Original Article

Comparative evaluation of oral tramadol and gabapentin for prophylaxis of post-spinal shivering

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ABSTRACT

Background and Aims: Shivering in the peri-operative period is a common problem which is associated with various complications. Prophylaxis of shivering can thus help in reducing the cost and risk of complications. The present study was designed to compare prophylactic oral gabapentin, tramadol and placebo for prevention of post-spinal shivering. **Methods:** A total of 150 adult patients of either sex belonging to American Society of Anesthesiologists physical status I–III scheduled for elective orthopaedic surgeries were randomised to receive tramadol 100 mg (group A), gabapentin 600 mg (group B) or placebo (group C) orally 30 min before administration of spinal anaesthesia. The primary outcome was to study the incidence and severity of shivering, whereas the secondary outcome was to evaluate the incidence of adverse effects. Data were analysed by analysis of variance test, Student t-test, Mann–Whitney U test and Chi-square tests. **Results:** Incidence of shivering was comparable among groups A and B ($P = 0.8$) whereas it was significantly less than in group C ($P = 0.00$). Severity of shivering (grade 1 and 2) was comparable in all the groups ($P = 0.6$ and 0.36), whereas shivering grade 3 and grade 4 was significantly lesser in groups A and B as compared to group C ($P = 0.01$ and 0.01). The incidence of nausea and vomiting was more in group A (26%) as compared to group B (20%) ($P = 0.48$) but was significantly lesser than group C (48%) ($P = 0.01$). Incidence of sedation (sedation score ≥ 2) was significantly more in group B (22%) as compared to group A (4%) and group C (0%). **Conclusion:** Prophylactic oral gabapentin 600 mg and tramadol 100 mg are equally effective for prevention of post-spinal shivering.

Key words: Gabapentin, shivering, tramadol

INTRODUCTION

Shivering is a common complication after subarachnoid block with a reported incidence of 40 to 50%.[1] Shivering increases oxygen consumption and may result in metabolic derangements, such as lactic acidosis, adversely affecting the perioperative outcomes.[2] Various pharmacological and non-pharmacological methods have been employed for prevention as well as treatment of post-spinal shivering with variable results.[2-5] Amongst the pharmacological methods, tramadol has been the most commonly studied and employed agent for prevention and treatment of post-spinal shivering.[6,7] Tramadol, a μ–opioid receptor agonist also inhibits neuronal uptake of noradrenaline and promotes hydroxytryptamine secretion. Both these actions reset the temperature regulation centre, thereby controlling the shivering. However, use of tramadol is often associated with nausea, vomiting, increased incidence of drowsiness and opioid-induced hyperalgesia.[8]

Recently, gabapentin premedication is being used due to its analgesic, anxiolytic and opioid sparing effects.[9]

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In a study by Ozgencil *et al.*, it was incidentally observed to have anti-shivering effect. This anti-shivering effect was postulated to be due to anti-convulsive, anxiolytic and analgesic effect of gabapentinoids.[10]

This formed the basis of a hypothesis that gabapentin might exert significant anti-shivering effect which can be employed for prevention of post-spinal shivering. Thus, the present study was planned to compare premedication with oral gabapentin, tramadol and placebo for prophylaxis of post-spinal shivering. The primary outcome was to study reduction of the incidence and severity of shivering among the three groups, whereas incidence of adverse effects of both the drugs was the secondary outcome. To our knowledge, this is the first study conducted to evaluate the anti-shivering effect of gabapentin.

METHODS

After approval from the institutional ethics committee and obtaining written informed patient consent, the study was conducted in a controlled, randomised, double-blind manner over a period of 15 months(March 2018 to May 2019). 150 adult patients of either sex, aged 20–60 years and belonging to American society of Anesthesiologists (ASA) grade I-III, scheduled for elective orthopaedic surgery under spinal anaesthesia were included in the study. Exclusion criteria included history of allergy to opioids or gabapentin, patients already taking tramadol or gabapentinoids, history of opioid abuse, febrile patients, patients with diabetic autonomic neuropathy, prolonged surgical time leading to supplementation/conversion to general anaesthesia and patients requiring blood transfusion in the perioperative period. Uncooperative patients and patients with psychiatric illness or communication difficulties were excluded from the study. Patients were randomly allocated into three groups of 50 patients each using computer-generated random numbers which were kept in opaque envelopes. Group A was administered two capsules of tramadol 50 mg each, Group B was administered two capsules of gabapentin 300 mg each after removing the packaging and Group C was administered two sugar filled capsules.

All the study drugs were administered orally 30 min before spinal anaesthesia, by an anaesthesiologist who did not further participate in the study. All observations were recorded by an anaesthesiologist who was unaware of the group to which the patient belonged.

After shifting the patients to the operation theatre and securing intravenous access, standard monitoring and baseline parameters were recorded. Axillary temperature by digital thermometer (Microgene), forehead and tympanic membrane temperature by a Food and Drug administration (FDA) approved professional thermometer, the iProven Dual Mode Thermometer-489 were recorded. Constant temperature (22 ± 1°c) and humidity (70%) were maintained inside operation theatre and post-anaesthesia care unit.

Subarachnoid block was given in a sitting position at L3-4 or L4-5 intervertebral space using 26 gauge Quincke's spinal needle with 3 ml of inj bupivacaine 0.5% (heavy) after preloading with 500 ml crystalloid. Patient was made supine following the block and the highest dermatomal level attained noted. Patients were covered with drapes but not actively warmed. Fluids administered during the perioperative period were at room temperature. Heart rate (HR), respiratory rate, non-invasive blood pressure (NIBP), oxygen saturation (SPO2), body temperatures (axillary, forehead and tympanic membrane) were recorded immediately when the patient was made supine and thereafter at every 5 min for 1 h and every 10 min till the effect of block weaned off. Any episode of shivering was recorded and graded as per Wrench grading.[11]

Shivering was managed by standard rescue treatment which included reassurance to patients, administration of oxygen via face mask, warming blanket, injection ondansetron 4 mg and injection tramadol 50 mg intravenously. If shivering persisted, injection tramadol 50 mg could be repeated after 30 min up to a total dose of 250 mg in 6 h and maximum of 400 mg over 24 h. The time of onset of shivering after spinal anaesthesia and time to disappearance of shivering after treatment were noted. Nausea and vomiting were noted on nausea five-point scale as per Kim where 1- no nausea, 2- mild nausea, not requiring treatment, 3- moderate nausea, tolerable for patient but treatment is desirable, 4- severe nausea, treatment is necessary, 5- intractable nausea, patient complains despite treatment.[12] Assessment of sedation was done according to four-point scale as per Filos, where 1- awake and alert, 2- drowsy, responsive to verbal stimuli, 3-drowsy, arousable to physical stimuli, 4- unarousable.[13]

Other adverse effects like bradycardia (HR <50/min), hypotension (>20% decrease in blood pressure)

and sedation/dizziness were noted till the effect of block weaned off. Bradycardia, hypotension and vomiting were treated with atropine (0.6 mg), mephenteramine (6-10 mg) and metoclopramide (10 mg), respectively, in titrated doses when required.

All statistical calculations were done using Statistical Package for the Social Science (SPSS) version 21 for Microsoft Windows. Kolmogorov–Smirnov and Shapiro–Wilk test were used to access normalcy of data. Comparison of quantitative variables between the study groups was done using Student t-test, Mann–Whitney U test and analysis of variance (post hoc) for independent samples for parametric and non-parametric data. For comparing categorical data, Chi square (χ^2) test was performed and exact test was used when the expected frequency was less than 5. A probability value (p value) less than 0.05 was considered statistically significant.

In study by Ozgencil *et al.*, gabapentin was seen to decrease the incidence of shivering by 20% as compared to placebo group.[10] In a study by Tewari *et al.*, tramadol was observed to reduce the incidence of shivering by 30% as compared to placebo.[8] In a pilot study conducted by the investigators, a 15% decrease in the incidence of shivering with gabapentin as compared to tramadol was observed. We randomly allocated 50 persons to each of the three groups for the study. A *post hoc* power analysis was conducted using the software package, G* Power (Faul and Erdfelder 1992). Power of the study came out to be 0.92 with 10% chance of error and effect size of 0.306 for total sample size 150 i.e., 50 patients per study group assuming 15% decrease in incidence of shivering as shown in the pilot study.

RESULTS

In this study, a total of 174 patients were assessed for eligibility, out of which 150 patients completed the study with 50 patients in each group [Figure 1]. All three groups were statistically comparable with regards to mean age, body weight, height, sex distribution, body mass index (BMI), ASA physical status, total amount of fluid administered, operation theatre temperature and duration of surgery and anaesthesia ($P > 0.05$) [Table 1].

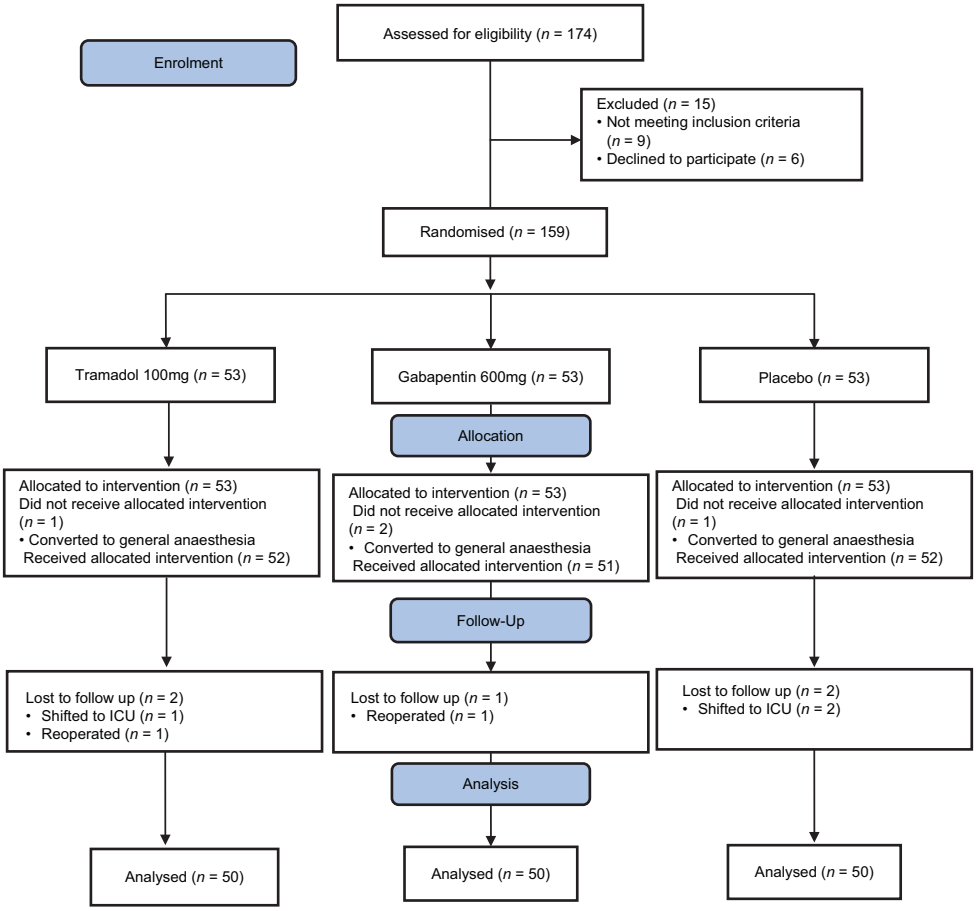

Figure 1: Consolidated standards of reporting trials flow diagram showing patient progress through the study phases; ICU: Intensive care unit

Mean axillary, forehead and tympanic membrane temperature recordings throughout the observation period were comparable among the three groups ($P > 0.05$). All the mean temperatures showed a downward trend during the course of surgery which was comparable in all the groups and was statistically insignificant ($P > 0.05$). Mean HR, systolic and diastolic blood pressure, mean arterial pressure, oxygen saturation and respiratory rate were comparable in all the groups during the peri-operative period. Highest dermatomal level attained after spinal anaesthesia was comparable in all the groups ($P = 0.37$) [Figure 2].

The incidence of shivering in group A (18%) and group B (20%) was statistically similar. However, both the groups had significantly reduced incidence of shivering as compared to group C (46%) ($P = 0.00$). Incidence of grade 1 and grade 2 shivering was comparable in all the groups ($P = 0.6$ and 0.3). Incidence of grade 3 and grade 4 shivering was significantly less in group A (14% & 0%) and B (8% & 6%) as compared to group C (30% & 16%)($P = 0.01$ and 0.01) [Table 2]. Two patients in group C had recurrence of shivering which was grade 2, whereas none of the patients in group A and B had recurrence of shivering. However, both the repeat episodes did not warrant treatment since these occurred and subsided within 30 min of rescue tramadol administration.

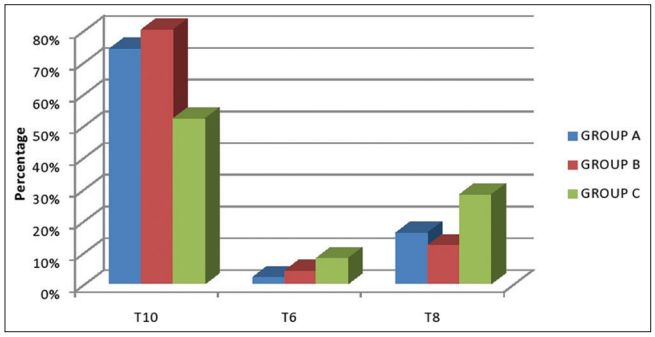

Figure 2: Highest dermatomal level achieved in three groups

The mean time for onset of shivering was maximum in group B (38 ± 9.19 min) followed by group A (34.44 ± 7.26 min) and group C (32.61 ± 7.52 min) but the difference was statistically not significant ($P = 0.21$). The mean time taken for cessation of shivering after administration of rescue drug was least in group A (3.67 ± 0.71 min), followed by group B (4.10 ± 0.99 min) and maximum in group C (6.91 ± 2.04 min). This difference was statistically significant between groups A vs. C ($P = 0.00$), B vs. C ($P = 0.00$) and non-significant between groups A vs. B ($P = 0.57$) [Table 3].

Rescue tramadol consumption for management of shivering was similar in group A (9.0 ± 19.4 mg) and B (10.0 ± 20.02 mg) ($P = 0.82$), whereas both groups consumed significantly less tramadol than group C (23.0 ± 25.2 mg) ($P = 0.00$ and 0.00).

Table 1: Demographic characteristics of the patients, OT temperature and duration of surgery and anaesthesia in three groups

	Group A	Group B	Group C	*P*	*P*		
					A vs. B	A vs. C	B vs. C
Age (years)*	43.44±4.24	39.66±14.82	39.26±13.84	0.276	0.189	0.146	0.889
Weight (kg)*	75.06±12.88	75.12±2.43	75.43±12.47	0.988	0.981	0.884	0.903
Height (m)*	1.72±0.07	1.71±0.08	1.72±0.09	0.868	0.614	0.914	0.691
BMI (kg/m^2)* †	25.41±4.36	25.83±5.13	25.69±4.63	0.902	0.657	0.761	0.888
Gender (M/F)	46/4	37/13	41/9	0.059	0.031	0.137	0.334
ASA PS (I/II/III) ‡	20/22/8	23/15/12	24/21/5	0.305	0.311	0.583	0.142
Operating theatre temperature (°C)*	21.10±0.89	20.92±0.78	20.82±0.80	0.230	0.276	0.091	0.544
Duration of surgery (min)*	82.10±20.53	83.70±20.47	85.50±21.12	0.714	0.700	0.413	0.665
Duration of spinal anaesthesia (min)*	187.60±13.18	189.40±14.90	191.20±12.88	0.423	0.512	0.190	0.512
Intravenous fluid administered (ml)*	1486±261.87	1466±259.99	1442±240.82	0.688	0.695	0.389	0.638

*Mean±standard deviation, † BMI=body mass index, ‡ ASA PS=American Society of Anesthesiologists Physical Status, OT=Operation Theatre

Table 2: Incidence of grades of shivering in three groups

Grade	Number of patients (%)			Total	Chi-square value	*P*	*P*		
	Group A	Group B	Group C				A vs. B	A vs. C	B vs. C
Grade 0	41 (82%)	40 (80%)	27 (54%)	108	12.103	0.002	0.798	0.002	0.005
Grade 1	1 (2%)	1 (2%)	0 (0%)	2	1.014	0.602	1.000	0.315	0.315
Grade 2	1 (2%)	2 (4%)	0 (0%)	3	2.041	0.360	0.558	0.315	0.495
Grade 3	7 (14%)	4 (8%)	15 (30%)	26	9.026	0.011	0.525	0.090	0.009
Grade 4	0 (0%)	3 (6%)	8 (16%)	11	9.614	0.008	0.242	0.006	0.200

The incidence of nausea/vomiting in group A (26%) and B (20%) was significantly less than in group C (48%). Incidence of dizziness/sedation (sedation score ≥2) was significantly more in group B (22%) as compared to group A (4%) and group C (0%). The incidence of hypotension and bradycardia was similar in all the three groups. No patient in any group had allergic drug reaction. [Table 4].

DISCUSSION

Post-operative shivering can be extremely distressing to the patients. Thus, prophylaxis would be highly desirable as this approach has the potential to avert many possible complications. The dose of tramadol administered in this study is within the recommended therapeutic dose of 100 mg for anti-shivering effects.[6,7] Similarly, the dose of gabapentin premedication was well within the recommended therapeutic dose range of 300–1200 mg.[9,10,14] The duration of surgery and anaesthesia was similar in all the three groups. This is important as increased duration of surgery has been shown to be associated with greater incidence of shivering.[15] The baseline mean temperature was comparable in all three groups. This again is extremely important as low core body temperature is an independent predictor of increased post-anaesthesia shivering.[3] The mean temperature showed a downward trend during the course of surgery in all three groups but the difference was statistically insignificant. This decrease in temperature is expected as spinal anaesthesia induced vasodilatation results in heat loss with progressive reduction in temperature.[15]

Under spinal anaesthesia, multiple etiological factors contribute towards hypothermia which includes vasodilation secondary to sympathetic nerve fibre blockade, core to periphery redistribution of heat and administration of intravenous fluids. In our study, incidence of shivering in tramadol group (18%) was significantly less as compared to placebo group (46%). Similarly Tewari *et al.* reported 7.5% incidence of shivering in tramadol group as compared to 40% in placebo group.[8] Adinehmehr *et al.* reported shivering in 10% patients administered tramadol prophylactically as compared to 30% patients in placebo group, which is similar to our study.[16]

Incidence of shivering in gabapentin group in our study was 20% which was comparable to tramadol group and was significantly lower than placebo (46%). Ozgencil *et al.* noticed a reduction in incidence of shivering in gabapentin group (6.7%) as compared to placebo (26.7%) in their study on perioperative administration of gabapentin for pain relief.[10] Vasigh *et al.* also reported 10.5% incidence of shivering in gabapentin group as compared to 42.1% in control group, which is similar to our study.[17]

Grade 3 and 4 shivering was observed in 46% patients in placebo group in our study. Similarly, Mittal *et al.* and Kundra *et al.*, have also reported 72.4% and

Table 3: Onset of shivering and cessation of shivering in three groups

	Group A	Group B	Group C	*P*	*P*		
					A vs. B	A vs. C	B vs. C
Onset of shivering (min)*	34.44±7.26	38.00±9.19	32.61±7.52	0.209	0.333	0.557	0.079
Cessation of shivering after rescue drug (min)*	3.67±0.71	4.10±0.99	6.91±2.04	0.000	0.568	0.000	0.000

* Mean±standard deviation

Table 4: Incidence of adverse effects in three groups

Adverse effect	Number of patients (%)			Chi-square value	*P*	*P*		
	Group A	Group B	Group C			A vs. B	A vs. C	B vs. C
Dizziness/sedation								
< 2	48 (96%)	39 (78%)	50 (100%)	23.741	0.000	0.015	0.495	0.001
> 2	2 (4%)	11 (22%)	0 (0%)					
Nausea vomiting								
Grade 1	37 (74%)	40 (80%)	26 (52%)	10.102	0.006	0.475	0.022	0.003
Grade 2	1 (2%)	2 (4%)	4 (8%)	2.098	0.350	0.558	0.168	0.399
Grade 3	8 (16%)	6 (12%)	14 (28%)	4.567	0.102	0.564	0.147	0.045
Grade 4	2 (4%)	2 (4%)	5 (10%)	2.128	0.345	1.000	0.239	0.239
Grade 5	2 (4%)	0 (0%)	1 (2%)	2.041	0.360	0.495	0.315	0.558
Hypotension	6 (12%)	3 (6%)	7 (14%)	1.819	0.403	0.487	0.766	0.318
Bradycardia	0 (0%)	0 (0%)	0 (0%)					
Allergic reaction	0 (0%)	0 (0%)	0 (0%)					

40.9% incidence of grades 3 and 4 shivering in control groups in their studies.[1,18] Sahi *et al.*, reported only 10% incidence of grade 3 shivering in control group.[19] These differences can be explained by usage of active rewarming when core temperature fell below 35°C in study by Sahi *et al.*, whereas no rewarming was done in our study.

In our study, the incidence and severity of shivering was comparable in both tramadol and gabapentin group; hence, we suggest that gabapentin 600 mg is equally effective as tramadol 100 mg as an anti-shivering agent.

After rescue drug (tramadol) administration, shivering subsided significantly earlier in tramadol group (3.67 ± 0.71 min) as compared to placebo group (6.91 ± 2.04 min). Guha *et al.*, also reported similar time for cessation of shivering after tramadol administration (2.5 ± 0.7 min).[20] Notably, the time for shivering to subside after rescue drug was similar with tramadol and gabapentin. Thus, both tramadol and gabapentin appear to be equally effective in decreasing the duration of shivering after rescue drug administration. These observations highlight the anti-shivering effect of gabapentin not only in reducing the incidence/severity of shivering but also in earlier cessation of shivering after rescue drug.

The incidence of nausea and vomiting was significantly higher in placebo group as compared to tramadol and gabapentin. This may be attributed to higher amount of rescue tramadol used in this group. The incidence of sedation was greater in gabapentin group which may be explained by the sedative effects of gabapentin.[21] However, none of the patients were excessively sedated so as to require airway intervention.

Certain limitations of our study are worth mentioning. Firstly, we used only single dose of gabapentin. Further dose-finding studies may be planned to arrive at an optimal dose of gabapentin. Secondly, studies evaluating different kind of surgeries under regional/general anaesthesia are required before making any recommendations about use of gabapentin as a prophylactic agent for prevention of shivering.

We conclude that the prophylactic oral administration of both tramadol 100 mg and gabapentin 600 mg is equally effective for prevention of shivering in patients undergoing orthopaedic surgeries under spinal anaesthesia. Use of gabapentin is associated with increased sedation score but lesser incidence of nausea and vomiting as compared to tramadol.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mittal G, Gupta K, Katyal S, Kaushal S. Randomised double-blind comparative study of dexmedetomidine and tramadol for post-spinal anaesthesia shivering. Indian J Anaesth2014;58:257-62.
2. Wason R, Jain N, Gupta P, Gogia AR. Randomized double-blind comparison of prophylactic ketamine, clonidine and tramadol for the control of shivering under neuraxial anaesthesia. Indian J Anaesth 2012;56:370-5.
3. Lopez MB. Postanaesthetic shivering-from pathophysiology to prevention. Rom J Anaesth Intensive Care 2018;25:73-81.
4. Bajwa SS, Gupta S, Kaur J, Singh A, Parmar SS. Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study. J Anaesthesiol Clin Pharmacol 2012;28:86-91.
5. 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;55:242-6.
6. Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering – A new look at tramadol. Anaesthesia 2002;57:394-8.
7. Mohta M, Kumari N, Tyagi A, Sethi AK, Agarwal D, Singh M. Tramadol for prevention of postanaesthetic shivering: A randomised double-blind comparison with pethidine. Anaesthesia 2009;64:141-6.
8. Tewari A, Dhawan I, Mahendru V, Katyal S, Singh A, Narula N, *et al*. A comparative study evaluating the prophylactic efficacy of oral clonidine and tramadol for perioperative shivering in geriatric patients undergoing transurethral resection of prostate. J Anaesthesiol Clin Pharmacol 2014;30:340-4.
9. Syal K, Goma M, Dogra RK, Ohri A, Gupta AK, Goel A. "Protective premedication": A comparative study of acetaminophen, gabapentin and combination of acetaminophen with gabapentin for post-operative analgesia. J Anaesthesiol Clin Pharmacol 2010;26:531-6.
10. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y. Perioperative administration of gabapentin 1,200 mg day-1 and pregabalin 300 mg day-1 for pain following lumbar laminectomy and discectomy: A randomised, double-blinded, placebo-controlled study. Singapore Med J 2011;52:883-9.
11. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW.

The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. Anaesthesia 1977;52:32-6.
12. Kim ES, Lee J, Choi JH. Optimal dose range of epidural naloxone to reduce nausea in patients receiving epidural morphine. Can J Anaesth 2004;51:1048-9.
13. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose- response study. Anesthesiology 1994;81:591-601.
14. Salama ER, Amer AF. The effect of preemptive gabapentin on anaesthetic and analgesic requirementsin patients undergoing rhinoplasty: A prospective randomised study. Indian J Anaesth 2018;62:197-201.
15. Eberhart LHJ, Döderlein F, Eisenhardt G, Kranke P, Sessler DI, Torossian A, *et al*. Independent risk factors for postoperative shivering. Anesth Analg 2005;101:1849-57.
16. Adinehmehr L, Salimi S, Majedi MA, Alizadeh A, Sane S. Comparison the effects of oral tizanidine and tramadol on intra- and post- operative shivering in patients underwent spinal anesthesia. Adv Biomed Res 2018;7:140.
17. Vasigh A, Jaafarpour M, Khajavikhan J, Khani A. The effect of gabapentin plus celecoxib on pain and associated complications after laminectomy. J Clin Diagn Res 2016;10:UC04-08. doi: 10.7860/JCDR/2016/17923.7346.
18. Kundra TS, Kuthiala G, Shrivastava A, Kaur P. A comparative study on the efficacy of dexmedetomidine and tramadol on post-spinal anesthesia shivering. Saudi J Anaesth 2017;11:2-8.
19. Sahi S, Singh MR, Katyal S. Comparative efficacy of intravenous dexmedetomidine, clonidine, and tramadol in postanesthesia shivering. J Anaesthesiol Clin Pharmacol 2016;32:240-4.
20. Guha Banerjee S, Nath PK, Halder R, Bandyopadhyay U. Prophylactic use of intravenous clonidine compared to tramadol in prevention of intraoperative shivering under regional anesthesia. Anesth Essays Res 2017;11:477-82.
21. Lunn TH, Husted H, Laursen MB, Hansen LT, Kehlet H. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: A randomized, double-blind, placebo-controlled dose-finding study. Pain 2015;156:2438-48.