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Comparison of Clonidine, Dexmedetomidine and Tramadol for Control of Post Spinal Shivering: A Randomized Double Blind Clinical Study

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ABSTRACT- BACKGROUND: 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, Dexmedetomidine and Tramadol in the treatment of post spinal intra-operative shivering.
METHODS: In this prospective, double blind, randomized study, 90 ASA grade I and II patients of patients aged 18–50 rears, scheduled for various routine surgical procedures under spinal anaesthesia with hyperbaric Bupivacaine and who developed shivering were selected. The patients were divided into three groups of 30 each. Group- C (n=30) comprised of the patients who received Clonidine 0.5mcg/kg intravenously, Group-D (n=30) who received Dexmedetomidine 0.5mcg/kg IV and Group T (n=30) receiving Tramadol 2 mg/kg (maximum 100mg) IV. The efficacy and response rate of the study drugs were evaluated and recorded. Side effects like, nausea, vomiting, hypotension, bradycardia, sedation and headache, if present, were recorded. All data were analyzed using Chi-square test and student-t test and expressed in >0.05, (which is insignificant) and < 0.05, (which is significant differences).
RESULTS: There were significant differences in the total response rate between the drugs ($p > 0.05$). Tramadol showing the highest response rate (100%). Time taken from the start of treatment to cessation of shivering was significantly less ($p<0.05$) in Dexmedetomidine group, but Tramadol group shows complete control of post spinal shivering with none or lesser and mild degree of side effects with a single dose.
CONCLUSION: Complete control of post spinal intra-operative shivering with less or no severe side effects could be achieved with Tramadol in comparisons to clonidine and Dexmedetomidine.

Key-words- Post spinal Shivering, Clonidine, Dexmedetomidine, Tramadol

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INTRODUCTION

Intra-operative shivering, which is defined as involuntary oscillatory muscular activity, is one of the most common complication of spinal anaesthesia which is very uncomfortable for the patients and interfere with monitoring of electrocardiogram, blood pressure and arterial oxygen saturation.

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Its incidence has been reported in 50-60% in different reports[1,2]. This complication generally occurs following unwanted hypothermia during operation[3]. Spinal anaesthesia impairs the thermo-regulation by inhibiting vasomotor and shivering responses and by redistribution of heat from core to periphery of the body resulting in hypothermia during spinal anaesthesia[4]. It is considered to be a physiological response to core temperature in an attempt to raise the metabolic heat production. It increases oxygen demand, heart rate, cardiac output, lactic acidosis, increased intra ocular pressure, increased intra cranial pressure, increased carbon dioxide production, hemodynamic changes and increased pain perception[5]. Thus it may cause distress to patients with low cardio pulmonary reserve. To prevent and treat this complication, warming of the patients with warm IV infusion, increasing the operation room temperature is undertaken[6]. Apart from

this various therapeutic agents are used, which include Meperidine, Clonidine, Dexmedetomidine, Nefopam, Anticholinergics Opiate agonist, Dexamethasone and Tramadol, however every aforesaid agents has its own adverse effects and the most ideal anti-shivering agent is still not found[7,8]. Among the pharmaceutical agents, pethidine (meperidine) has been shown to be the most effective treatment[9]. Although the mechanism of action is not completely understood, it probably acts directly on the thermos-regulatory center or via opioid K-receptors[10]. α-2 receptor agonists like Clonidine and Dexmedetomidine are another important class of anti-shivering agents that, unlike meperidine, causes little respiratory depression. Among the two, Dexmedetomidine is a highly selective α-2 receptor agonist with potent effects on central nervous system. Various clinical trials investigated its efficacy in established shivering[11]. Tramadol is an opioid analgesic with opioid action possibly mediated through mu-receptor with minimal effect on kappa and delta binding sites. Tramadol also activates the mononergic receptor of the descending neuraxial inhibiting pain pathway. The anti-shivering action of Tramadol is probably mediated via its opioid or serotonergic and noradrenergic activity or both[12]. The aim of this prospective double blind randomized clinically controlled study was to clinically compare the efficacy, haemodynamic responses, complications and side effects of the three commonly used anti shivering agents: Clonidine, Dexmedetomidine and Tramadol, and find the most suitable post spinal anti shivering drug among the three.

MATERIALS AND METHODS

After obtaining approval from the ethical committee and written informed consent, 90 American Society of Anaesthesiologists grade-I and grade-2 (ASA I& II) patients of either sex aged 18 to 45 years scheduled for elective abdominal, gynecological and orthopedic surgeries under spinal anaesthesia were included in this study, at the department of Anaesthesiology, JLN Medical College & Hospital, Bhagalpur from a period of January 2016 to June 2016. Patients with known hypersensitivity to clonidine, Dexmedetomidine and Tramadol, known alcoholic and drug abuse, hyperthyroidism, cardio-vascular diseases, psychological disorder, severe diabetic neuropathy and urinary tract infection were excluded. All patients who developed post spinal intra-operative shivering were randomly allocated to three groups: Group C (n=30) received clonidine 0.5 mcg/kg IV, Group D (n=30) received Dexmedetomidine 0.5 mcg/kg IV and group T (n=30) received 1.5 mg/kg (maximum 100 mg) of Tramadol IV. All the three drugs samples were diluted with distilled water to make it 10 ml each.

Anaesthesiologists, who were not involved in the study made the trial preparation and recorded group randomization separately. We, who were conducting the cases and recording the data, were unaware of the preparation administered.

The operation room temperature was maintained around 22-24°C and humidity around 70%. Plasma volume expanders to be used were brought to room temperature and preloading was given rapidly @10 ml/kg body weight as practiced in all subarachnoid blocks. Standard monitoring for pulse, NIBP, ECG, SpO_2 and axillary-temperature were established and pre-procedural readings were recorded. Blocks were given with 15 mg (3 ml) of 0.5% Bupivacaine heavy without any adjuvant, at L 3-4 interspace using 27 gauze Quincke's needle with patients in lateral position, which was brought to supine position immediately with a pillow underneath the shoulder to raise it. Oxygen was administered to all patients of all three groups at the rate of 3 L/Minute with a face mask and was covered with cotton drapes. All monitored readings were recorded every 5 minutes in the first hour of the subarachnoid block and every 15 minutes there after grading of shivering was done according to Tsai and Chu classification[13].

Grade 0: No shivering

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

Grade 2: Visible muscle activity confined to one muscle group

Grade 3: Visible muscle activity in more than one muscle group but not generalized

Grade 4: Gross muscle activity involving the whole body

Patients who developed Grade 2, 3 or grade 4 of shivering were included in the study and the prepared solution of drugs in study was given IV very slowly in 2 minutes time. We recorded the time in minutes at which shivering started after subarachnoid block (onset of shivering), severity of the shivering, time of disappearance of severing (in minutes) and response rate (whether shivering ceased after 15 minutes or not). Duration of surgery and total duration of spinal anaesthesia effect (spontaneous recovery of sensory block using pin-prick method and return of motor block) were noted. If the shivering did not subside in 15 minutes, the treatment was considered to be ineffective. Any recurrence of shivering was noted and additional measures were taken into consideration. Side effects like nausea, vomiting, bradycardia (pulse rate < 50/minute), hypotension (BP < 20% of base line, or systolic pressure less than 90 mm of Hg), Dizziness and sedation. Sedation was recorded using the four point sedation score of Filos[13].

Score -1 - Awake and Alert

Score -2 - Drowsy and responsive to verbal stimuli

Score-3 - Drowsy but just arousable to verbal stimuli

Score -4 – Unarousable

Complications were controlled by standard methods: Atropine for bradycardia, fast intravenous fluid and Mephentermine for hypotension and Ondansetron for vomiting, all in titrated doses. After the conclusion of operative procedures, patients were transferred to post-operative recovery ward, where temperature of the room was set at 26 degree C and humidity at 70%. Patients were kept covered by cotton blankets and standard monitoring was maintained. Data were recorded every 15 minutes and documented for another two hours after recovery from sensory and motor block. Statistical analysis was done using Student t test and Chi-square test for interpretation of results. P value <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic data

Patients	Group- C, Clonidine group (n=30)	Group- D, Dexmedetomidine group (n=30)	Group- T, Tramadol group (n=30)	P value
Age (years)	30.03±11.97 (18-50)	30.76±10.29 (19-50)	29.82±9.76 (18-50)	P>0.05 ns
Sex (M/F)	19 / 11	18 / 12	17 / 13	p>0.05ns
Weight (Kg)	52.1±10.3 (40-76)	54.8±9.21 (43-70)	56.60±7.20 (48-80)	p>0.05 ns
Duration of surgery(min)	56.60 ±2 7.20 (45-78)	60.29±2 7.20 (50-80)	60.37±17.20 (50-82)	p>0.05 ns
ASA (I/II)	21 / 9	20 / 10	22 / 8	P>0.05 ns
Duration of motor Block (min)	188.88±35.76 (180-220)	186.48 ± 36.79 (182-223)	188.98±35.33 188-230)	P>0.05 ns
Duration of Sensory block (min)	265.66±42.88 (240-255)	277.16 ± 45.08 (249-260)	270.38±44.57 (245-250)	p>0.05ns

Data are presented as mean ± SD, range, number and frequency
Significant difference between groups is at p- value < 0.05
ns = no significant difference
The groups were comparable with respect to age, sex, weight, duration of surgery, duration of motor and sensory block

Table 2: Shivering characters in the studied groups

	Group- C, Clonidine group (n=30)	Group- D, Dexmedetomidine group (n=30)	Group- T, Tramadol group (n=30)	P value
Shivering onset Time (min)				
Mean ± SD	26.8±13.5	26.8±13.5	26.8±13.5	p>0.05 ns
Range	(13 – 46)	(13 – 46)	(13 – 46)	
Shivering cessation time (sec)				
Mean± SD	122.54±31.76	92.54±31.76	113.54±31.76	p<0.05
Range	81 - 154	42 - 154	81 - 194	
Shivering control				
Complete	22 (73.33%)	27 (90%)	30 (100%)	P<0.05
Incomplete	6 (29%)	3(10%)	0 (0%)	

Failed	2 (6.66%)	0(0%)	0(0%)	P< 0.05
Response Rate (%)	74.34%	97%	100%	P< 0.05
Shivering recurrence				
Number	5	3	0	5< 0.05
Percentage	16.7%	10%	0%	
Need for 2nd dose	5 (16.7%)	3 (10%)	0 (0%)	0.05

Date is presented as mean ± SD
Range, Number & frequency
ns= No significant
Difference between groups: p < 0.05 is not significant

Table 2 shows that the shivering onset times are comparable in all the three groups. Shivering cessation times are 122.54±31.76 and 113.54±31.76 in Clonidine and Tramadol groups respectively, whereas the fastest recovery is with Dexmedetomidine group as the mean times are 92.54±31.76, this is significant. Shivering control is 100% with Tramadol group whereas Dexmedetomidine and Clonidine show complete control in 90% and 73.33% respectively. Control is not achieved at all in 2 patients (6.66%) in clonidine group, this is highly significant. Thus overall response rates are 74.34%, 97% and 100% with group C, group D and group T respectively, which is again significant. Recurrence is observed in 5 patients in Clonidine group, 3 patients in Dexmedetomidine but none in Tramadol group and so second doses were needed in 5 patients in Clonidine and 3 patients in Dexmedetomidine group and none in Tramadol group, indicating the advantage of Tramadol over Clonidine and Dexmedetomidine as far as the control of post spinal shivering is concerned, this is significant.

Table 3: Perioperative Changes in mean axillary temperature, Systolic and diastolic blood pressure, heart rate and sedation score

Patients	Group-C, Clonidine group (n=30)	Group-D, Dexmedetomidine group (n=30)	Group-T, Tramadol group (n=30)	P value
Mean axillary temperature (degree C)	36.2±1.1 (36.2-37.1)	36.3±1.1 (36.3-37.1)	36.2±1.2 (36.3-37.3)	p>0.05ns
Mean systolic blood pressure (mm of Hg.)	108±31.12 (92-118)	109±34.45 (90-108)	113 ±10.98 (98-130)	p>0.05ns
Mean Diastolic blood pressure (mm of Hg.)	55.08±11.76 (55-70)	56.67±12.09 (52-68)	67.94±19.98(65-81)	p>0.05ns
MeanHeart rate(per minute)	54.88±12.99) (60-65)	55.63±14.98 (62-70)	61.78±9.81 (66- 80)	p>0.05ns
Mean sedation score (Filos)	2-3	2-3	1-2	P<0.05

Date is presented as mean ± SD, Range Number & frequency
p< 0.05 is not significant
ns = No significant difference between groups

Table 3 shows that mean axillary temperature is comparable in all three groups. Mean systolic and diastolic blood pressures are comparable but the highest fall is observed with Dexmedetomidine group, whereas lowest in Tramadol group. Mean heart rates are also almost comparable in all the three groups. Filos sedation score is also favorable in Tramadol group with the score ranging from 1 to 2 score, whereas patients were more sedated with score 2-3 in Clonidine and Dexmedetomidine groups, which is significant.

Table 4: Intra- operative & Post - operative adverse events

	Group-C, Clonidine group (n=30)	Group-D, Dexmedetomidine group (n=30)	Group-T, Tramadol group (n=30)	P value
Hypotension	10 (33.33%)	6 (20%)	3 (10%)	P<0.05
Bradycardia	3 (10%)	2 (6.66%)	1 (3.3%)	P<0.05s
Sedation	10 (33.33%)	9 (30%)	2 (6.66%)	p>0.05ns
Nausea	4 (13.33%)	4 (13.33%)	3 (10%)	p> 0.05ns
Vomiting	1 (3.3%)	1 (3.33%)	0 (0%)	p> 0.05ns
Headache	0	0	0	p> 05ns

Data are presented as number, frequency and percentage
Significant difference between groups atp value < 0.05
No significant difference = ns

Table 4 shows that hypotension is observed in highest number of patients (33.33%) in Clonidine, 20% of Dexmedetomidine group patients but only 10% of Tramadol group, which is significant. Occurrence of Bradycardia is comparable but sedation was observed 33.33% and 30% in Clonidine and Dexmedetomidine groups respectively but only in 6.66% cases of Tramadol group, which is again significant. Occurrence of nausea and vomiting incidence is comparable and headache is not observed in any patient of any group.

DISCUSSION

Spinal anaesthesia carries two dreaded side effects, one is hypotension and another is shivering. Ironically every anaesthesiologist and allied persons are well prepared to deal with the hypotension and every pre and para operative arrangement and precautions are taken to counter it because it may become life threatening, whereas shivering is least taken care off unless it appears, though it happens in 40-70% of cases[15], and is very agonizing to the patient.

Various pharmaceutical agents are being used to treat it. Our present study is a Comparative randomized double blind clinical study of the effects of clonidine, dexmedetomidine and tramadol. The patients were divided into three groups of 30 each. Group- C (n=30) comprised of the patients who received Clonidine 0.5mcg/kg intravenously, Group-D (n=30) who received Dexmedetomidine 0.5mcg/kg IV and Group T (n=30) receiving Tramadol 2 mg/kg (maximum 100mg) IV. Clonidine is a centrally acting selective α2 agonist and apart from being well known for its sedative effects, it is an established anti shivering agent[16,17]. It exerts its anti-shivering effect at three levels: Hypothalamus, Locus coereleus and spinal cord. At the hypothalamic level, it decreases thermoregulatory threshold for vasoconstriction and shivering, because hypothalamus has high density of α2 adrenoreceptors and hence is effective in treating the established post-anaesthetic shivering[16,18]. It also reduces spontaneous firing in Locus coereleus– a pro-shivering center in pons[19]. At the spinal cord level, it activates the α2 adrenoreceptors and release of dynorphine, norepinephrine and acetylcholine[19]. The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs[20]. Clonidine is highly lipid soluble and easily crosses the blood brain barrier[21]. Due to these merits, interaction at the α2 adreno receptors at spinal and supraspinaly sites occurs within the central nervous system[22]. Dexmedetomidine like Clonidine is a α2 adrenoreceptors agonist with higher lipid solubility. It does not change the sweating threshold and thus decreases the concentration response curves for vasoconstriction and shivering in a linear fashion[23]. Therefore, the thermoregulatory responses were inhibited within a wider range of temperature. Just like clonidine, Dexmedetomidine displays specific and selective α2adreno-receptorsagonism in the brain and spinal cord. The responses to activation of these receptors include decreased sympathetic tone with attenuation of neuro-endocrine and hemodynamic responses to anaesthesia and surgery. Thus, Dexmedetomidine can mediate both the beneficial and unwanted effects of shivering provoked by hypothermia, such as increased catecholamine concentration, increased oxygen concentration, hypertension and tachycardia[24].

Tramadol is an opioid analgesic with opioid action preferably mediated through 'μ' receptors with minimal effect on kappa and delta binding sites. Tramadol also activates the mononergic receptors of the descending neuraxial pain inhibiting pathway. The mechanism of anti-shivering actions of Tramadol is not fully understood as yet though it is probably mediated through its opioid or

serotonergic and noradrenergic activity or both[13,25,26]. Our study was designed to compare the efficacy of two α-2 adrenoreceptors agonists, namely Clonidine (group: C, n=30, 0.5 mcg/kg) and Dexmedetomidine (group: D, n=30, 0.5 mcg/kg) and Tramadol, an opioid analgesic (group: T, n=30, 1mg/kg to maximum 100mg). Our study did not control tightly the various factors such as the temperature of drugs and intravenous fluid. However this would not have affected the validity of our comparison, as this study was focused on the response after the treatment rather than the incidence of shivering. Again, the randomization of all the three groups had been subjected to a similar degree of influence of these factors. According to the study of Mohta[27], three doses of Tramadol, i.e., 1mg, 2mg and 3mg per kg were effective for prophylaxis of shivering. Since the adverse effects, particularly nausea is dose dependent and comparably more likely to appear with a high loading dose[28], so we in our study choose a dose of 2 mg/kg, to a maximum of 100 mg, tat too by dissolving it with NS to make it 10 ml and the rate of IV infusion was very slow taking two minutes. Slow infusion of Tramadol results in; less or no incidence of nausea and vomiting is also reported [29,30]. This dilution and slow infusion was carried out in all the groups. Results shown in Table I, regarding age, sex, weight, duration of surgery, ASA grade, duration of motor block and duration of sensory block shows that they are comparable and not significant, as same method and agent were used to achieve spinal anaesthesia. Table 2 shows that the shivering onset time was comparable in all groups and not significant. Shivering cessation time is least with group D (92.54±31.76 seconds) in comparison to group C (122.54±31.76 S) and group T (113.54±31.76 S) and it is significant difference and the result is comparable to the study [31], and many others .complete Shivering control rate is 100% in Tramadol group in comparison to 73.33% and 90% respectively in Clonidine and Dexmedetomidine groups. This difference in result in comparison to other studies is mainly due to the fact that almost all studies are with the use of this agent in very insufficient doses of eight her 0.5mg/kg or 1 mg/kg body weight for fear of nausea and vomiting which was countered in our study with slow and diluted transfusion. Likewise, the response rate % was also highest in our study with Tramadol. Recurrence of shivering and need for repeating the dose was needed in 5 patients (16.7%) and 3 patients (10%) respectively in Clonidine and Dexmedetomidine in comparison to none in Tramadol group, particularly if the operative times were extended. This is very significant observation in our study. Table 3 also shows that the sedation score in C and group D was higher (Filos sedation scores ranging from 2 to 3), whereas the patients of group T were experiencing less sedation (Filos score 1-2 only), thus making the patients awake all the times. Many observers in the past liked their patients to be sedated, whereas we liked our patients to be awake and conversing, unless the patients desire such so as to elicit anything going wrong would be reported by the patients itself.

Table 4 shows lesser incidence of hypotension in Tramadol group (3 patients, 10% incidence) in comparison to 10 patients (33.33%) in group C and 6 patients (20%) in group D. This is significant. Likewise bradycardia incidence was also lesser in group T (1 patient, 3.3%) in comparison to 3 patients (10%) in group C and 2 patients (6.66%) in Dexmedetomidine group. This is also significant. 10 patients (33.33%) in group C and 9 patients (30%) in group D were sedated whereas only 2 patients (6.66%) in group T felt sedation. This is also significant. Incidence of nausea and vomiting were very insignificant with our doses and methods in this study, in contrary to many other studies with similar agents, particularly Tramadol. So, our study finds Tramadol 2 mg/kg (maximum 100 mg) being diluted to 10 ml and given IV slowly over two minutes is a superior post spinal anti-shivering agent in comparison to Clonidine 0.5 mcg/kg diluted to 10 ml and Dexmedetomidine 0.5 mcg/kg diluted to 10 ml. There are some limitations of this study, as the sample size is small and the sample population consisted of adult patients, who were comparatively healthy and undergoing an elective procedure of less blood loss or major fluid shift.

CONCLUSIONS

Tramadol was found to be safe and effective in prevention and treatment of post spinal shivering. This drug has no hemodynamic, cardio respiratory and neurological side effect in comparison to Clonidine and Dexmedetomidine. All the shortcomings of Tramadol as far as its use as post spinal anti shivering drug, compared to Clonidine or Dexmedetomidine, reported by score of observer might have been due to the doses and methods of administration. Away from the preview of this study, we have used Tramadol in the said dose and method in thousands of cases with 100% good results without any hemodynamic, cardio-respiratory or neurological adversity. Single injection of Dexmedetomidine or Clonidine in the doses used in this study was not sufficient and either repetition or continuous intra-venous infusion was needed, particularly in the events of prolonged operation times. Although the cost factor has not been compared in this study, yet it is also considerable as the total treatment cost with Tramadol is the lowest of all.

Ethical Clearance: No deviation from standard care of treatment.

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