Comparative Assessment of Clonidine and Tramadol on Post-Spinal Anaesthesia Shivering among Patients with Lower Abdominal and Lower Limb Surgeries: A Randomized Controlled Trial

Mansi Jain[1], Malay Patel[2], Monal Ramani[3], Monisha Pukayastha[4]

ABSTRACT

Introduction: Spinal anaesthesia is commonly used as a safe anaesthetic technique for both elective and emergency operations. Shivering is known to be a frequent complication reported in 40 to 70% of the patients undergoing surgery in regional anaesthesia. Hence, the aim of the present study was to compare the efficacy of clonidine, and α2-agonist with that of tramadol, a non-opioid analgesic for control of shivering after spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries.

Material and methods: The present study was a randomized controlled trial which was conducted among 60 patients aged between 18 to 70 years, who were scheduled for abdominal and lower limb surgeries and who developed shivering following spinal anaesthesia. These 60 patients of ASA grade I and II which were selected randomly after taking informed and written consent from their relatives. Once patient developed shivering, they were randomly allocated into two groups named as Group C and Group T.

Results: Patients who developed shivering grade 3 or 4 were included in study. There was no significant difference between both the groups regarding shivering grade. Out of 30 patients in Group C, shivering subsided in 29(96.7%) patients. While in group T, shivering subsided in 26(86.7%) patients out of 30. There was significant difference in both groups for control of shivering (p= 0.0001) which proved that the rate of success after clonidine was more than that of tramadol.

Conclusion: Both clonidine (75 µg) and tramadol (0.5 mg/kg) can effectively treat patients with post-spinal anaesthesia shivering, but tramadol took longer time for complete cessation of shivering than clonidine.

Keywords: Clonidine, Tramadol, Post-Spinal Anaesthesia Shivering, Randomized Controlled Trial

INTRODUCTION

Central neuraxial anesthesia (spinal anesthesia) is widely used as a safe anesthetic technique for abdominal and lower limb surgeries for elective as well as emergency operative procedures. Shivering is one of the most common complications of a central neuraxial blockade, reported in 40-70% of patients undergoing surgery under regional anesthesia. Shivering is defined as an involuntary, spontaneous, oscillatory mechanical activity of skeletal muscle associated with increased oxygen consumption.[1,2]

Amongst the various causes shivering can be divided into thermoregulatory and non-thermoregulatory in nature. Thermoregulatory shivering occurs as a consequence of hypothermia, and in order to maintain normothermia, vasoconstriction and shivering occurs. Non thermoregulatory shivering is less well understood and may be associated with postoperative pain, release of endogenous pyrogens, uninhibited spinal reflexes and adrenal suppression. In neuraxial anesthesia, it mainly occurs due to impairment of thermoregulatory control secondary to autonomic blockade. Other contributing factors are cold operation theatre environment, cold IV fluids and drug reaction etc.[3,4,5]

Shivering is very unpleasant, physiologically stressful for the patient undergoing surgery and some patients even find the accompanying cold "sensation to be worse than surgical pain."

Complications are increased metabolic rate, increased oxygen consumption (upto100-600%) along with increased CO2 production, ventilation and cardiac output; adverse post-operative outcomes such as wound infection, increased surgical bleeding and morbid cardiac events. It causes arterial hypoxemia, lactic acidosis, increased IOP, ICT as well as it interferes with pulse rate, BP, and ECG monitoring. Shivering per se may aggravate postoperative pain, simply by stretching of surgical incision.[6,7,8]

Shivering is regarded as a final means to increase metabolic heat production when behavioral modification and vasoconstriction together with peripheral arterio-venous shunting of blood in an attempt to increase core body temperature is inadequate. The shivering threshold is an entire 10ºC less than the vasoconstriction threshold. Shivering is not well developed in new-born infants.[9]

Intra operative management of shivering is usually done by either non-pharmacological methods or pharmacological

[1]Senior Resident, Department of Anaesthesia, VMMC & Safdarjung Hospital, New Delhi, [2]Consultant and Head of Cardiac Anaesthesia, Rhythm Heart Institute, Vadodra, [3]Associate Professor, Department of Anaesthesia, BJ Medical College, Ahmedabad, [4]ICU Registrar, Department of Columbia, Asia Hospital, Kolkata, India

Corresponding author: Mansi Jain, D-235, First Floor, Nirman Vihar, New Delhi 110092, India

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agents. In non-pharmacological methods, simple physical measures have been described including increasing the ambient temperature of the operative room, preventing convective heat loss by insulation with surgical drapes, space blankets, warm cotton blankets, ensuring warm skin disinfectant is used prior to draping, and the use of warm intravenous fluids and warm local anaesthetics for neuraxial blockade.[10]

Many drugs of various classes have been documented in the prevention and treatment of post anaesthesia shivering. Various pharmacological treatments like IV opioids, alfentanil, pethidine nalbuphine and meperidine opioid analgesic tramadol and 5-HT antagonists ondansetron have been used. The drugs are substances of several classes including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-Methyl-D-aspartate.[11] Hence, the aim of the present study was to compare the efficacy of clonidine, and α2-agonist with that of tramadol, a non-opioid analgesic for control of shivering after spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries.

MATERIAL AND METHODS

The present study was a randomized controlled trial which was conducted after obtaining institutional ethics committee approval. It was conducted among 60 patients aged between 18 to 70 years, who were scheduled for abdominal and lower limb surgeries and who developed shivering following spinal anaesthesia. These 60 patients of ASA grade I and II which were selected randomly after taking informed and written consent from their relatives. Once patient developed shivering, they were randomly allocated into two groups. In the process of randomization, patients were divided into two groups named as Group C and Group T.

Group-C (Control): Received Inj. clonidine 75µg slow I.V injection diluted in 10ml NS intra-operatively.

Group-T (Treatment): Received Inj. tramadol 1 mg/kg slow I.V injection diluted in 10ml NS intra-operatively.

The patients aged 18 years and above with ASA grade I and II were included in the study. Also, the patients who were scheduled for abdominal and lower limb surgery were taken in the present study. Patients using α2-adrenergic receptors antagonists, opioids, calcium channel blocker, angiotensin converting enzyme inhibitors, patients having dysrhythmia by ECG with body weight more than 120 Kg, heart rate less than 60 beats/min, second- or third degree heart block were not included in this study. Also, patients with systolic blood pressure less than 90 mm Hg, history of hypersensitivity to clonidine and/or tramadol, history of alcohol/substance abuse, history of psychological disorders, known case of autonomic/ diabetic neuropathy and lactating mothers were not taken in this study.

Procedure

All patients were pre-hydrated with 500 ml of Ringer's Lactate solution via an 18-gauge IV cannula. No premedication given to patients. Patients were monitored by non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and SpO2. All patients received 4 L/min of O2 by simple face mask with the patient in the sitting position; spinal analgesia was performed at the level of L3-L4 or L2-L3 through a midline approach using a 23-gauge Quincke spinal needle with the hole pointing upwards.

Hyperbaric 0.5% bupivacaine was injected intrathecally in all patients. Immediately after spinal analgesia patients were laid back to supine position. All operation theatres in which the operations were performed maintained constant humidity (70%) and an ambient temperature of around 21°C to 23°C. Intravenous fluids and anaesthetic drugs were administered at room temperature.

Intravenous fluids were not warmed in order to avoid effect of warm fluid to alter the results of the study. Patients were covered with drapes but not actively warmed. No means of active re-warming were used. Patients were included in the study only if patients developed shivering. Once patients developed shivering, they were divided into two groups. Patients in group C were given inj. clonidine 75µg slow IV injection and patients in group T were given inj. tramadol 1mg/kg slow IV injection. Both the study drugs were given slowly after diluting with 10ml NS.

STATISTICAL ANALYSIS

The calculation was done with statemate 2.0 (graphpad software) where less than 35 patients were required in each group with type I error of 0.05 and the power of the study with 30 cases in each group was taken as 90%. In this study, quantitative data i.e. age, spinal drug dose, time of loss of shivering and hemodynamic variables were presented in terms of mean, SD or range. Unpaired T-test was used for analysis of differences in hemodynamic variables and quantitative demographic data. ASA physical status, sex, sensory block level, shivering grade, number of cases with reappearance were analyzed with chi-squared test. A p value of < 0.05 was considered to be statistically significant. All comparisons were accomplished with EpiInfo software (version 3.5.3, CDC Atlanta) and online graphpad software prism 6.05,2014 at http://www.graphpad.com/quickcalcs.

RESULTS

In the present study, it was found that the present study was conducted among 60 ASA grade I or II patients, aged 18-70 years which were scheduled for abdominal and lower limb surgery. There was no significant difference among the groups regarding age, sex and ASA grading (Table 1). There was no significance difference regarding dose of drug given for spinal anesthesia (0.5% bupivacaine) and sensory level achieved by it (Table 2).

As described earlier, patients who developed shivering grade 3 or 4 were included in study. There was no significant difference between both the groups regarding shivering grade (Table 3). Out of 30 patients in Group C, shivering subsided in 29(96.7%) patients. While in group T, shivering subsided in 26(86.7%) patients out of 30. There was significant difference in both groups for control of shivering

Parameters	Group C (n=30)	Group T (n=30)	p value
Age (years)	39.47±16.027	39.73±14.300	0.946
Sex ratio (Male/Female)	20/10	22/8	0.317
ASA grading (I/II)	14/16	14/16	1

Table-1: Shows the distribution of data based on age group, gender and ASA grading among the study subjects (Values are mean ± SD or numbers)

Parameters		Group C (n=30)	Group T (n=30)	p value
Spinal drug (ml,0.5% bupivacaine)		3.4700±0.305	3.4730±0.330	0.968
Sensory block	T4	1	0	0.313
	T6	10	9	0.781
	T8	6	8	0.541
	T10	9	9	1
	12	4	4	1

Table-2: Shows the comparison between the spinal drug and sensory block level among the study subjects

Shivering grade	Group C (n=30)	Group T (n=30)	P value
3	14	15	0.796
4	16	15	0.796

Table-3: Shows the comparison between the shivering grades among the study subjects

Control of shivering	Group C (n=30)	Group T (n=30)
Yes	29(96.67%)	26(86.67%)
No	1(3.33%)	4(13.33%)

Table-4: shows the comparison of the control of shivering among the study subjects

Time(minute)	Group C (n=30)	Group T (n=30)	p value
0	89.37±12.96	96.47±16.32	0.0670
5	67.13±10.99	92.90±14.96	0.0002
10	71.60±10.37	91.20±13.90	0.0001
15	75.13±7.89	89.27±12.38	0.0001
20	75.53±8.38	88.30±11.96	0.0001
25	77.44±7.70	87.62±11.19	0.0001
30	78.70±8.46	87.70±11.23	0.0009

Table-5: shows the comparison of heart rate (in minutes) among the study subjects

Time (minutes)	Group C(n=30)	Group T(n=30)	p value
0	121.25±11.55	120.60±10.28	0.8187
5	115.33±14.71	118.70±10.66	0.3138
10	111.30±13.11	118.53±11.56	0.0272
15	113.83±9.74	117.97±10.08	0.1111
20	116.53±8.54	117.60±8.54	0.5293
25	117.83±7.59	117.93±8.77	0.9525
30	116.57±10.57	117.77±9.38	0.6436

Table-6: Shows the comparison of systolic blood pressure among the study subjects

(p= 0.0001) which proved that the rate of success after clonidine was more than that of tramadol (Table 4).

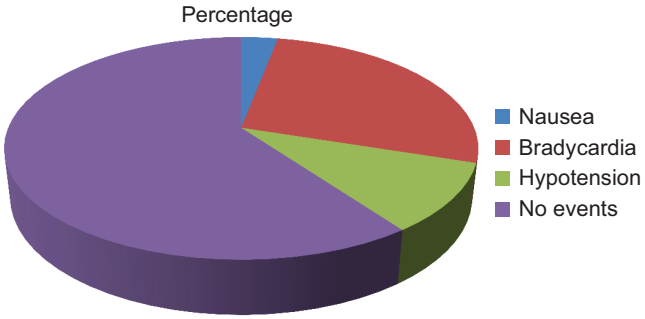
The heart rate was comparable between two groups at the time of administration of study drugs (p>0.005). The heart rate was significantly lower in Group C throughout the period of observation there after (Table 5). The baseline systolic, diastolic and mean pressure was comparable in both groups.

Time (minutes)	Group C (n=30)	Group T (n=30)	p value
0	68.83±11.02	72.20±7.91	0.1789
5	52.60±10.28	71.03±8.17	0.0009
10	61.23±8.06	69.40±8.62	0.0004
15	64.67±7.23	69.83±7.62	0.0093
20	65.93±7.07	68.83±7.11	0.1186
25	66.00±5.18	68.60±7.96	0.1392
30	66.20±5.49	69.27±7.26	0.0698

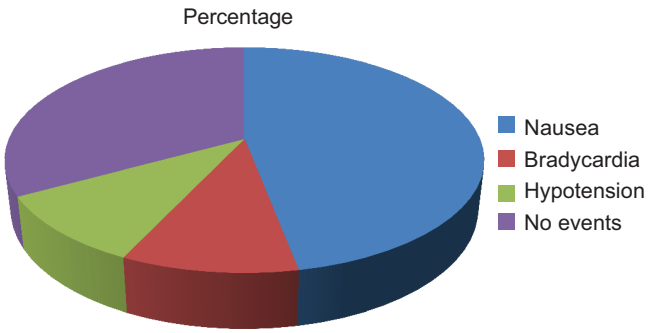
Table-7: shows the comparison of diastolic blood pressure among the study subjects

Time (minute)	Group C(n=30)	Group T(n=30)	p value
0	86.39±9.92	88.33±8.40	0.4170
5	80.18±10.44	86.92±8.69	0.0087
10	77.92±8.32	85.78±9.28	0.0010
15	81.06±6.22	85.88±8.25	0.0133
20	82.80±5.81	85.09±7.17	0.1794
25	83.28±4.87	85.04±7.93	0.3046
30	82.99±6.17	85.43±7.58	0.1768

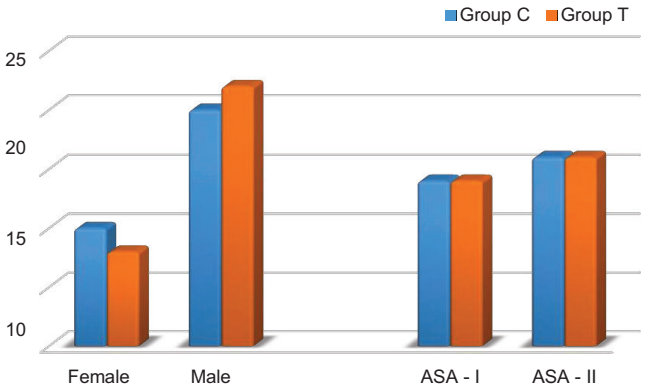
Table-8: shows the comparison of mean arterial pressure (MAP) among the study subjects



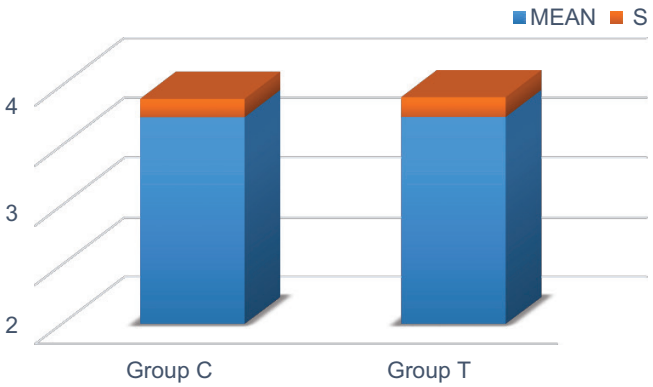
Pie chart-1: Shows the distribution of data based on the adverse events in control group among the study subjects



Pie chart 2: Shows the distribution of data based on the adverse events in control group among the study subjects



Graph-1:



Graph-2:

There was no significant difference in SBP in both groups after study drug administration. The DBP was significantly lower in Group C at 5, 10 and 15 minutes observations. The MAP was significantly lower in Group C at 5 and 10 minutes (Table 6, 7 and 8).

It was found that the known side effects of clonidine, hypotension in 3 cases and bradycardia in 8 cases in Group C. Nausea occurred in about 1 case in Group C while in Group T it was observed in 14 (47%) cases. In Group T, about 3 cases of vomiting and dizziness each observed (Pie chart 1, 2). No adverse events were encountered in 18 (60%) cases in Group C and 10 (33%) cases in Group T. Thus, adverse events were significantly lower in Group C (p=0.004).

DISCUSSION

The present study was designed to measure and compare effectiveness of tramadol and clonidine for control of shivering that occurs following spinal anesthesia. A large number of studies have been done to assess the role of prophylactic pharmacological intervention for post-spinal anesthesia shivering. In spite of high incidence (40-60%) of shivering found in different epidemiological studies, the author of the present study have chosen to do pharmacological interventions only after shivering develops.[12]

In this study, there was shortage of data about long term anti-shivering effectiveness of intravenous drugs while shivering can develop any time after neuraxial anesthesia depending on interaction of different environmental factors and internal thermoregulatory mechanisms and treatment of established shivering was also shown to be very effective. Thus, in a study conducted by Kranke et al, have concluded that it causes many patients to receive a drug they did not need and be unnecessarily exposed to adverse drug reactions.[13]

The fact that intra-operative body warming and maintaining core temperature per se have a major effect on the incidence of post-operative shivering further puts into question the usefulness of pharmacological shivering prophylaxis. There may be a special case for selected patients with compromised cardiac oxygen supply; in these patients, it may be worthwhile to give an anti- shivering drug prophylactically, and clonidine may be the most rational choice, because in addition to its anti-shivering effect, it has a favorable effect on cardiac outcome.[14]

In the current study, patients were included who developed grade-3 or 4 shivering as this grades of shivering have widespread muscular contraction which increase metabolic requirement and affect core body temperature significantly. Patients with higher grade of shivering are more prone to core hypothermia and these patients are the one who gets benefited the most by anti-shivering therapy.

There are many non-pharmacological and pharmacological methods used to prevent heat loss and decrease shivering. Non-pharmacological methods include radiant heat warmers, warming the operation theatre, blankets, warm IV fluids and using anesthetic drugs at body temperature. The present study was designed to standardize these possible compounding factors, while reflecting the common practice in our institution.[15,16]

The temperature in the operating room was maintained constant at 21°C to 23°C. IV fluids and drugs were given at room temperature. In the present study, the factors that influence the occurrence of shivering, like temperature of IV fluids and drugs, were not tightly controlled, but this should not affect the validity of our study because the present study focused on response to treatment used rather than incidence of shivering; and by randomization, both groups were subjected to similar degrees of influence of these factors. The same is true about extent of neuraxial blockade.[17]

We have taken tramadol 1mg/kg dose for treatment of shivering which is supported by many study of S. Mathew et al compared prophylactic 1mg/kg of tramadol with placebo for shivering and found the incidence of post-operative shivering was 4% in tramadol and 48% in the control group. It is also supported by Mohta M et al who compared

intravenous tramadol 1, 2 and 3 mg/kg with pethidine 0.5 mg/kg for prophylaxis of post-anesthetic shivering. They found all three doses are effective in controlling shivering while 2mg/kg and 3mg/kg have profound sedation which is not found with 1mg/kg.[18,19]

Our study was comparable with the study done by Kulshrestha S et al (2013) who found shivering disappeared in 95.5% patients who received clonidine and 91.11% who received tramadol. Reappearance rate was 6% with tramadol while 0% with clonidine. The mean interval between the injection of drug and the complete cessation of shivering was 2.59 ± 0.66 minutes in clonidine group and 5.11 ± 0.08 minutes in tramadol group. Similar results were found in study by Shukla U et al who found response rate of 97.5% and 92.5% with clonidine and tramadol respectively. The mean interval between the injection of drug and the complete cessation of shivering was 2.54±0.76 and 5.01±1.02 minutes respectively. Recurrence occurred in 7.5% in tramadol, but not in clonidine group.[20,21]

In a study done by Bansal P and Jain G found that the significant difference in SBP and DBP at 5, 10 and 15 minute observation as well as MAP at 5 and 10 minutes observation point. While Shukla U et al and Kulshrestha S et al found no significant difference in blood pressure changes in both groups. In other studies, hemodynamic parameters were not mentioned in detail.[22,21,20]

CONCLUSION

It can be concluded from the results of the present study that both clonidine (75 µg) and tramadol (0.5 mg/kg) can effectively treats patients with post-spinal anaesthesia shivering, but tramadol took longer time for complete cessation of shivering than clonidine. Clonidine offers better thermodynamics than tramadol, with fewer side effects. The more frequent incidence of side effects of tramadol, like nausea, vomiting and dizziness, may limit its use as an anti-shivering drug.

REFERENCES

1. Sessler DI, Ponte J. Shivering during epidural anaesthesia. Anaesthesiology 1999; 72:816 -21.
2. De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology Anaesthesiology 2002; 96:467-84.
3. Butterworth JF, Mackey DC, Wasnik JD. Thermoregulation, hypothermia and malignant hyperthermia. Morgan and Mikhail's Clinical Anaesthesiology. 5th edition. 2013; 1183- 85.
4. Sessler DI. Temperature monitoring. In: Miller RD, 3rd ed. Anaesthesia. New York, Edinburgh, London, Madrid, Melbourne, Milan, Tokyo: Churchill Livingstone, 1994:1362-82.
5. Bhatnagar S, Saxena A, Kannan TR, Punj J, Panigrahi M, Mishra S. Tramadol for postoperative shivering: A double-blind comparison with pethedine. Anaesthesia Intensive Care 2001; 29:149-54.
6. Katyal S, Tewari A. Shivering Anaesthetic considerations. J Anaesth Clin Pharmacol2002; 18:362-76.
7. Honarmand A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine and ketamine plus midazolam for prevention of shivering during regional anaesthesia, British Journal of Anaesthesia 2008; 101:557-52.
8. Crowley LJ, Buggy DL. Shivering and neuraxial anaesthesia. Regional Anaesthesia and Pain Medicine 2008; 33: 241-52.
9. Bhattacharya et al. Post Anaesthesia Shivering (PAS): A Review. Indian J Anaesthesia 2003; 47: 88-93.
10. Brauchi S et al. A hot sensing cold receptor: C-terminal domain determines thermosensation in transient receptor potential channels. J Neuroscience 2006; 26:4834-40.
11. Moqrich et al. Impaired thermosensation in mice leaking TPPV3, a heat and camphor in the skin. Science 2005; 307:1468-72.
12. Najafianaraki et al. The effects of warm and cold intrathecal bupivacaine on shivering during delivery under spinal anaesthesia Saudi Journal of Anaesthesia 2012; 6:123-36.
13. Kranke P, Eberhart LH, Roewer N, Tramer MR. Single dose parenteral pharmacological interventions for the prevention of postoperative shivering: a quantitative systematic review of randomised controlled trials. Anaesthesia and Analgesia 2004; 99: 718–27.
14. Link RE, Desai K, Hein L, Stevens ME, Chruscinski A, Bernstein D, Barsh GS, Kobilka BK. Cardiovascular regulation in mice lacking a2-adrenergic receptor Subtypes b and c. Science 1996; 273:803-5.
15. Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE. Substitution of a mutant a2A-adrenergic receptor via 'hit and run' gene targeting reveals the role of this subtype in sedative, analgesic and anaesthetic-sparing responses in vivo. Proc Natl Acad Sci 1997; 94:950-55.
16. Bailey PL, Sperry RJ, Johnson GK, Eldredge SJ, East KA, East TD, Pace NL, Stanley TH. Respiratory effects of clonidine alone and combined with morphine, in humans**.** Anesthesiology.1991; 74:43-48.
17. Surprenant A, North RA. Mechanism of synaptic inhibition by noradrenaline acting at a2- adrenoceptors. Proc R SocBiol 1988; 234:85-114.
18. Mathew S, Mulle AL, Verhes PK. Post anaesthetic shivering – a new look at tramadol. Anaesthesia 2002; 57:394-8.
19. Mohta M, Kumari N, Tyagi A, SethiAK, Agarwal D, Singh M. Tramadol for prevention of post-anaesthetic shivering: a randomised double-blind comparison with pethidine Anaesthesia 2009;64:141–46.
20. Kulshrestha S, Mehta RK, Efficacy of Intravenous Clonidine & Tramadol on Post Spinal Anaesthesia Shivering in Elective Lower Segment Caesarean Section: A Randomized Comparative Study. People's Journal of Scientific Research 2014; 7:7-11.
21. 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.
22. Bansal P, Jain G. Control of shivering with clonidine, butrophenol and tramadol under spinal anaesthesia. Local and Regional Anaesth 2011; 4:29-34.

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