Original Research Paper

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RANDOMIZED DOUBLE BLIND COMPARATIVE STUDY OF INTRAVENOUS CLONIDINE AND TRAMADOL IN POST SPINAL ANAESTHESIA SHIVERING

Anaesthesiology

KEYWORDS: Clonidine, Post spinal Shivering, spinal anaesthesia, Tramadol, Thermoregulatory center

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ABSTRACT

BACKGROUND & OBJECTIVES: Control of post spinal shivering is essential for optimal peri-operative care as shivering is a cause of discomfort and dissatisfaction in patients undergoing operations under spinal anaesthesia. The aim of the study is to assess the efficacy and safety of intravenous Clonidine and Tramadol in the treatment of post spinal intra-operative shivering. **MATERIALS AND METHODS:** In this prospective, double blind, randomized study, 80 ASA grade I and II patients of patients aged 20 –60 years, scheduled for various elective surgical procedures under spinal anaesthesia with hyperbaric Bupivacaine and who developed shivering grade 3 or 4 were selected. The patients were divided into three groups of 40 each. Group- C (n=40) comprised of the patients who received Clonidine 30mcg intravenously, and Group T (n=40) receiving Tramadol 50mg IV. The efficacy and response rate of the study drugs were evaluated and recorded. Side effects like, nausea, vomiting, dizziness, hypotension, bradycardia, and sedation if present, were recorded. **RESULTS:** Tramadol group shows complete control of post spinal shivering with none or lesser and mild degree of side effects..The mean interval between the injection of drug (tramadol and clonidine) and the complete cessation of shivering was 2.77 and 5.47 minutes, respectively (P=.0059). Response rate is 95% in Group T and 82.5% IN Group C. **CONCLUSION:** We can derive at a conclusion that Tramadol in dose of 50mg is more effective than clonidine (30mcg), in treating post spinal anaesthesia shivering due to its rapid onset, effective control and minimum side effects.

INTRODUCTION

In the year 1956 Pickering wrote; "The most effective system for cooling a man is to subject him to anaesthesia. In practice its importance was still not understood, till mid 1960's when first case of clinical hyperthermia was observed. The combination of anaesthetic induced thermoregulatory impairment and exposure to a cool environment makes warmed surgical patients hypothermic. Regulation of core temperature is achieved by means of behavioral and autonomic mechanism that actively balance heat production and heat loss. These mechanisms are controlled largely from hypothalamus and depend on input of afferent neurons from various sites within the body.[1] Surgery and general anaesthesia impair the normal balance between heat production and loss. Anaesthetic agents, opioids and sedatives inhibit behavioral and autonomic responses, leaving patients essentially poikilothermic. Hypothermia during neuraxial anaesthesia develops initially from core to peripheral redistribution of body heat. Redistribution of body heat during spinal or epidural anaesthesia typically decreases core temperature 0.5-1.0^{0}C. The discovery of importance for temperature monitoring dates back to mid 1600 when Santorio discovered the clinical value of intra-operative temperature monitoring but his efforts were not recognized. After two centuries Wunderlich recognized temperature monitoring as a key parameter.[2] However, it was in 1960 when intra-operative temperature monitoring become a standard for all anaesthetic procedures. However, it was difficult to monitor temperature intra-operatively because of difficulty in placing probes at usual sites like nasopharynx and oropharynx which were not tolerated by patients under spinal anaesthesia. Temperature disturbances are common during both Neuraxial and General anaesthesia. However, core temperature monitoring still remains rare during regional anaesthesia and substantial hypothermia goes undetected. Inadvertent hypothermia is associated with numerous adverse outcomes. Although hypothermia may provide protection with numerous adverse outcomes. Although hypothermia may provide protection against ischemia, there is ample clinical evidence that hypothermia causes multiple physiological derangements.[3] Some of these include coagulation abnormalities due to impaired platelet function, wound infection with delayed wound healing due to impaired immune regulation. Shivering is another complicated response of the body to hypothermia. It is an involuntary, oscillatory muscular activity that can double or triple the oxygen consumption and carbon dioxide production. It is specifically disturbing to the mothers during labour and delivery. Vigorous shivering increases the metabolic heat up to 600% above the base level.[4] Usually lots of attempts have been made to treat shivering rather than prevent it. Various non-pharmacological measures have been studied to control Shivering under Spinal anaesthesia. Spinalanaesthesia is popular and safe anaesthesia technique for various surgeries. Shivering that develops following spinal anaesthesia is common problem due to impairment of thermoregulatory control. It occur in 19%-33% of patients receiving spinal anaesthesia.[5,6] Shivering is unpleasant for the patient, anaesthesiologist and the surgeon besides being physiologically stressful for the patient. The physiologic role of shivering is to provide heat, but its occurrences in relation to anaesthesia is inconsistent and incompletely understood.Shivering occur in patients receiving regional anaesthesia as well as those patients receiving general anaesthesia. The main cause of shivering intra or post operative are temperature loss, decreased sympathetic tone and systemic release of pyrogens.[7]It causes several undesirable physiologic consequences including increase in oxygen consumption, carbon dioxide production and minute ventilation. It may induce arterial hypoxemia, lactic acidosis, increased intra ocular pressure (IOP), intra cranial pressure (ICP) and interference with patient monitoring like EGG, NIBP and SpO2 etc. Shivering may damage dental prosthesis and poor quality teeth. It may negate orthopedic procedures like fractures and dislocations and can be detrimental to patients with low cardiopulmonary reserve.[8,9]

Spinal anaesthesia is known to decrease the vasoconstriction and shivering threshold. There is core to periphery redistribution of heat due to spinal induced vasodilatation and shivering is preceded by core hypothermia following spinal anaesthesia may not trigger sensation of cold as the cutaneous vasodilatation resulting from sympathetic blockade increases skin temperature leading to a sensation of warmth although accompanied by thermoregulatory shivering.[10]

Various methods are available for the control of shivering. These may be non-pharmacological or pharmacological. Intra-operative

hypothermia can be minimized by any technique that limits cutaneous heat loss to the environment such as those due to cold operating room, evaporation from surgical incisions and conductive cooling produced by administration of cold intravenous fluids. Various non-pharmacological methods are radiant warmer, pre warming of patients, space blankets, warm fluids, electric warming blankets etc.Various pharmacological treatments like i.v. opioids, alfentanil, pethidineondansetron, dolasetron; and cholinomimetic agent physostigmine, nalbuphine and meperidine, 5-HT3 antagonisthave been used; however, side effects like hypotension, hypertension, sedation, respiratory depression, nausea and vomiting limit their use. Our study was designed to compare a small dose of clonidine, an α_2-adrenoceptor agonist with that of tramadol a opioid analgesic for control of post-spinal anaesthesia shivering. These drugs are easily available and cost effective.

METHODS

This was a prospective, randomized, double-blind study, which was conducted after taking approval from Institutional Ethics Committee. All subjects gave written informed consent to participate in the study. 80 American Society of Anaesthesiologists (ASA) Grade I and II consenting patients of either gender aged 20-60 years scheduled for elective surgeries under spinal anaesthesia were included in the studyAll contraindications to spinal block, hypertension, diabetes mellitus, respiratory disease, epilepsy and cardiac disease, thyroid disorder, alcoholics, Chronic history of headache and backache, Spinal deformity or infection at the local site, Patient allergic to drug ,Failed spinal block, Patient refusal.All patients who fulfilled the inclusion criteria and developed post-spinal anaesthesia shivering were enrolled and randomized using chit in box method either of the two groups. Group T (n = 40) were administered tramadol 50 mg IV and Group C (n = 40) received clonidine 30mcgIV as per randomization by colleague (not a part of the study) who prepared either of the drugs, at the onset of shivering. The anaesthesiologist conducting the case as well as recording the data were unaware of the drug being administered.

Patient was taken to the OT, fasting status was confirmed, monitors were attached to the patient; base line HR, SBP, DBP, ECG and SpO2 were recorded. All operation theatres in which the operations were performed maintained constant humidity (70%) and an ambient temperature of around 21°C to 23°C. A good IV line was secured with 18G cannula RL was started and Inj. Ranitidine (50mg) &Inj. Metoclopramide (10mg) was given intravenously. No means of active re-warming was used. Under all aseptic precautions spinal anesthesia was performed at the $L_3 - L_4$ interspace, with the patient in sitting position. A volume of 3 ml of inj. bupivacaine 0.5% (heavy) was injected over 30 seconds through a 25-gauge spinal needle. Patient was placed in supine position with a 15° head down tilt immediately after spinal injection to achieve level of block of T5-T6. Oxygen (4L/min) was administered via a ventimask.

Vitals was checked every 5 minute for 20 minutes and after that every 10 minutes till the end of the surgery. Temperature was recorded with thermometer in axilla every 5 minute for 20 minutes and after that every 10 minutes till the end of the surgery. 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 and Grade 4: Gross muscle activity involving the whole body. When patient would developed shivering, grading of shivering noted (3&4) and was randomized in two groups (using CHIT IN BOX method) and study drug was given. Time taken to relieve shivering was recorded. Reappearance of shivering/ refractory shivering (not relieved by study drug in 15 min. of administration) if occur inj. Dexamethasone 8mg as a rescue drug was injected. The degree of sedation was graded 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. Hypotension, defined as a decrease of systolic blood pressure > 30% from baseline or a fall below 90 mmHg, was treated with incremental IV doses of mephentermine 5 mg and IV fluid as required. Bradycardia, defined as heart rate < 50 bpm, was treated with IV atropine 0.3-0.6 mg.

Statistical analysis was done using suitable statistical software. A P value <.05 was considered statistically significant.

2.RESULTS

A total of 80 patients were randomized into two groups of 40 each (n=40), 53 of whom were male and 27 were female [Table 1]. Both the groups were comparable with respect to age, sex, weight. The mean age of the patients in group T was 32.15 ± 9.38 years; and patients in Group C, 28.98 ± 5.0 years (P=.063)

2.1 [Table 1].

Parameter		Group T (n=40)	Group C (n=40)
Age (years)		32.15 ± 9.38	28.98 ± 5.0
Sex	Male	26	27
	Female	14	13
Weight		61.30 ±4.7	61.65±2.13

Table 1Demographic data of patients in the two groups

Shivering disappeared in 38 (95%) patients who received tramadol and 33 (82.5%) who received clonidine

2.2 [Table 2]

.Both the drugs were found to be effective in reducing shivering. 2 patient in group Tand 7 patients in group C(severity of shivering unchanged) were given rescue doses of dexamathasone, respectively. 9 (11.25%) patients out of a total of 80 patients received rescue doses.]

Parameter	Group T (n=40)	Group C (n=40)	P-value
Onset of shivering (min.)	22.5±2.23	22.5±2.15	P=1
Severity of shivering (grade)	3.5	3.5	P=1
MeanTime interval from Rx to cessation of shivering (min.)	2.77	5.47	P=.0059
Response rate (%)	95	82.5	
Recurrence	Nil	nil	-

Table 2Post-spinal anaesthesia shivering and responses

The mean interval between the injection of drug (tramadol and clonidine) and the complete cessation of shivering was 2.77 and 5.47 minutes, respectively (P=.0059). Time for onset of shivering and severity of shivering were not statistically significantly different between the two groups. However, the time interval between administration of drug after onset of shivering and disappearance of shivering was significantly shorter in the clonidine group

[Table 2](P=.0059).

There was no statistically significant difference with respect to heart rate, blood pressure, axillary temperature and oxygen saturation between the two groups. No statistically significant difference in complication rates

2.3 [Table 3]

Nausea, vomiting and dizziness between the two groups. More patients of group C (3 patients) were sedated than of group T.

Complication (%)	Group T (n=40)	Group C (n=40)
Nausea	1 (2.5)	1 (2.5)
Vomiting	1 (2.5)	1 (2.5)
Dizziness	0	0
Bradycardia&Hypotension	0	2 (5)
Sedation	0	3 (7.5)

Table 3Complications in both groups

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In group C,bradycardia and hypotension occurred in 2 patients, both of which were not present in group T [Table 3].

DISCUSSION

Regional anesthesia, either central neuraxial block or peripheral nerve block is a safe and very popular technique used for various surgeries. However 19-33% of patients undergoing regional anesthesia develop shivering, though it is also found to occur after general anesthesia.6,7 The mechanism which leads to shivering after regional anesthesia is not very clear, but the probable mechanisms could be decrease in core body temperature secondary to sympathetic block7; peripheral vasodilatation; increased cutaneous blood flow, which leads to increased heat loss through skin; cold temperature of operation theatre; rapid infusion of cold IV fluids; and effect of cold anaesthetic drugs upon the thermosensitive receptors in the spinal cord. There are many pharmacological and non-pharmacological methods used to prevent heat loss and decrease shivering. Non-pharmacological methods include radiant heat warmers,7 warming the operation theatre,8 warm IV fluids,10 blankets, and using anaesthetic drugs at body temperature.We had to resort to continuous measurement of axillary temperature by thermometer as we felt that a nasal, oesophageal or rectal probe would be uncomfortable for the patients. A number of factors including age, duration of surgery, temperature of the operating room, and infusion solution, are risk factors for hypothermia and shivering. So in our study, patients over the age of 60 years were excluded. The temperature of operating room was maintained at 21 to 23° C and infusions of crystalloid solution were warmed. We also excluded the patients having history of acute infections, sepsis and fever to reduce their confounding effect.

Pharmacological intervention have been tried to prevent or treat shivering, including opioids (e.g. pethidine, nalbuphine, butorphanol or tramadol, ketanserin, propofol, ondansetron, granisetron, doxapram, physostigmine,clonidine, and nefopam etc., but debate for an ideal anti-shivering drug still continues.

In the present study, we compared the efficacy of tramadol and clonidine for treatment of poat spinal anaesthesia shiveringin patients undergoing various surgeries. All groups were comparable with regard to demographic characteristics.

Tramadol's distinct feature in the treatment of shivering is its weak sedative and smaller respiratory depressive properties than morphin, particularly patients with low cardiopulmonary reserve. Tramadol inhibits the neuronal reuptake of norepinephrine and 5 hydroxytrytpamine, facilitate 5-hydroxytrytpamine release, and activates μ-¬opioid receptors Each of these actions is likely to influence thermoregulatory control. However tramadol had only slight thermoregulatory effects. Thus, it is unlikely to provoke hypothermia or to facilitate fever. The main opioid effect of tramadol is mediated via the mu-receptor. The O-desmethyl metabolite (M1) of tramadol and its enantiomers are bound with higher affinity than the parent compounds at μ¬-opioid receptors with less affinity for kappa and sigma opioid receptors, although still with a much lower affinity than morphine. Tramadol may induce its anti shivering effect via the additive or synergistic action of both kappa opioid receptor and 2 adrenergic mechanisms. The interaction of kappa opioid and 2 adrenoceptor mechanisms working in a complementary or synergistic manner to produce anti shivering effects seems a possible explanation.11,12 Clonidine is a α2adrenoceptor agonist, with antihypertensive, sedative, analgesic and anti-shivering properties. The anti-shivering effects of alpha (α2) adrenoceptor agonists are mediated by binding to α2 receptors mainly the α2b receptors that mediate vasoconstriction and the anti-shivering effect. In addition clonidine has hypothalamic thermoregulatory effects, as it may exert an inhibitory action on the hypothalamus, by decreasing the noradrenaline synaptic release through α2 receptors located at the presynaptic nerve terminals, thus contributing to its anti-shivering effect.13-15 In the present study, we found that mean time required for control of shivering is 2.77 minutes in tramadol group and 5.47 minutes in clonidine group. (p=.0059) Response rate was higher in tramadol group than in clonidine group, but the difference was not statistically significant.

The complication were found to be higher in case of clonidine group compared to tramadol group. In present study, no difference found in the incidence of nausea, vomiting and dizziness. Studies suggested slow injection of Tramadol reduces and prevents nausea and vomiting16. In case of group C, 3 (7.5%) patients had sedation of grade 2. One patient of group C had dry mouth, which was not present in group T.

Bradycardia and hypotension occurred in 2 patients of group C which were not present in group T.

It was noted in the present study that tramadol was quicker than clonidine in providing relief from shivering. Velayudha S. Reddy et al17 studied the clonidine and tramadol for post spinal shivering during caesarean section. They concluded that time required for control of shivering in tramadol group shorter than clonidine group.

CONCLUSION

We can derive at a conclusion that Tramadol in dose of 50mg is more effective than clonidine (30mcg), in treating post spinal anaesthesia shivering due to its rapid onset, effective control and minimum side effects.

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