

A Clinical Comparative Study of Dexmedetomidine, Clonidine And Tramadol in Post Spinal Shivering in Lower Limb And Lower Abdominal surgeries.

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Abstract:

Background and Aims: Dexmedetomidine (α_2 adrenergic agonist) has been used for prevention of post anaesthesia shivering. Its use for the treatment of postspinal anaesthesia shivering has not been evaluated. The aim of this study was to evaluate and compare the efficacy, haemodynamic and adverse effects of dexmedetomidine with those of tramadol and clonidine, when used for control of post spinal anaesthesia shivering.

Material And Methods: The study was conducted in 60 patients of ASA Grade I and ASA grade II of either gender, aged between 18 and 60 years, scheduled for lower limb and lower abdominal surgical procedures under spinal anaesthesia. The study was prospective and randomised. The patients were randomised in three groups of 20 patients each to receive either dexmedetomidine 0.6 μ g/kg, tramadol 1.0 mg/kg or clonidine 0.6 μ g/kg as a slow intravenous bolus. Grade of shivering, onset of shivering, time for cessation of shivering, recurrence, response rate, and adverse effects were observed at scheduled intervals. Unpaired test was used for analysing the data.

Results: Time taken for cessation of shivering was significantly less with DEXMEDETOMIDINE when compared to Tramadol And Clonidine. Nausea and vomiting was observed only in TRAMADOL group (28% and; 20% respectively). There was not much difference in the sedation profile of all the three drugs.

Conclusion: We conclude that although all the three drugs are effective, the time taken for cessation of shivering was less with Dexmedetomidin when compared to TRAMADOL and CLONIDINE. Moreover, dexmedetomidine and clonidine have negligible adverse effects, whereas tramadol is associated with significant nausea and vomiting.

Keywords: Dexmedetomidine, postspinal anaesthesia shivering, tramadol, clonidine

I. Introduction

Shivering, a common post anaesthesia occurrence is defined as an involuntary, repetitive activity of skeletal muscles. The incidence of shivering has been found to be quite high, approximately 40-50% in different studies. It can double or even treble oxygen consumption and carbon dioxide production. Shivering also increases intraocular and intracranial pressure, and may contribute to increased wound pain, delayed wound healing, and delayed discharge from postanaesthetic care. Apart from being an uncomfortable experience, its deleterious effects deserve primary prevention and rapid control on occurrence.

Shivering is a physiological response to core hypothermia in an attempt to raise the metabolic heat production. The main causes of intra/postoperative shivering are temperature loss, increased sympathetic tone, pain, and systemic release of pyrogens. Spinal anaesthesia significantly impairs the thermoregulation system by inhibiting tonic vasoconstriction, which plays a significant role in temperature regulation. It also causes a redistribution of core heat from the trunk (below the block level) to the peripheral tissues. These factors predispose patients to hypothermia and shivering.

The treatment of shivering includes both pharmacological and nonpharmacological methods. The nonpharmacological management is by external heating like the use of forced air warming, warming blankets, warmed fluids etc., According to the results of a metaanalysis, the most frequently reported pharmacological interventions include clonidine, pethidine, tramadol, nefopam and ketamine. Unfortunately, no gold standard treatment is known for shivering.

The administration of all the available drugs is associated with various adverse effects. During the last decade, Tramadol has become a favoured and commonly used drug for postspinal anaesthesia shivering. However, it has many adverse effects like nausea, vomiting, dizziness etc., which cause further discomfort to the patient. Clonidine, is another agent which has gained popularity during the last few years. Various studies, which have been conducted to compare them have concluded that clonidine has better efficacy and less adverse

effects as compared to tramadol. But there was 5-10% incidence of hypotension and bradycardia with clonidine. Dexmedetomidine, a congener of clonidine, is a highly selective α_2 adrenoceptor agonist. It has been used as a sedative agent and is known to reduce the shivering threshold. Few studies which have explored its antishivering potential have inferred that dexmedetomidine is an effective drug without any major adverse effect and provides good haemodynamic stability.

Hence, we planned to do a comparative study of the efficacy, haemodynamic, and adverse effects of tramadol, clonidine and dexmedetomidine when used for the control of postspinal anaesthesia shivering.

II. Material and Methods

The Study Was Conducted At M L N Medical College Allahabad And Associated S R N Hospital Allahabad After Taking Approval From Institutional Ethics Committee. All Subjects Gave Written Informed Consent To Participate In The Study.

Inclusion Criteria:

- 1) Patients of ASA I and ASA II
- 2) Patients with age 18 to 60 years.
- 3) Patients with written valid consent.
- 4) Patients undergoing elective lower abdominal surgeries, orthopaedics lower limb surgeries and plastic surgeries.

Exclusion criteria:

- 1) ASA III or IV patients.
- 2) Patient refusal
- 3) Patients with age < 18 and > 60 years.
- 4) Uncooperative patients
- 5) Infection at the site of injection
- 6) Coagulopathy
- 7) Anticoagulant medications
- 8) Patients with pre-existing neurological disease.
- 9) Patients with known hypersensitivity to dexmedetomidine, clonidine or tramadol, cardiopulmonary, renal or hepatic disease, hyperthyroidism, psychiatric disorder, urinary tract infection, severe diabetes or autonomic neuropathies, known history of substance or alcohol abuse.

All patients who fulfilled the inclusion criteria and developed postspinal anaesthesia shivering were enrolled and randomised into either of the three groups.

1. Group D ($n = 20$) were administered dexmedetomidine 0.6 $\mu\text{g}/\text{kg}$ IV,
2. Group T ($n = 20$) received tramadol 1.0 mg/kg IV and
- Group C ($n=20$) received Clonidine 0.6 $\mu\text{g}/\text{kg}$ at the onset of shivering .

Upon arrival in the operation theatre, an 18G venous cannula was inserted and preloading done with Ringer's Lactate solution 10 ml/kg before giving spinal anaesthesia and maintained at 6 ml/kg/h after spinal anaesthesia. Before starting the procedure, standard monitors were attached and all the baseline parameters such as heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SPO₂), electrocardiography (ECG), and body temperature (axillary) were recorded. Subarachnoid anaesthesia was administered with 0.5% heavy bupivacaine (15 mg) at L 3-4 or L 4-5 interspace using 26G Quincke's spinal needle under aseptic conditions. All operation theatres were maintained at an ambient temperature of around 24°C-25°C. Supplemental oxygen was administered to all the patients at the rate of 5 l/min with face mask and patients were covered with drapes but not actively warmed. IV fluids and anaesthetics were administered at room temperature. Vital parameters such as HR, NIBP, and SPO₂ were recorded at intervals of every 5 min for first 30 min and every 15 min for the rest of the observation period. Continuous ECG monitoring was done. Shivering was graded using a four point scale as per

Wrench.: Grade 0: No shivering,

Grade 1: One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity,

Grade 2: Visible muscle activity confined to one muscle group,

Grade 3: Visible muscle activity in more than 1 muscle group

Grade 4: Gross muscle activity involving the whole body.

Patients who developed either Grades 3 or 4 shivering were included in the study. Either of the three drugs was given as slow IV bolus injection. The drugs were diluted to a volume of 5 ml in a 5 ml syringe. The attending anaesthesiologist recorded the time in minutes at which shivering started after spinal anaesthesia (onset of shivering), severity of the shivering, time to the disappearance of shivering and response rate (shivering ceasing within 15 min after treatment). Duration of surgery was recorded and duration of spinal anaesthesia was noted by assessing spontaneous recovery of sensory block using the pinprick method and observing spontaneous movements of limbs in the postoperative period. Recurrence of shivering was also noted. In case there was recurrence of shivering, patients were treated with an additional dose of dexmedetomidine (0.6µg/kg IV), clonidine (0.6µg/kg IV) or tramadol (1.0 mg/kg IV) in the respective groups. Adverse effects such as nausea, vomiting, bradycardia (<50/min), hypotension (>20% of baseline), dizziness; and sedation score were noted. The degree of sedation was graded on a four point scale as per

Filoset al.:

Grade1: Awake and alert,

Grade2: Drowsy, responsive to verbal stimuli

Grade3: Drowsy, arousable to physical stimuli,

Grade 4: Unarousable.

Nausea and vomiting were treated with injection ondansetron 4 mg IV as and when required. Power analysis was based on the detectable difference between the means of time taken for cessation of postspinal shivering after treatment with dexmedetomidine, clonidine or tramadol = 180 s. With a standard deviation (SD) of 180 s considering $\alpha = 0.05$ and power of 90% (two-tailed test), sample size calculated to be 20 patients per group. To increase the power of study we enrolled 20 patients per group. Numerical data were presented as mean \pm SD and categorical data as proportions (%). The comparison of the mean levels of all variables between three groups was made by the unpaired *t* test. *P* value was calculated, and $P < 0.05$ was considered to be statistically significant.

III. Results

In the present study, a total of 60 patients out of 69 consecutive patients met the inclusion criteria and consented for study. These 60 patients were randomized into three groups of 20 each. Out of the total patients, 40 were male, and 20 were female. As it was an intraoperative study, no patient was lost to followup.

All groups were comparable with respect to age, gender, ASA grade, duration of surgery and the duration of spinal anaesthesia. Duration of surgery varied from 90 min to 110 min. Duration of spinal anaesthesia ranged from 90 min to 150 min.

All the patients had Grade 3 shivering. There was no statistically significant difference in time for the onset of shivering between the three groups. However, the difference in the time interval between administration of drug after the onset of shivering and cessation of shivering was significantly shorter in the dexmedetomidine group when compared to tramadol and clonidine group. There was recurrence of shivering in 2 patients in dexmedetomidine group and 4 patients in tramadol group and 3 patients in clonidine group. The patients were given rescue doses of dexmedetomidine, clonidine or tramadol respectively.

Nausea and vomiting was observed only in tramadol group, and there was no incidence in the dexmedetomidine and clonidine group. Almost similar number of patients were sedated in dexmedetomidine, Tramadol and clonidine group and the sedation score was 2. There was no evidence of respiratory depression in all the three groups. Hypotension and bradycardia was reported only in clonidine group.

IV. Discussion

Intra and postoperative shivering is a distressing experience for the patient. The exact mechanism of shivering during spinal anaesthesia has not been fully recognized. The possible mechanisms include impairment of central thermoregulation, internal redistribution of body heat, and heat loss to the environment. Potential risk factors for hypothermia in spinal anaesthesia include ageing, level of sensory block, temperature of the operation theatre and IV solutions. In this study, all operation theatres (OTs) maintained an ambient temperature of 23-25° C, and all fluids and drugs were at room temperature during the surgery. Demographic factors such as age, gender, duration of anaesthesia and surgery have also been matched to reduce any confounding bias.

The neurotransmitter pathways involved in shivering are multiple and involve opioids, α_2 adrenergic, serotonergic, and anticholinergic receptors. Hence, drugs acting on these systems which include opioids (pethidine, nalbuphine, or tramadol), ketanserin, propofol, doxapram, clonidine, ketamine and nefopam are utilized in the treatment of shivering. However, adverse effects such as hypotension, hypertension, sedation, respiratory depression, nausea and vomiting limit their use. Hence, the hunt for an ideal anti shivering agent is continuing. Tramadol is an opioid analgesic with opioid effect mainly mediated via mu receptor with minimal

effect on kappa and delta receptors. It also activates the monoaminergic receptors of the descending spinal inhibitory pain pathway.

The antishivering action of tramadol is probably mediated via its opioid or serotonergic and noradrenergic activity or both. Alpha₂ adrenergic agonists are widely used nowadays in anaesthesia and intensive care settings. Dexmedetomidine is an α_2 adrenoceptor agonist, with antihypertensive, sedative, analgesic, and anti shivering properties. The antishivering effects of alpha adrenoceptor agonists are mediated by binding to α_2 receptors that mediate vasoconstriction and the antishivering effect. In addition, it has hypothalamic thermoregulatory effects.

Dexmedetomidine comparably reduces the vasoconstriction and shivering thresholds, thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally. It has been successfully used as an adjunct to local anaesthetics in spinal anaesthesia and peripheral nerve blockade, for the sedation of mechanically ventilated patients in the Intensive Care Unit, as well as supplementation of postoperative analgesia. The role of dexmedetomidine in the treatment of shivering has been evaluated in a few studies. It may be a good choice because of its dual effects related 'antishivering' and sedation. With the dose of 0.6 mg/kg of tramadol, the response rate reported by Shukla *et al.* was 92.5%, by Reddy and Chiruvella as 95.56% and by Tsai and Chu, 87%. We found 100% response rate in our study. Maheshwari *et al.* reported similar recurrence rate with tramadol as in our study (8%) with the dose used of 1 mg/kg. The recurrence rate in the study by Shukla *et al.* was 5%, which is similar to our results. The incidence of nausea and vomiting with tramadol in our study was 28% and 20%, respectively. The results correspond with that of other studies by Reddy and Chiruvella, Tsai and Chu; Bansal and Jain. However, in the study by Shukla *et al.*, the incidence of nausea was quite high (77.5%), whereas Wason *et al.* have reported the incidence of nausea as only 4%. These variations could be explained by the peculiar patient characteristics in different studies. Maheshwari *et al.* have reported a very high incidence of sedation to the extent of 84%, which as mentioned earlier could be due to the higher dose as opposed to 28% sedation in our study. In a study by Easley, all children who had postanaesthesia shivering were treated with a single IV bolus dose of dexmedetomidine 0.6 μ g/kg over 35 min. All children had cessation of shivering behaviour within 5 min following the completion of dexmedetomidine administration. There was no recurrence of shivering and no adverse effects occurred. We found a response rate of 100% and apart from sedation, there was no other adverse effect observed. But there was recurrence in 1 patient who had to be given a rescue dose. All other studies have used higher dose of dexmedetomidine (1 μ g/kg), so comparison of results would not be appropriate.

In our study, the incidence of sedation was 21.4%, which is similar to other studies. One contradictory report was by Karaman *et al.* according to whom intraoperative dexmedetomidine infusion caused negligible sedation in spite of using a loading dose of 1 μ g/kg followed by a maintenance infusion of 0.5 μ g/kg/h. The other α agonist clonidine is associated with a high incidence of hypotension and bradycardia. In this respect, dexmedetomidine has an edge as it causes less variations in haemodynamics. The results of this study indicate that dexmedetomidine takes lesser time to control shivering. The incidence of adverse effects like nausea and vomiting was found to be higher in case of tramadol compared to dexmedetomidine. More studies need to be undertaken with varying dose ranges to extrapolate the results of this study. There was not much difference in the number of patients who were sedated in either group. The sedation seen with dexmedetomidine, in the absence of nausea and vomiting, is beneficial for the surgeon, anaesthetist as well as the patient. It provided more comfort to the patient, maintained more cardiorespiratory stability, improved surgical conditions and also provided amnesia during surgery. The major limitation of our study is the small sample size. A bigger sample size would have increased the robustness of our results. Another limitation was that the present study included short duration surgeries as the mean duration of surgical period was calculated to be approximately 1 h in both groups. The antishivering effect of dexmedetomidine needs to be seen in surgeries of longer duration where chances of developing hypothermia are more. Also, we did not assess different doses of dexmedetomidine; further studies are needed to evaluate the antishivering and haemodynamic effects of dexmedetomidine with various doses. The search continues for drugs that sufficiently improve the tolerance of thermoregulation without simultaneously producing respiratory depression, or haemodynamic instability. Dexmedetomidine might prove to be a valuable addition in the current armamentarium of the available drugs..

V. Conclusion

All the three drugs dexmedetomidine (0.6 μ g/kg), clonidine (0.6 μ g/kg) and tramadol (1.0 mg/kg) are effective in treating patients with postspinal anaesthesia shivering, but time taken for complete cessation of shivering was shorter with dexmedetomidine as compared to tramadol and clonidine. The difference being statistically significant. Furthermore, dexmedetomidine causes fewer adverse effects like nausea and vomiting.

References

- [1]. De Witte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. *Anesthesiology* 2002;96:46784.
- [2]. Bhattacharya P, Bhattacharya L. Postanaesthetic shivering (PAS): A review. *Indian J Anaesth* 2003;47:8893.
- [3]. Katyal S, Tewari A. Shivering: Anaesthetic considerations. *J AnaesthClinPharmacol* 2002;18:36376.
- [4]. Kranke P, Eberhart LH, Roewer N, Tramèr MR. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. *AnesthAnalg* 2002;94:45360.
- [5]. Sessler DI. Temperature regulation and monitoring. In: Millar RD, editor. 7th ed. *Textbook of Anaesthesia*. New York: Churchill Livingstone Inc.; 2010. p. 153356.
- [6]. Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy spectrum of antishivering medications: Metaanalysis of randomized controlled trials. *Crit Care Med* 2012;40:307082.
- [7]. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on postspinal shivering during caesarean section: A randomized double blind clinical study. *J ObstetAnaesthCrit Care* 2011;1:269.
- [8]. Bajwa SJ, Gupta S, Kaur J, Singh A, Parmar S. Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study. *J AnaesthesiolClinPharmacol* 2012;28:8691.[PUBMED]
- [9]. Usta B, Gozdemir M, Demircioglu RI, Muslu B, Sert H, Yaldiz A. Dexmedetomidine for the prevention of shivering during spinal anesthesia. *Clinics (Sao Paulo)* 2011;66:118791.
- [10]. Karaman S, Gunusen I, Ceylan MA, Karaman Y, Cetin EN, Derbent A, *et al.* Dexmedetomidine infusion prevents postoperative shivering in patients undergoing gynaecologic laparoscopic surgery. *Turk J Med Sci* 2013;43:2327.
- [11]. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethidine and doxapram in the treatment of postanaesthetic shivering. *Anaesthesia* 1997;52:326.
- [12]. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. *Anesthesiology* 1994;81:591601.
- [13]. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993;46:31340.
- [14]. Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering A new look at tramadol. *Anaesthesia* 2002;57:3948.
- [15]. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepiduralanesthetic shivering in parturients. *AnesthAnalg* 2001;93:128892.
- [16]. Grewal A. Dexmedetomidine: New avenues. *J AnaesthesiolClinPharmacol* 2011;27:297302.
- [17]. [PUBMED]
- [18]. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, *et al.* Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. *Indian J Anaesth* 2011;55:11621.
- [19]. [PUBMED]
- [20]. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. *Anesthesiology* 1997;87:835
- [21]. Kamibayashi T, Maze M. Clinical uses of alpha2 adrenergic agonists. *Anesthesiology* 2000;93:13459.
- [22]. Maheshwari BS, Shah SK, Chadha IA. Tramadol and butorphanol for control of shivering: Randomised double blind comparative study. *J AnaesthClinPharmacol* 2008;24:3436.
- [23]. Bansal P, Jain G. Control of shivering with clonidine, butorphanol, and tramadol under spinal anesthesia: A comparative study. *Local RegAnesth* 2011;4:2934.
- [24]. Wason R, Jain N, Gupta P, Gogia AR. Randomized doubleblind comparison of prophylactic ketamine, clonidine and tramadol for the control of shivering under neuraxial anaesthesia. *Indian J Anaesth* 2012;56:3705.
- [25]. [PUBMED]
- [26]. Blaine Easley R, Brady KM, Tobias JD. Dexmedetomidine for the treatment of postanesthesia shivering in children. *PaediatrAnaesth* 2007;17:3416.41.