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A CLINICAL COMPARATIVE STUDY OF INTRAVENOUS CLONIDINE AND TRAMADOL FOR CONTROL OF SHIVERING IN PATIENTS UNDERGOING SPINAL ANAESTHESIA

Anaesthesiology

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ABSTRACT

Background & Objectives: Shivering after neuraxial anaesthesia is a precarious complication resulting in increased metabolic rate, increased oxygen demand along with raised CO2 production, ventilation rate and cardiac output, adverse post operative outcomes, including increased surgical site bleeding, wound infection and morbid cardiac events in cardio -respiratory compromised patients. The aim of the study is to assess the efficacy and safety of intravenous Clonidine and Tramadol for control of control of shivering in patients undergoing spinal anaesthesia. **Materials And Methods:** In this prospective, double blind, randomized study, 60 ASA grade I and II patients of patients aged 18 – 70 years, scheduled for various routine surgical procedures under spinal anaesthesia , who developed shivering were selected. The patients were divided into two groups of 30 each. Group- C (n=30) comprised of the patients who received Clonidine 0.5mcg/kg intravenously and Group T (n=30) receiving Tramadol 1 mg/kg IV. The efficacy and mean interval between the injection of the study drugs and complete cessation of shivering were evaluated and recorded. Side effects like, nausea, vomiting, hypotension, bradycardia, sedation and headache, if present, were recorded. All data were analyzed using SSPS version 21. Everywhere necessary one way ANOVA test , two tailed test , student-t test and chi-square test were used and expressed in p value >0.05, (which is insignificant) and p value < 0.05, (which is significant differences). **Results:** Shivering control occurred in both groups but clonidine group had early control (2.17± 0.24 mins) and no recurrence, tramadol group had delayed control (3.84±0.30 mins) Haemodynamic parameters were maintained within 15% of baseline values in both groups. Complications like nausea, vomiting occurred in both groups but no significant difference. **Conclusion:** Complete control of post spinal intra-operative shivering with less or no severe side effects could be achieved with clonidine in comparison to tramadol.

KEYWORDS

Post spinal Shivering, Spinal anaesthesia, Clonidine and Tramadol.

INTRODUCTION

Surgery and anaesthesia cause shivering,a compensatory mechanism which occurs due to thermal dysregulation. This is worsened by vasodilation due to spinal anaesthesia; which causes redistribution of more body heat. Shivering is a physiological response to cold exposure and the body's next step is heat preservation leading to peripheral vasoconstriction 1. It is an involuntary oscillatory muscular activity seen as fasciculations of face, jaw , head and the upper part of the body 2. Shivering occurs often under neuraxial (epidural and spinal anaesthesia) and general anaesthesia; the incidence being 40%–60% in patients receiving regional anaesthesia and up to 60% in those receiving general anaesthesia [1].

Hence, the aim of our study is to compare the effectiveness of clonidine, an Alpha-2 agonist with that of tramadol which is an opioid analgesic with opioid action mainly mediated through mu-receptor with minimal effect on kappa and delta binding sites. Tramadol also activates the mononergic receptor of the descending neuraxial inhibitory pain pathway. The anti shivering action of tramadol is thought to be mediated by either its opioid or serotonergic and noradrenergic activity , or both .

Consequently, these two medications are chosen for the clinical comparative study for control of shivering in patients undergoing spinal anaesthesia.

AIMS AND OBJECTIVES

The aim of our study is to compare the effectiveness of clonidine, an Alpha-2 agonist with that of tramadol which is an opioid analgesic with opioid action mainly mediated through mu-receptor with minimal effect on kappa and delta binding sites. Tramadol also activates the mononergic receptor of the descending neuraxial inhibitory pain pathway.

The anti shivering action of tramadol is thought to be mediated by either its opioid or serotonergic and noradrenergic activity , or both .

MATERIALS AND METHODS

The study was designed as a hospital based, prospective randomized double blinded study conducted in the Department of Anaesthesiology and Critical care, Silchar Medical College and Hospital, Silchar, Assam. The study was done for one year w.e.f. 1st May 2021 to 30th April 2022 after obtaining Institutional Ethical Committee clearance and written informed consent from patients.60 patients of American Society of Anaesthesiologist (ASA) I & II, age of 18-70 years were divided into group-C and group-T of 30 in each group (n=30)

Inclusion Criteria

Only ASA I and II ,who had given valid informed consent & patients scheduled for elective surgical procedure including elective LSCS , under spinal anaesthesia were included.

Exclusion Criteria

a) Patient's refusal
b) Patients with contraindication for the specified drugs
c) Obesity (BMI >30)
d) Patients undergoing any emergency surgery
e) Patients taking any other long term medication
f) Local skin infection
g) Coagulopathy or any other bleeding diasthesis
h) Severe hypovolemia
i) Increased intra-cranial pressure
j) Structural and functional cardiac abnormalities
k) Severe spinal deformity

Group-C: All the patients in group-C received inj clonidine 0.5 mcg/kg body weight IV.
Group-T: All the patients in group-T received inj tramadol 1 mg/ kg body weight I.V.

Pre anaesthethic evaluation was done prior to the surgeries. A detailed system wise clinical examination including airway was done. Basic laboratory investigations like complete blood count , urine analysis , blood sugar, , kidney function test , chest x-ray, viral markers and ECG were done. Echocardiography, serum electrolytes, PT/INR were advised as required and all patients were kept NPO for 6 hrs prior to surgery.

On the day of the surgery, on arrival in the operation theatre, body weights of all patients were recorded. Basic monitoring devices including ECG, NIBP, pulse oximeter were connected and baseline

values of haemodynaemic variables like heart rate(HR) , Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) and peripheral oxygen saturation (SPO2) were recorded and IV line was secured with one 18 G IV cannula. Fluid pre-loading is carried out using a 15 minute infusion of 10 ml/kg of Ringer's lactate infusion.

Anaesthetic Procedure

All operating rooms, in which the operations were performed, maintained a constant humidity of 70% and an ambient temperature of around 21°C to 23°C.

The warming of intravenous fluids was not done so as to prevent the effects of warm fluid on the study's Outcomes . Patients were covered with drapes but not actively warmed .

Under strict aseptic precautions, spinal anesthesia was given in L3-L4 space in lateral decubitus position, with a 25 G sterile , disposable Quincke's spinal needle using standard midline approach. Consciousness levels, sedation levels, Oxygen saturation (SpO2), ECG, respiratory rate, body temperature with a clinical thermometer), and NIBP were continually monitored.

All Cases Were Screened For Shivering If Any, And Graded With A 4 Point Scale Validated By "crossly And Mahajan" Where :

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

DATA COLLECTION

The effect of the drug administration were assessed based on the format provided. All the patients were assessed for time of onset of shivering , severity of the shivering , time of disappearance of shivering (in minutes) and response (whether shivering ceased after 15 minutes or not), hemodynamic status and side effects if any.

Patients were observed at the intervals of 0min, till 5min and thereafter 10,15,20,25,30,35,40,45,50,55 and 60 minutes. Baseline heart rate, systolic blood pressure, diastolic blood pressure,SPO2, recurrence of shivering and mean body temperature were noted, during shivering and thereafter at regular intervals after the administration of the study drugs. Recurrence of shivering and sedation characteristics were noted and graded as discussed later. Recurrence of shivering was managed through non pharmacological method of administration of warm IV fluids and covering the patient with blankets, subsequently the shivering subsided within 10 minutes .

Level Of Sedation: Level Of Sedation Was Assessed By Ramsay Sedation Scale:

1: Patient is anxious and agitated or restless, or both
2 : Patient is co-operative , oriented , and tranquil.
3: Patients responds to commands only
4: Patients exhibits brisk response to light glabellar tap or loud auditory stimulus .
5: Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6: Patient exhibits no response

Intra and Postoperative Nausea and Vomiting were noted.All patients received oxygen intraoperatively at a rate of 4 -6 liters/min through face masks. Adverse reactions like bradycardia, hypotension , respiratory depression were also noted .

Statistical Evaluation

Appropriate statistical tools were used to conduct the analysis. The information gathered was tallied and examined. Using one-way ANOVA, the data between the groups were compared. Repeated analysis of variance was used to examine the within-group data. For non normal data Mann and Whitney test and Kushkar wallis test is used. All the data were analysed using SSPS version 21. Everywhere necessary, the two-tailed test, chi square test, paired and unpaired t tests were used. The outcomes were given as mean and standard deviation. $P < 0.05$ was regarded as significant

RESULTS AND OBSERVATION

Demographic variables including age, sex , ASA physical status, type of surgery were comparable in both groups and were statistically not significant.

Shivering score , time duration taken for stoppage of shivering, recurrence of shivering and side effects associated with the study drugs were assessed and recorded during the study.

Table 1.1 Demographic Comparison Of Ages And Sex In Group C And Group T

	Group T	Group C	p value
Age (in Years)	44.00±11.64	41.57±9.10	0.371
Sex (M/F)	25/26	21/9	0.222

Table 1.2 Age Distribution Among The Groups (mean +/- S.d)

	Group			p value
Age	Group T	Group C	Total	
20-29	4(13.3%)	2(6.7%)	6(10%)	0.135
30-39	7(23.3%)	11(36.7%)	18(30%)	
40-49	5(16.7%)	10(33.3%)	15(25%)	
50-59	14(46.7%)	7(23.3%)	21(35%)	
Total	30(100%)	30(100%)	60(100%)	

The minimum age of the patient was 22 years and the maximum age was 59 years. The Mean age of the patient in group T is 44 +/- 11.64 and in group C is 41.57 +/- 9.10. The statistical analysis is not significant for age ($p = 0.135$) between groups .

Table 3 Comparison Of Shivering Score (mean +/- S.D)

	Mean Shivering score	SD	Median (IQR)	p value
Group T	2.00	0.00	2 (2-2)	1
Group C	2.00	0.00	2 (2-2)	

In our present study , the shivering grade of 2 (two) was noticed in both the groups. For shivering the two tailed p value >0.05 indicate that there is no significant differences in shivering scores across the two groups.

Table 4 Comparison Of Time Interval At Which Shivering Stops (in Minutes) With (mean +/- S.D)

	Mean Shivering stops	SD	Median (IQR)	p value
Group T	3.84	0.30	4 (3.725-4.00)	<0.001
Group C	2.17	0.24	2.0 (2.0-2.425)	

The average time taken for stoppage of shivering is more for tramadol in comparison to clonidine.in group T mean time interval for disappearance of shivering was 3.84 +/- 0.30 minutes , where as in group C it is 2.17 +/- 024 minutes. There is a statistical between the Groups Tand C, with p value <0.05 I.e 0.001.

Table 5 Showing Recurrence Of Shivering (mean +/- S.D)

	Group			p value
Shivering reoccurs	Group T	Group C	Total	
NIL	29(96.7%)	30(100%)	59(98.3%)	0.313
YES	1(3.3%)	0(0%)	1(1.7%)	
Total	30(100%)	30(100%)	60(100%)	

In our there is no recurrence of shivering in group C, in group T one patient with was observed to have recurrence of shivering . The statistical analysis revealed both the groups were statistically comparable .

Table 6 Showing Comparison Of Side Effects /complications (mean +/-S.D)

Complications/Side effects	Group			p value
	Group T	Group C	Total	
Nausea and vomiting	3(10%)	0(0%)	3(5%)	0.026
N	2(6.7%)	0(0%)	2(3.3%)	
S	22(73.3%)	30(100%)	52(86.7%)	
S,N	3(10%)	0(0%)	3(5%)	
Total	30(100%)	30(100%)	60(100%)	

Comparison of side effects between study groups showed three patients with nausea and sedation in group T. For side effects/complications . Two tailed p value < 0.05 i.e. 0.026 indicates that there is significant statistical difference of side effects such as nausea and sedation across the groups T and C.

DISCUSSION

The actual cause of post-spinal anaesthesia shivering is unknown, however there are several theories to explain it[2]. Probable mechanisms attributing to shivering can be the decrease in core body temperature

secondary to sympathetic blockade, uninhibited spinal reflexes , peripheral vasodilatation, increased cutaneous blood flow leading to faster heat loss through skin , psychological stress , hypercapnia , hypoxia , pain and effects of cold anaesthetic drugs on the thermosensitive receptors in the spinal cord.

The vasoconstriction and shivering thresholds are both decreased during regional anaesthesia namely spinal and epidural blockade[3]. Regional anaesthesia reduces the maximum intensity of shivering , because the muscles below the block are unable to shiver ,thus shivering of muscles above the block makes up for it. The core temperature drops by 0.6°C to 1.5°C during the first hour of regional anaesthesia because of the heat transfer from the core to the periphery and vasodilatation.

Numerous non-pharmacological techniques have been used in different studies, like active and passive warming systems , warming of intravenous fluids , inspired air , blood and its products. However, using such methods in clinical settings would necessitate the deployment of expensive, specialized equipment .

Comparing pharmacological and non-pharmacological approaches, the former is more economical. There is no gold standard drug for treatment of shivering. Many drugs have been tried with effectiveness rates ranging from 30-95%, including tramadol, pethidine, clonidine,doxapram, propofol, physostigmine,alfentanil, ondansetrone etc.

Tramadol is a synthetic opioid analgesic , which exerts its effects primarily through agonistic action on mu-receptor ,and has little to no effect on the kappa and delta receptors. The anti-shivering effect is most likely mediated by its opioid, serotonergic and noradrenergic activities or both .Tramadol stimulates 5-HT3 release while inhibiting 5-HT3 reuptake. Additionally, it also inhibits synaptosomal NA reuptake ,which contributes to its anti-shivering effect.

Animal experiments using electrophysiology , neurophysiology, and neuropharmacology have helped in establishing the role of noradrenaline and serotonin in the regulation of body temperature[4]. Serotonin acts as neurotransmitter in the nucleus raphe magnus, which when activated ,has an inhibitory effect on shivering.

Tramadol has a good clinical use as an anti-shivering drug. It may be used to regulate shivering and is more practical and safer than nalbuphine as it causes less sedation and less respiratory depression. Time taken to control shivering is lower with tramadol than nalbuphine. The dose of Tramadol in our study was 1mg/kg body weight ,and the results are comparable to the study conducted by Sonalika Tudimilla et al ,in 2021[5]. In a study conducted by Mahesh Sharma et al, it was observed that pethidine in the dose of 0.5mg/kg body weight, controlled shivering better than tramadol in a dose of 0.5mg/kg body weight, as it produces less dizziness and nausea and vomiting when compared to tramadol[6].

Similar study was conducted in 2016 by Fidelis Anayo Onyekwulu et al,who performed a prospective randomised double blinded cross sectional study evaluating the efficacy of intravenous tramadol in the control of shivering following spinal anesthesia for caesarean section[7]. They divided the patients receiving inj tramadol in two groups, Group A received inj tramadol in dose of 0.5mg/kg body weight and Group B received inj tramadol in the dose of 0.25mg/kg body weight. They concluded that tramadol is effective in control of post spinal anaesthesia shivering when used in the dose of 0.5mg/kg body weight. Clonidine,is a centrally acting Alpha-2 agonist . For anti-shivering effects, Clonidine acts at three levels , the hypothalamus,spinal cord and locus coeruleus . Due to the large density of Alpha-2 receptors in the hypothalamus , it lowers the thermoregulatory threshold for contraction of the blood vessels and shivering. Clonidine lowers the spontaneous activity in the locus coeruleus , a pro-shivering Centre in the pons . At the spinal cord level , it activates the Alpha-2 adreno receptors and release acetylcholine , norepinephrine and dynorphine . These nuero-transmitters have depressor effect at the dorsal horn that modulate thermal inputs. Clonidine is lipid soluble and crosses the blood brain barrier and has quick onset of action[8]. Because of these benefits , the central nervous system experiences interaction between Alpha -2 adrenoreceptors at the spinal and supraspinal levels. The dose of clonidine chosen is 0.5 mcg/kg , the results of our study were comparable to the study carried out by Dr. Partha Sarathi Halder et al.[9]

In our study , 60 patients were randomly divided into two groups ,who underwent surgeries under spinal anaesthesia and developed shivering. These patients were included for the treatment with the study drugs namely clonidine and tramadol. Group – C received injection clonidine 0.5 mcg/kg IV (n=30) and Group-T received injection tramadol 1mg/kg IV and data were collected as per protocol. Statistical analysis of collected data showed no statistical significance among demographic data, age distribution , sex distribution and ASA grading between the two groups . Results and observations from our study are further discussed.

Shivering

In our study , the comparison of shivering score done between the two groups showed grade 2 shivering score as per Crossley and Mahajan grades of shivering .Both groups of patients had grade 2 shivering , statistical analysis of which showed no significance between the groups.

The time interval of disappearance of shivering or time taken for stoppage of shivering after the drug administration were noted and it was found that Group C had a mean of 2.17 +/- 024 minutes and Group T had a mean time 3.84 +/- 0.30 minutes. The difference between the time taken to stop shivering is statistically significant, p value being 0.001,as analysed by ANOVA test. These results were in accordance with the study conducted by Dhrubajyoti Biswa et al[10] , where they concluded that clonidine is better than tramadol in controlling post spinal anaesthesia shivering, as tramadol took longer time for cessation of shivering than clonidine . Also , it was seen that clonidine had fewer side effects than tramadol. Similar observations were made in the study conducted by Dr Partha Sarathi Halder et al[9].

The recurrence of shivering after 15 minutes of response time was noted . In our present study , Group C showed no recurrence of shivering where as Group T showed recurrence in 1 patient (3.3%) and Group C showed 0% recurrence , this is similar to the study conducted by Varsha Vyas et al in 2018[11]. They conducted a prospective double blind randomized clinical study of 60 patients with treatment for shivering after spinal anaesthesia . They concluded recurrence of shivering was more with tramadol as compared to clonidine. However these observations are in contrast with the study conducted by Dhruv Jariwala et al[12] .

In 2016, Saumya M Jois et al, conducted a randomized comparative study of clonidine and tramadol for controlling post spinal anaesthesia shivering[13]. They concluded that clonidine took shorter time to achieve cessation of shivering compared to tramadol, however both effectively control post spinal anaesthesia shivering.

Evaluation Of Side Effects

The evaluation of side effects in our study revealed that 3 patients in group T had nausea and vomiting, and 2 patients with nausea alone and others with sedation were noted. These results were in accordance with the study conducted by Dr Partha Sarathi Halder et al[9].

Recurrence of shivering was observed in 1 patient in group T, and no recurrence of shivering was observed in any patients in group C. The patients in Group C did not complain of nausea and they remain calm, sedated and easily arousable.

The incidence of adverse effect like nausea and vomiting was found to be higher in case of tramadol compared to clonidine however, more studies need to be undertaken with varying dosages to extrapolate the results of this study. There was not much difference in the number of patients who were sedated in either group.

CONCLUSION

In conclusion both the drugs used in this study namely Tramadol (1mg/kg), and Clonidine (0.5µg/kg) effectively treated post spinal anaesthesia shivering.

Among them Clonidine took lesser time to achieve complete cessation of shivering and also maintained better side effect profile and showed no recurrence of shivering after its administration. Tramadol was equally effective in controlling post spinal anaesthesia shivering and can be used as a safe alternative, though the problem of nausea and vomiting remains with few patients.

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