –27.
26. Abdelrahman RS. Prevention of shivering during regional anaesthesia: Comparison of Midazolam, Midazolam plus ketamine, Tramadol,and Tramadol plus Ketamine. Life Science Journal, 2012; 9(2)
27. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. Anesth Analg 2001; 93: 1288-92
28. Moniruzzaman M. Prophylactic use of tramadol hydrochloride and ondansetron for the prevention of post spinal shivering. FCPS dissertation, 2014
29. Karim KI. Control of preoperative shivering after regional anaesthesia: a comparative study between tramadol and ketamine. FCPS dissertation 2009
30. Kamal MM. Prevention of postspinal shivering by using ketamine plus midazolam in comparison with nefopam. Egyptian Journal of Anaesthesia (2011)27,1–5
31. 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.
32. 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.
33. Ikeda T, Kazama T, Sessler DI, et al. Induction of anesthesia with ketamine reduces the magnitude of redistribution hypothermia. Anesth Analg 2001;93:934–8.
34. Sagir O, Gulhas N, Toprak H, Yucel A, Begec Z, Ersoy O. Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. Acta Anaesthesiol Scand 2007;51:44–9.