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A Randomized Controlled Trial for Comparison of Inj. Nalbuphine Hydrochloride Versus Inj.Tramadol Hydrochloride for Treatment of Perioperative Shivering in Regional Anaesthesia

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Abstract

Background: Peri-operative shivering remains a common issue often encounteredduring surgery. Various pharmacological and nonpharmacological methods are employed to control shivering. Nalbuphine and tramadol are shown to possess potent anti-shivering effects. Hence the present study was undertaken to compare the effect of Inj. Nalbuphine Hydrochloride and Inj. Tramadol Hydrochloride for treatment of perioperative shivering in regional anaesthesia. **Method:** Total 90 patients of either sex, aged 18-65years, ASA I/II, who scheduled for elective surgeries under regional anaesthesia were randomly divided into three groups of 30 patients in each. Group N received 0.08μg/kg Nalbuphine diluted in 5 ml of 0.9% normal saline, Group T received 0.5 mg/kg Tramadol diluted in 5 ml of 0.9% normal saline and Group C (Controlled) received 5ml of 0.9% normal saline. **Results:** In group T, mean score according to Filos sedation was found to be 1.10±0.31, and in group N it was 1.10±0.31 whilein controls it was 1.10±0.30, ($p>0.05$). Tramadol shows lesser cessation time of shivering (3.73±1.43min) as compared to nalbuphine (4.08±1.28 min), though the difference was not statistically significant, ($p=0.36$).Theinsignificant difference found between the response intramadol and nalbuphine groups, ($p=0.36$) but significant difference was observed between the response of normal saline and tramadol ($p<0.0001$) and between the response of normal saline and nalbuphine ($p<0.0001$).The groups were found to be matched regarding recurrence ($p=0.120$), hypotension($p=0.200$), nausea ($p=0.133$), vomiting ($p=0.133$)and

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pruritis (p=0.364). **Conclusion:** Tramadol administration in dose of 0.5mg/kg or Nalbuphine administration in dose of 0.08mg/kg is recommended to counteract perioperative shivering in subjects undergoing surgery under regional anaesthesia with central neuraxial blockade.

Keywords:Shivering; Nalbuphine; Tramadol; Regional anaesthesia;Recurrence; Pruritis

Introduction

Perioperative shivering during anaesthesia is a common problem encountered in the operation theatre and it has an incidence of 30% to 40% following regional anesthesia[1]. For the benefit of the patients, adequate management of shivering during operation is one of the goals of anesthesiologists. This is because of the various unpleasant and harmful effects caused by shivering in many patients; especially, respiratory, and cardiac disease patients. For this reason, aggressive and optimal treatment of perioperative shivering is essential to reduce the morbidity of the patients [2].

Various nonpharmacological and pharmacological interventions are used to control post spinal anesthesia shivering. Nonpharmacological methods include convection warming system and radiant heat system which uses specialized equipment’s to control or prevent shivering which are often expensive and are not practical in all clinical settings. Pharmacological agents used to control shivering include pethidine, clonidine, tramadol, nalbuphine, ondansetron, ketanserin, magnesium sulphate, propofol, alfentanil, sufentanil, physostigmine, doxapram, methylphenidate, ketamine, etc. However,a number of drugs have been attributed to potent anti-shivering properties [3, 4], but due to their different adverse effects, search for an ideal anti-shivering agent is still going on.

Nalbuphine hydrochloride, a semisynthetic agonist/antagonist opioid, is an intravenous analgesia having significant anti-shivering effects on post-anesthetic shivering. Nalbuphine hydrochloride binds to kappa, mu, and delta opioid receptors but not to sigma opioid receptors. It exerts the analgesic actions primarily through kappa opioid receptor agonism and partially through mu opioid receptor agonism [5]. This intravenous analgesia commences in 2-3 min, reaches a maximum in 30 min and lasts 2-6 h. Nalbuphine has been shown to have many side effects, including dizziness, sweatiness, dry mouth, nausea, sedation, vomiting, vertigo, clamminess, and headache [6].

Tramadol hydrochloride (TH), a well-known centrally acting analgesic is known for its strong analgesic activity. TH lasts only 4 h and in order to maintain the effective plasma

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concentration, TH has to be administered more than 5 times per day to achieve the expected therapeutic effect [7]. It has certain side effects such as nausea, vomiting, drowsiness, and dizziness. In addition, they can cause a depressive effect on the cardiovascular and respiratory systems. When tramadol is taken at higher doses it may cause psychological addiction[8].

Moreover, nalbuphine and tramadol both delivers a rapid and potent anti-shivering effect. Nirala et al observed that response rate of tramadol was 84% and that of nalbuphine was 80%. There are mixed notions regarding the efficacy of nalbuphine and tramadol HCl for the treatment of shivering [9]. Also, to our knowledge no such comparison has been done in perioperative shivering in regional anesthesia in the Indian population. Thus, we aimed to compare the effects of Nalbuphine 0.08mg/kg IV with Tramadol 0.5mg/kg IV for treating shivering developed perioperatively after regional anaesthesia.

Materials and Methods

After obtaining Institutional Ethics Committee approval and written informed consent from all the patients, this randomized controlled trial was conducted in the Department of Anesthesiology of medical college during aperiod from January 2020- November 2021. Total 90 patients aged 18-65years, ASA I/II, of either sex who developed Wrench grade 3 or grade 4 shivering post regional anesthesia for lower limb, lower abdominal surgeries, and gynaecological procedures and orthopaedic surgeries and with hemodynamics HR>60/min, SBP>100 mmHG, after at least 15 minutes of administering regional anesthesia were included in the study.Patients with morbid obesity (BMI>40%), systemic co-morbidities like cardiovascular disease, hepatic diseases, renal disease, chronic obstructive lung diseases, etc, patient's allergy or contraindication to drugs used in study, pregnant ladies and lactating mothers were excluded from the study.

On the day prior to surgery a thorough pre-operative assessment of the patient was performed including general physical examination and systemic examination. Patients were kept nill per oral for 8-10 hrs prior to surgery. Theselected patients were divided into 3 groups of 30 patients in each by computer generated allocation. Group N (n=30)received 0.08mg/kg IV diluted up to 5cc with normal saline for treatment of shivering. Group T (n=30)received 0.5mg/kg IV diluted up to 5cc with normal saline for treatment of shivering. Group C (n=30): control group received 5cc of Normal Saline IV.

Upon arrival in the operation theatre, standard monitors were attached and all the baseline parameters such as heart rate (HR), noninvasive blood pressure (NIBP), oxygen

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saturation (SPO2), electrocardiography (ECG), and body temperature (axillary) was recorded. The 18G intravenous cannula was inserted and preloading was done with Ringer's lactate solution 10 ml/kg before giving regional anaesthesia. All operation theatres were maintained at an ambient temperature of 22 +/: 2˚C. Supplemental oxygen was administered to all the patients at the rate of 5 lit/min with face mask and patients were covered with drapes but not actively warmed. I.V. fluids and anesthetics were administered at room temperature. Vital parameters such as HR, SPO2, NIBP was recorded at intervals of every 5 min. Attention was given to complications if occurred after giving the study drug.

The level of sedation was assessed on a four-point scale as per Filos et al: Grade 1: Awake and alert, Grade 2: Drowsy, responsive to verbal stimuli, Grade 3: Drowsy, arousable to physical stimuli, Grade 4: Unarousable [10].Shivering was graded using a four-point scale as per CROSSLEY AND MAHAJAN or WRENCH 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) and grade 4 (gross muscle activity involving the whole body).

In case of recurrence of shivering, patients were treated with warm forced air blankets and warm fluids. These groupswere monitored for time of onset of shivering, response to shivering after treatment, time taken for cessation of shivering, and recurrence of shivering. Also, hemodynamic profile of the respective groups was monitored and was noted if there was any hypotension or bradycardia. Monitoring of regional anesthesia dermatome level was done. Adverse effects such as nausea, vomiting, pruritus, hypotension, oxygen desaturation and sedation scores were also noted.

Statistical Analysis

Data was expressed as percentage and mean ± S.D. Kolmogorov Smirnov analysis was performed for checking linearity of the data. Student's t test was used to check the significance of difference between two parameters in parametric data. ANOVA was used to test the significance of difference between more than two parameters in parametric data. Fisher's exact test or Chi square test was used to analyse the significance of difference between frequency distribution of the data. P value<0.05 was considered as statistically significant.SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

Observations and Results

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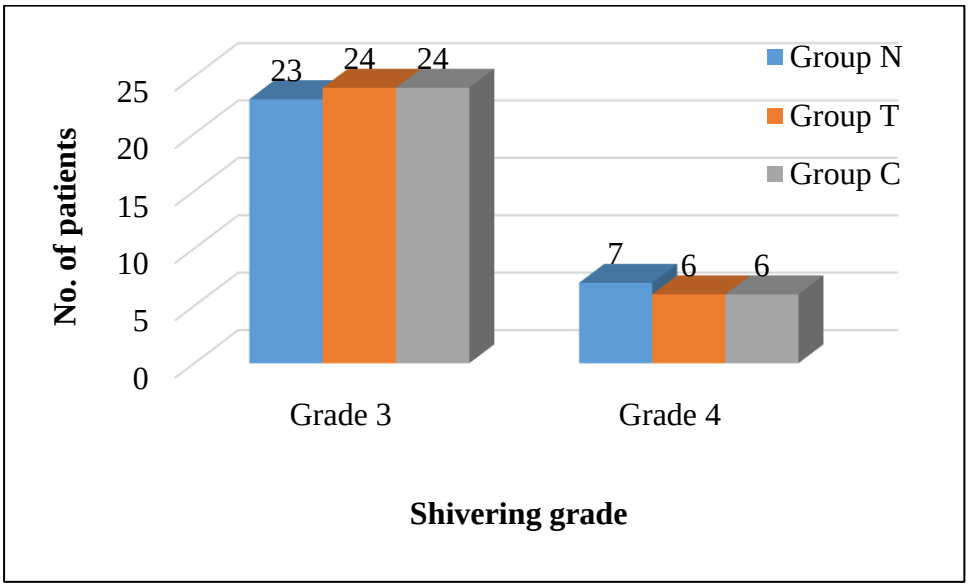
The most common age group of patients was found to be 51-60 years (35.6%)followed by 31-40 years (32.2%), 41-50 years (23.3%) and≥60 years (7.8%). Out of 90 subjects, 74 (82.2%) were found to have ASA score of one while, 16 (17.8%) subjects belonged to ASA score two category, (p>0.05). However, all the three groups were comparable and found no significant difference with respect to demographic data of the patients as shown in table 1.

Table 1: Comparison of demographic data in the study groups

Parameters		Group N	Group T	Group C	P value
Age years	Mean	46.50±10.75	46.07±8.71	41.57±10.16	0.108
Gender	Male	17 (56.7%)	14 (46.7%)	15 (50.0%)	0.733
	Female	13 (43.3%)	16 (53.3%)	15 (50.0%)	
BMI	Normal	21 (70.0%)	19 (63.3%)	28 (93.3%)	0.018
	Overweight	09 (30.0%)	11 (36.7%)	02 (6.7%)	
Mallampati classification	1	15 (50.0%)	16 (53.3%)	16 (53.3%)	0.956
	2	15 (50.0%)	14 (46.7%)	14 (46.7%)	

All the three groups were found to be matched regarding shivering grade (p=0.935) as depicted in figure 1.

Figure 1: Comparison of shivering grade in the study groups



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The mean Filos Sedation score in group N was 1.10±0.31 and in group T it was 1.10±0.31. The groups were found to be matched regarding Filos sedation score (p=1.00). The mean cessation time in group N and group T was 4.08±1.28 min and 3.73±1.43 min respectively which was not significant with p value of 0.36.

There was no significant difference between the response in thetramadol and nalbuphine groups (p=0.36). While significant difference was observed between the response of normal saline and tramadol (p<0.0001) as well as significant response between normal saline and nalbuphine (p<0.0001), (Table 2).

Table 2: Comparison of response in the study subjects

Group	Response		P value
	Yes	No	
Nalbuphine	24 (80.0%)	06 (20.0%)	0.36
Tramadol	26 (86.7%)	04 (13.3%)	
Normal saline	04 (13.3%)	26 (86.7%)	<0.0001
Tramadol	26 (86.7%)	04 (13.3%)	
Normal saline	04 (13.3%)	26 (86.7%)	<0.0001
Nalbuphine	24 (80.0%)	06 (20.0%)	

There was no difference in terms of recurrence of shivering between these two medications, (p=120). However, the groups were found to be matched regarding hypotension(p=0.200), nausea (p=0.133), vomiting (p=0.133)and pruritis (p=0.364) as shown in table 3.

Table 3: Recurrence of shivering and side effectsin the study groups

Side effects	Group N	Group T	Group C	P value
Recurrence	03 (12.5%)	03 (11.5%)	02 (50.0%)	0.120
Hypotension	03 (10.0%)	03 (10.0%)	00 (0.0%)	0.200
Nausea	03 (10.0%)	04 (13.3%)	00 (0.0%)	0.133
Vomiting	03 (10.0%)	04 (13.3%)	00 (0.0%)	0.133
Pruritus	01 (3.3%)	00 (0.0%)	00 (0.0%)	0.364

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Discussion

Shivering is a common side effect of anaesthesia, and it leads different outcomes and inconvenience to the patient; appropriate efforts must be taken for its avoidance and treatment. The actual mechanism of shivering during spinal anaesthesia, however, is still unknown. It is believed that a combination of anesthesia-induced thermoregulatory impairment and exposure to a cool environment makes most unwarmed surgical patients hypothermic [11]. In present study, to exclude confounding factors, intravenous fluids and drugs were maintained at room temperature and operation theatres were kept an ambient temperature of 22°C–24°C.Shivering is still a widespread concern in the peri- and post-operative period despite different medicines and strategies to prevent it. All three groups were comparable and found no significant difference in regard to demographic dataof patients which is comparable with the previous studies [9, 12, 13].

During regional anaesthesia, all patients were awake and alert with a sedation score of 1. And after treatment for shivering, the sedation score was 2. No patients in current study were noticed with a score of 3 or 4. There was no statistical significance between three groups. The groups were found to be matched regarding the Filos sedation score (p=1.000). It was similar to study conducted by Vanderistappen et al, where they evaluate the efficacy of clonidine on post operative shivering and concluded there was no increase in post operative sedation [14]. The shivering grades were statistically analysed, and the difference between them was shown to be statistically insignificant at various intervals, (p=0.935). This findingis in accordance with the study done by Nirala et al [9], and Shukla et al [15]. The time taken for disappearance of shivering was shorter in group T than group N (3.73±1.43 minutes and 4.08±1.28 minutes, p=0.36). Though the difference between them was shown to be statistically insignificant, (p=0.36).These findings are in line with those of a few other studies [12, 16].

The comparison of response between nalbuphine and tramadol was found to be statistically not significant, (p=0.36). but significant difference found between normal saline and tramadol response (p<0.0001) as well as normal saline and nalbuphine response (p<0.0001). This implies both- nalbuphine and tramadol had significantly better response as compared to control with no anti-shivering drug. Thus, according to our findings both the drugs are effective. Similar findings are reported in study conducted byNirala et al [9].

There was no difference in terms of recurrence of shivering between the two medications which is comparable with the earlier studies [12, 17]. The adverse effects such as hypotension, hypertension, sedation, respiratory depression, nausea, and vomiting limit the

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use of drugs such as nalbuphine and tramadol. Hence, the hunt for an ideal anti-shivering agent is continuing. Three subjects in the nalbuphine group and three in the tramadol group were found to have hypotension. We did not find any subject in the control population to present with hypotension. Though, we did not find any significant difference in the use of tramadol and nalbuphine regarding nausea (p=0.133), vomiting (p=0.133)and pruritis (p=0.364). Multiple studies have observed higher incidences of nausea as well as vomiting in the tramadol group [9, 18, 19]. However, Jyothi et al who compared analgesic effect of different doses of intrathecal nalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal and orthopaedic surgeries, did not find any complication of pruritis in their study subjects [20].

The role of nalbuphine in the treatment of post-anesthetic shivering was assessed previously [2, 21]. It could be a good choice because of its antishivering and sedative properties. When 10 mg nalbuphine was used to treat shivering and suppression of shivering was accomplished, Götz et alreported that nalbuphine 10mg suppresses postoperative shivering as efficiently as meperidine within 4.6±4.1 min following the injection of nalbuphine [22]. Tramadol's anti-shivering effect is thought to be due to its opioid, serotonergic, and noradrenergic activities, or both [23]. Various studies reported about different response rate of treatment with a dose of 0.5 mg.kg of tramadol, [23-25] and the response rate of treatment in current study was 95.56% which was in accordance with Reddy and Chiruvella [24].

Limitations

The study was conducted in a single centre and a limited population. Thus, we recommend such studies to be done in diverse group of population and higher sample size.

Conclusion

In the present study, both nalbuphine and tramadol causes effective response for shivering relief.Nalbuphine at a dose of 0.08μg/kg I.V. and Tramadol used at a dose of 0.5mg/kg I.V. both attenuated shivering when given after development of post-regional anesthesia shivering in patients undergoing lower limb, lower abdominal surgeries, gynaecological procedure, and orthopaedic surgeries. Hence, they are recommended for use to counteract perioperative shivering in subjects undergoing surgery under regional anaesthesia with central neuraxial blockade.

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References

1. Nallam SR, Cherukuru K, Sateesh G. Efficacy of intravenous ondansetron for prevention of postspinal shivering during lower segment cesarean section: A double:blinded randomized trial. Anesthesia, essays and researches. 2017;11(2):508.
2. Haque MF, Rashid MH, Rahaman MS, Islam MR. Comparison between tramadol hydrochloride & nalbuphine hydrochloride in the treatment of per-operative shivering after spinal anaesthesia. Mymensingh Med J. 2011;20(2):201-5.
3. De Witte JL, Kim J:S, Sessler DI, Bastanmehr H, Bjorksten AR: Tramadol reduces the shivering, vasoconstriction, and sweating thresholds. AnesthAnalg 1998; 87: 173–9.
4. Iwashita H, Matsukawa T, Ozaki M, Sessler DI, Imamura M, Kumazawa T. Hypoxemia decreases the shivering threshold in rabbits anesthetized with 0.2 minimum alveolar anesthetic concentration isoflurane. Anesthesia& Analgesia. 1998 Dec 1;87(6):1408:11.
5. Tavana T, Rezvani AR, Karimi:Maleh H. Pt:Pd:dopedNiO nanoparticle decorated at single:wall carbon nanotubes: An excellent, powerful electrocatalyst for the fabrication of An electrochemical sensor to determine nalbuphine in the presence of tramadol as two opioid analgesic drugs. Journal of pharmaceutical and biomedical analysis. 2020;189:113397.
6. Chen Y, Zhou A, Liu B, Liang J. Tramadol hydrochloride/ montmorillonite composite: Preparation and controlled drug release. Applied Clay Science. 2010;49(3):108:12.
7. Ege B, Ege M, Koparal M, Alan H. Comparison of the anesthetic efficiency of lidocaine and tramadol hydrochloride in orthodontic extractions: a split:mouth, prospective, randomized, double:blind study. Journal of Oral and Maxillofacial Surgery. 2020;78(1):52:62.
8. De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. The Journal of the American Society of Anesthesiologists. 2002;96(2):467:84.
9. Nirala DK, Prakash J, Ram B, Kumar V, Bhattacharya PK, Priye S. Randomized double:blinded comparative study of intravenous nalbuphine and tramadol for the treatment of postspinalanesthesia shivering. Anesthesia, Essays and Researches. 2020;14(3):510.
10. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose:response study. Anesthesiology. 1994;81(3):591:601.
11. Bhattacharya PK, Bhattacharya L, Jain RK, Agarwal RC. Post anaesthesia shivering (PAS): A review. Indian J Anaesth. 2003;47(2):88:93.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

12. Megalla SA, Mansour HS. Dexmedetomidine versus Nalbuphine for treatment of postspinal shivering in patients undergoing vaginal hysterectomy: a randomized, double blind, controlled study. Egyptian Journal of Anaesthesia. 2017;33(1):47:52.
13. Tudimilla S, Suryawanshi C, SaravanKumar K. A Comparative Evaluation of Nalbuphine and Tramadol for the Control of Post:Spinal Anaesthesia Shivering. Cureus. 2021;13(12).
14. Vanderstappen I, Vandermeersch E, Vanacker B, Mattheussen M, Herijgers P, Van Aken H. The effect of prophylactic clonidine on postoperative shivering: A large prospective double-blind study. Anaesthesia. 1996;51(4):351:5.
15. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post:spinal anaesthesia shivering. Indian journal of anaesthesia. 2011;55(3):242.
16. Thomas S, Pradhan A, and Chauhan D. A Randomised Clinical Trial to Compare the Efficacy of Tramadol and Nalbuphine for Treatment of Shivering after Spinal Anaesthesia in Patients Posted for Lower Limb Orthopaedic Surgery. Journal of Clinical & Diagnostic Research. 2021;15(5).
17. Taneja P, Bansal Y, Sharma N, Banotra KK. A randomized control trial for comparison among Nalbuphine, Tramadol and placebo for treating post anesthetic shivering undergoing spinal anesthesia in Cessarian section. Journal of Pharmaceutical Sciences and Research. 2019;11(5):2095:8.
18. Solanki RN, Gosai ND, Joshi GM, Patel BM, Modi HV, Jain R. A comparative study of intravenous nalbuphine HCl and tramadol HCl for post:operative pain relief following orthopaedic surgeries. Asian Pac J Health Sci. 2015;2(1):155:60.
19. Sharma M, Kharbuja K, Khadka B. Comparison of pethidine and tramadol for the control of shivering in patients undergoing elective surgery under spinal anesthesia. Journal of Lumbini Medical College. 2016;4(2):66:7.
20. Jyothi B, Gowda S, Shaikh SI. A comparison of analgesic effect of different doses of intrathecal nalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal and orthopedic surgeries. Indian Journal of Pain. 2014;28(1):18.
21. Sun J, Zheng Z, Li YL, Zou LW, Li GH, Wang XG, She BZ, Huang XL, Li YT. Nalbuphine versus dexmedetomidine for treatment of combined spinal:epiduralpost:anesthetic shivering in pregnant women undergoing cesarean section. Journal of International Medical Research. 2019;47(9):4442:53.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

22. Götz E, Bogosyan S, Müller E, Litz R. Treatment of postoperative shivering with nalbuphine. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie: AINS. 1995;30(1):28:31.
23. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepiduralanesthetic shivering in parturients. Anesthesia& Analgesia. 2001 Nov 1;93(5):1288:92.
24. Reddy VS, Chiruvella S. Clonidine versus tramadol for post spinal shivering during caesarean section: A randomized double blind clinical study. Journal of obstetric anaesthesia and critical care. 2011;1(1):26.
25. Mittal G, Gupta K, Katyal S, Kaushal S. Randomised double:blind comparative study of dexmedetomidine and tramadol for post:spinal anaesthesia shivering. Indian journal of anaesthesia. 2014;58(3):257.