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COMPARATIVE STUDY OF INTRAVENOUS DEXMEDETOMIDINE AND INTRAVENOUS TRAMADOL FOR CONTROL OF POST SPINAL SHIVERING.

Anaesthesiology

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ABSTRACT

Introduction- Dexmedetomidine has been used for prevention of post anaesthesia shivering. Its use for treatment of post spinal shivering is under-evaluated. We aimed to evaluate and compare effectiveness, hemodynamic and adverse effects of dexmedetomidine with those of tramadol for control of post spinal shivering.

Methods- Prospective randomized double blinded study in 100 patients undergoing surgery in spinal anaesthesia randomised in two groups to receive either Dexmedetomidine 0.5µg/kg or Tramadol 0.5mg/kg.Grade,onset,time to cessation of shivering, recurrence, response rate, side effects were noted.

Results- Time to shivering control was less with Dexmedetomidine but with minimal sedation. Nausea and vomiting seen only with Tramadol.

Conclusion- Dexmedetomidime 0.5µg/kg more efficient to control post spinal shivering than Tramadol 0.5mg/kg which causes nausea vomiting.

KEYWORDS

Dexmedetomidine, Tramadol, postspinal shivering.

I. INTRODUCTION

George Pickering, English physician, wrote in 1956, "The most effective system for cooling a man is to subject him to anaesthesia".(1).Combination of anaesthetic induced thermoregulatory impairment and cool environment makes surgical patients hypothermic.(2). Hypothermia,apart from protecting against tissue ischemia as in cardiopulmonary bypass, post cardiac arrest care, carotid and liver surgeries; causes multiple derangements including platelet dysfunction, wound infection, impaired immuneregulation and shivering.(3)(4).

Shivering,defined as involuntary, repetitive activity of skeletal muscles in response to hypothermia to generate heat, is among top 10 most common post anesthesia adverse event, has incidence 40–70%.(5)(6). Shivering is not only physically distressing but also have detrimental effects like wound pain , impede monitoring ,increase intraocular and intracranial pressures , increased oxygen consumption and carbon dioxide production which is hazardous with limited cardiorespiratory reserve.Regional anaesthesia is associated with greater heat loss than general anaesthesia. (6) Mechanisms could be decreased core body temperature secondary to sympathetic blockade; peripheral vasodilatation; increased cutaneous blood flow, which leads to increased heat loss; cold temperature of operation theatre; cold IV fluids; and effect of cold anaesthetic drugs upon thermo sensitive receptors in spinal cord.

Shivering can be treated by non-pharmacologically by use of forced air warming, warming blankets, warmed fluids and pharmacologically with clonidine, pethidine, tramadol, nefopam , ketamine as suggested by many meta-analyses. Still, no gold standard treatment is known as administration of available drugs causes various adverse effects.(7)(8).

Tramadol has been commonly used drug for post-spinal shivering, but has many adverse effects.(5) Dexmedetomidine is known to reduce shivering threshold. Few studies have inferred that dexmedetomidine is effective without major adverse effect and provides good haemodynamic stability(9)(10).Hence, we planned to study efficacy, haemodynamic and adverse effects of tramadol and dexmedetomidine when used for control of post-spinal shivering.

II. MATERIAL AND METHODS

After approval from Institutional Ethics Committee,100 patients scheduled for elective lower abdominal, lower limb, orthopaedic and plastic surgeries under spinal anaesthesia were included in study.

Study Design: Prospective randomized double blinded comparative study

Study Location: Tertiary care teaching hospital in Department of Anaesthesiology, at B.J. Medical College, Pune.

Study Duration: November 2014 to May 2016.

Sample size calculation: Keeping value of alpha = 0.05 and beta = 0.2. We hypothesized that test drug significantly better if it decreased time taken to abolish shivering by 1 min as compared to control drug . We took maximum standard deviation (SD)= 1.69 as per previous study.(11)

Applying formula for two-sided study:
n (size per group) =2c/δ2 + 1
where, δ = (µ2–µ1)/σ is standardised effect size
µ1 and µ2 are means of two groups
σ is common SD
c = 7.9 for 80% power
Hence, $n = 2 \times 7.9/(1/1.69)^2 + 1 = 46.1$.
Rounding off, sample size as 50 per group.

Subjects & selection method:

Inclusion Criteria

1) Age 18 to 65 years.
2) Sex : male or females
3) ASA grade I & II.
4) Surgeries lasting not more than 2 hours.

Exclusion Criteria

1) Cardio pulmonary, renal, liver disorder.
2) Hypersensitivity to Tramadol and Dexmedetomidine.
3) Thyroid disorders.
4) Psychological disorder.
5) Alcohol or drug abuse.
6) Diabetes mellitus.

Patients divided into two groups using computerized randomization.
Group D (n=50) (Study Group) -Patients receiving Dexmedetomidine.
Group T (n-50) (Control Group)-Patients receiving Tramadol.

Procedure methodology

After thorough preoperative assessment ,written informed consent was obtained. Intravenous cannula of 18G secured and preloading with Ringer's Lactate 10 ml/kg before spinal anaesthesia and maintained at 6 ml/kg/h after spinal anaesthesia. Monitors were attached, heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SPO_2), electrocardiography (ECG), and axillary temperature were recorded. Subarachnoid anaesthesia 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. Operation theatres temperature were maintained at 24°C-25°C. Supplemental oxygen administered at 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.

Patient who developed grade 3 or 4 shivering were included in study.(**Wrench** shivering grading (12) Grade 1- No shivering.;Grade 2-One or more of a)Piloerection,b)Peripheral vasoconstriction c)Peripheral cyanosis,d)Visible muscle activity;Grade 3-Visible muscle activity confined to one muscle group;Grade 4-Visible in more than one muscle group;Grade 5-Gross muscle activity involving whole body.)

Index anaesthesiologist (not a part of study) prepared either of the drugs diluted to 5 ml in a 5 ml syringe and presented as coded syringes given IV bolus over 5minutes.Attending anaesthesiologist recorded time of appearance and grade of shivering, time to disappearance of shivering and response rate (percentage of patients in which shivering controlled within 15minutes).

Side effects like bradycardia (<50/min, treated with atropine 0.6 mg IV), hypotension (fall in BP>20% of baseline, treated with ephedrine in 6 mg boluses IV titrated till BP within 20% of baseline),dry mouth, skin rash, sedation and complications were noted. Nausea and vomiting treated with metoclopramide 10 mg IV.Sedation was assessed using Filo's Scale(13):(1.Awake and alert 2.Drowsy, responsive to verbal stimuli3.Drowsy, arousable to physical stimuli 4.Unarousable). Also noted are duration of surgery and spinal anaesthesia, blood loss and intravenous fluids administered. Coding was opened after completion of study.

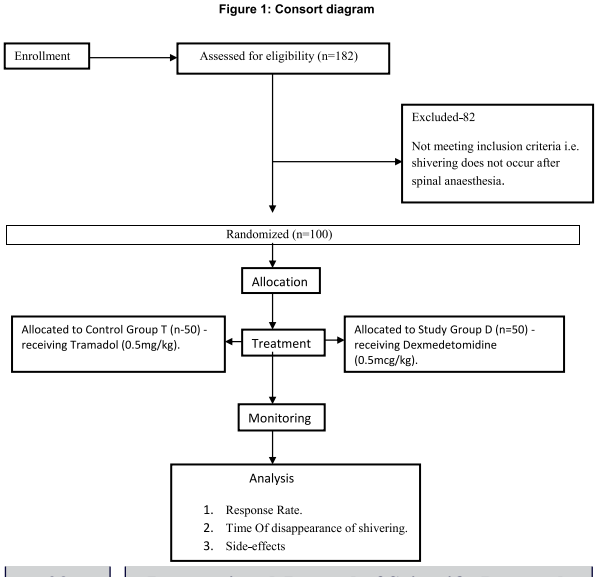
In case,failure to control shivering. (fifteen minutes after injection if shivering remained same) or recurrence of shivering, rescue treatment as intravenous Clonidine 0.5ug/kg or Pheniramine maleate 0.3-0.5 mg/kg administered.End point for study was either sensory or motor recovery from subarachnoid block.

Statistical analysis: Data analyzed using SPSS version 26 (Chicago, IL). Student's *t*-test used for continuous variables and Chi-square for categorical variables. $p < 0.05$ considered statistically significant. $p <$ 0.001 as highly significant.

III. RESULT

Out of 182 patients undergoing surgeries under SA, 100 developed shivering grade 3 or 4 were enrolled in study. Consort diagram is shown in [Figure 1].Incidence of shivering in our study was 55%. As it was an intra-operative study, no patient was lost to follow-up.

Figure 1: Consort diagram

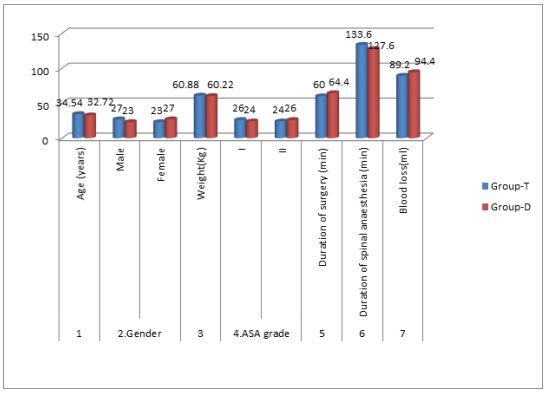


Both groups were comparable in demographics, ASA grade, duration of surgery and spinal anaesthesia, blood loss. (Table 2)

Table 2: Demographic Comparison

Parameter	Group-T	Group-D	P value
Age (years)	34.54 ±10.91	32.72± 9.75	0.381
Gender (male/female)	27/23	23/27	0.321
Weight(Kg)	60.88±4.78	60.22±4.10	0.460
ASA grade	I-26, II-24	I-24, II-26	0.814
Duration of surgery (min)	60.00±12.58	64.40±15.02	0.270
Duration of spinal anaesthesia (min)	133.60±16.30	127.60±20.26	0.250
Blood loss(ml)	89.20±45.79	94.40±50.79	0.592

Figure 2: Comparison of Demographics ,ASA grade,duration of surgery and anaesthesia and blood loss

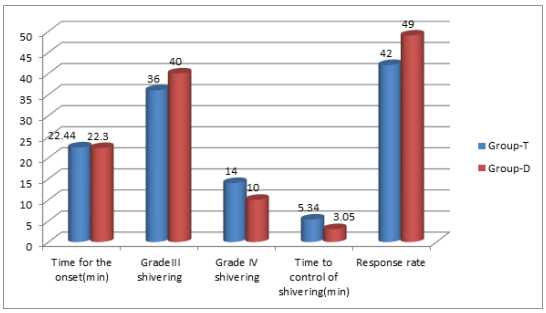


There was no statistically significant difference in time of onset and grade of shivering. However, time interval between drug administration and cessation of shivering was significantly shorter in Dexmedetomidine group when compared to Tramadol group. Also patients in Dexmedetomidine group had significantly better response rate than tramadol group.

Table 3: Parameters of post-spinal shivering

Parameter	Group-T	Group-D	P value
Time for the onset(min)	22.44±1.90	22.30±1.89	0.712
Grade of shivering	III-36 , IV-14	III-40 , IV-10	0.483
Time to control of shivering(min)	5.34±2.12	3.05±1.89	0.002
Response rate%	84%	98%	0.031

Figure3: Comparison of post spinal shivering parameters.



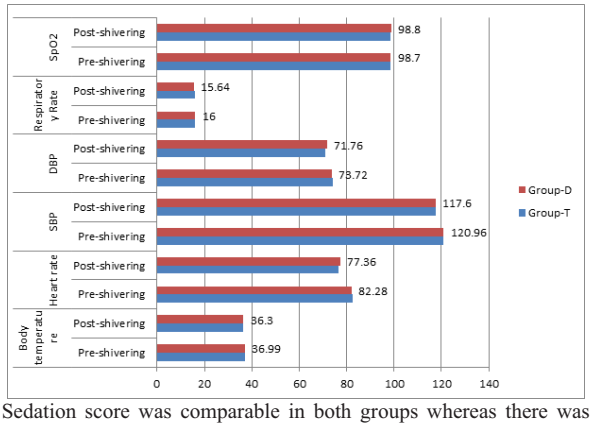
There was no significant difference in vital parameters at onset of shivering and after control of shivering in both groups.

Table 4: Comparison of vital parameters.

Parameter		Group-T	Group-D	P value
Body temperature	Pre-shivering	37.00±0.114	36.99±0.124	0.403
	Post-shivering	36.29±0.101	36.30±0.101	0.843
Heart rate	Pre-shivering	82.76±7.59	82.28±7.98	0.759
	Post-shivering	76.52±6.65	77.36±6.92	0.537
SBP	Pre-shivering	120.68±3.04	120.96±2.78	0.632
	Post-shivering	117.76±2.48	117.60±1.85	0.715

DBP	Pre-shivering	74.28±2.68	73.72±2.59	0.290
	Post-shivering	71.16±1.90	71.76±2.12	0.140
Respiratory Rate	Pre-shivering	16.20±1.68	16.00±1.43	0.523
	Post-shivering	16.00±1.37	15.64±2.00	0.296
SpO_2	Pre-shivering	98.48±0.76	98.70±0.61	0.115
	Post-shivering	98.62±0.60	98.80±0.53	0.117

Figure 4: Comparison of vital parameters



Sedation score was comparable in both groups whereas there was significant occurrence of nausea, vomiting in tramadol group. There was no recurrence of shivering or any complications.

Table 5: Comparison of side effects.

Parameter		Group-T	Group-D	P value
Sedation score(Filo's)	1	49	46	0.360
	2	1	4	
Side effects		6	0	0.027

IV. DISCUSSION

Regional anaesthesia is safe and popular technique for various surgeries. Shukla *et al*.have reported incidence of shivering under regional anesthesia at 40–70%(5) was 55% in our study.Demographic factors ,duration of anaesthesia and surgery were matched to reduce confounding bias.

Multiple neurotransmitters involved acting upon opioids, α_2 adrenergic, serotenergic and anticholinergic receptors. Drugs acting on these receptors like opioids (pethidine, nalbuphine, or tramadol), ketanserin, propofol, clonidine, ketamine are utilized. However, adverse effects like hypotension, hypertension, sedation, respiratory depression, nausea and vomiting limit their use. Hence, hunt for an ideal anti-shivering agent is continuing.(6)

Tramadol, well-established in treatment of post-anaesthetic shivering,probably mediated via opioid or serotonergic and noradrenergic activity.(14)Dexmedetomidine, α2 agonist, with antihypertensive, sedative, analgesic and anti-shivering properties. Anti-shivering effects are mediated by α_2 receptors that reduces vasoconstriction and reducing hypothalamic shivering thresholds, suggesting it has central as well as peripheral actoin(10)(15)

Response rate in our study was 84%, with same dose, that is, 0.5 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%.(5)(16)(17) ,100% by Mittal et al(6).

Maheshwari *et al*. reported recurrence rate 8% with tramadol but the dose used in their study was 1 mg/kg.(18)The recurrence rate in the study by Shukla *et al*.(5) was 5%, which is similar to results obtained by Mittal et al of 8%.(6) There was no recurrence of shivering in our study.

Incidence of nausea and vomiting in our study was 12% with tramadol and was 28% in study of Mittal et al (17)correspond with studies of Reddy and Chiruvella(16), Tsai and Chu(17), However, in the study by Shukla *et al*.,(5) the incidence of nausea was quite high (77.5%).Maheshwari *et al* reported a very high incidence of sedation to the extent of 84%(18), which could be due to the higher dose as opposed to 28% reported by Mittal et al(6). In our study, Grade 2 sedation observed 2% in Tramadol group. These variations could be explained by peculiar patient characteristics in different studies.

Easley et al found cessation of post-anaesthesia shivering in children treated with Dexmedetomidine 0.5 µg/kg within 5 min without recurrence or adverse effects.(19) We also found a response rate of 100%.In our study, incidence of sedation was 8% while Mittal et al found it as 21.4%.(6).

Clonidine causes significant hypotension and bradycardia, while dexmedetomidine in dosage of 0.5 µg/kg diluted to 5ml given over 5minutes causes less variations in haemodynamics.Results indicated dexmedetomidine takes lesser time to control shivering(3.05min vs 5.34min for Tramadol). The incidence of adverse effects like nausea and vomiting was found to be higher with tramadol. Although not significant statistically, minimal sedation seen with dexmedetomidine is actually beneficial as it provided more comfort to patient, maintained cardio-respiratory stability, improved surgical conditions and also provided amnesia.

Major limitation of our study was small sample size. A bigger sample size would have increased robustness of results. Anti-shivering effect needs to be evaluated in surgeries of longer duration where chances of hypothermia are more. Also, we did not assess different doses of dexmedetomidine.

Search continues for drugs that sufficiently improve 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.

IV. CONCLUSION

Both dexmedetomidine (0.5 µg/kg) and tramadol (0.5 mg/kg) are effective in treating patients with post-spinal shivering, but time taken for complete cessation of shivering was shorter with dexmedetomidine as compared to tramadol, difference being statistically significant. Furthermore, dexmedetomidine causes fewer adverse effects like nausea and vomiting.

More studies of different doses of dexmedetomidine need to be conducted in order to cement its position as efficient anti-shivering agent.

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