RANDOMISED DOUBLE-BLIND COMPARATIVE STUDY OF DEXMEDETOMIDINE AND TRAMADOL FOR PREVENTION OF PERIOPERATIVE SHIVERING IN TRANSURETHRAL RESECTION OF PROSTATE UNDER SPINAL ANAESTHESIA

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ABSTRACT

BACKGROUND AND AIMS

There are number of drugs like Tramadol, Clonidine, Pethidine, etc., which are being used as an anti-shivering agent during perioperative period. Perioperative shivering can be very harmful for the patients, thus focus should be on prevention rather than treatment. The aim of this study was to compare Dexmedetomidine and Tramadol for prevention of shivering in more susceptible group of patients–elderly age group (55 and above) being operated for Transurethral Resection of Prostate (TURP) under spinal anaesthesia.

METHOD

A prospective, randomised and double blind study conducted on 300 American Society of Anaesthesiologists (ASA) Grade I, II and III male patients posted for TURP surgery. The patients were randomized in two groups of 150 patients each to receive either intravenous Dexmedetomidine 1µg/kg/min over a period of 10 minutes followed by infusion of 0.4µg/kg/min during surgery or intravenous Tramadol 1mg/kg min over a period of 10 minutes followed by infusion of dextrose 0.4µg/kg/min during surgery. Appearance of shivering hemodynamics and any adverse effects were observed at scheduled intervals. Unpaired T-test was used for analyzing data.

RESULT

Both the drugs were equally effective in prevention of shivering (Dexmedetomidine and Tramadol).

CONCLUSION

Both the drugs are effective in prevention of shivering in the respective doses we used in the study with patients who were more predisposed to shivering. Tramadol is associated with significant more nausea and vomiting. Adequate sedation with no respiratory compromise seen in both group.

KEYWORDS

Dexmedetomidine, Tramadol, Shivering.

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INTRODUCTION

Perioperative shivering during Spinal Anaesthesia (SA) is a common complication in patients undergoing Transurethral Resection of Prostate (TURP). This is secondary to peripheral vasodilatation from sympathetic blockade caused by SA and use of cold irrigating fluids in TURP.[1] Elderly patients are especially at risk of hypothermia under anaesthesia as low core temperature may not initiate autonomic and protective responses.[2] It is associated with a number of deleterious sequelae like increased oxygen consumption (>200%) and CO_2 production that may result in myocardial infarction.[3,4]

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Shivering may also increase intraocular and intracranial pressure. The surgical wound healing may also be delayed by shivering.[5,6] Apart from these sensation of shivering is often perceived as pain and is highly uncomfortable for the patients and delays discharge from Post Anaesthetic Care Unit (PACU).[7] Thus our focus should be on prevention of perioperative shivering. Various pharmacological and non-pharmacological methods have been proposed to control shivering. The most common pharmacological interventions include use of drugs like clonidine, pethidine, tramadol, nefopam and ketamine.[8] Dexmedetomidine, a congener of clonidine more selective for α_2–adrenoreceptor is another drug which has potential to effect the shivering threshold. Some studies have been done to explore anti-shivering potential of Dexmedetomidine.[9,10,11,12] One recent study has compared the efficacy and adverse effects of Dexmedetomidine and tramadol when used for the control of intraoperative shivering not for prevention of its appearance.[13]

The major limitation of most of the mentioned studies are small sample sizes and inclusion of patients from different

types of surgeries. Thus, we planned our study to compare the efficacy and adverse effect of Dexmedetomidine and tramadol for their potential in prevention of shivering in TURP surgery keeping a large sample size.

MATERIAL AND METHODS

After taking approval from Institutional Ethics Committee, this prospective randomized double blind study was planned. We had assumed that there would be 80% reduction in occurrence of shivering with Dexmedetomidine in perioperative period. At 95% significance level and keeping power of study 80%, 127 patients were required in each group. Assuming 10% dropout total 300 patients were enrolled in the study. Thus 300 patients belonging to ASA grade 1, 2 and 3 aged between 55-75 years undergoing TURP surgery at a tertiary centre during period of April 2014 to November 2014 were included in the study. Written informed consent to participate in the study was taken from all the patients. Patients with known allergy to the drugs used in the study, on any treatment with alpha adrenoreceptor antagonists with any history of ischaemic heart disease, cerebrovascular events, respiratory insufficiency, thyroid dysfunction, severe diabetes, autonomic neuropathy, hepatic or renal disease, severe bradycardia or hypotension, any need of blood transfusion during study were excluded from the study. Subjects were randomised with a 1:1 allocation ratio. The allocated intervention was written on a slip of paper, placed in serially numbered opaque envelope and sealed. As consecutive eligible subjects got enrolled, the envelope were serially opened and the allocated intervention was implemented. Group D (n=150) were administered Dexmedetomidine 1μg/kg/min in 100ml normal saline over a period of 10 minutes followed by infusion of 0.4μg/kg/min prepared by dilution of 100μg of Dexmedetomidine in 50mL normal saline during surgery and group T (n=150) were administered Tramadol 1mg/kg min over a period of 10 minutes followed by infusion of dextrose 0.4μg/kg/min during surgery. The study was double blinded as drugs were prepared and administered by an anesthesiologist not involved in the study or data collection.

The patients were secured 18-gauge IV cannula in operation theatre and preloading was done with Ringers Lactate solution 10mL/kg before giving spinal anaesthesia. The bolus doses of both the drugs were given over a period of 10 minutes and then Infusion of drugs was started. The standard monitors (Phillips) were attached and all the baseline parameters such as Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), Oxygen Saturation (SPO_2), Electrocardiography (ECG) and body temperature (axillary) were recorded. Subarachnoid anaesthesia as administered with 0.5% heavy bupivacaine (15mg) at L_{3-4} or L_{4-5} interspace using 26G Quincke's spinal needle under aseptic conditions. All the operation theatres were maintained at an ambient temperature of around 24°C - 25°C and temperature of all patient was strictly maintained around 37±1° C. Supplemental oxygen was administered to all the patients at the rate of 5 l/min with face mask and patients were covered with surgical drape (Medline Proxima), but not actively warmed. IV fluids and anaesthetics were administered at room temperature. Vital parameters such as HR, NIBP and SPO_2 were recorded at intervals of every 5 min for first 30 min and every 15 min for rest of the surgical time and then 2 hours postoperatively. Continuous ECG monitoring was done. Infusion of the drugs were stopped after completion of surgery. Shivering was graded using a four point scale as per Wrench.[14] 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. The incidence and severity of shivering were recorded at 5 minutes intervals during the operation and in the recovery room. If grade was ≥3 prophylaxis was considered as failure. Perioperatively, if shivering occurs it was treated with warm blanket and reassurance till Grade 2. From Grade 3 onwards 25mg IV pethidine as used as rescue drug. Adverse effects nausea, vomiting, bradycardia (<50/min), hypotension (MAP <20% of baseline) and dizziness were noted. The degree of sedation was graded on a four point scale as per Filos et al.[15] Grade 1: Awake and alert, Grade 2: Drowsy, responsive to verbal stimuli, Grade 3: Drowsy, arousable to physical stimuli, Grade 4: Unarousable. Nausea and vomiting were treated with injection metoclopramide 10mg IV as and when required. Symptomatic bradycardia was treated with 0.3mg atropine intravenously. Hypotension was treated with 3mg Mephentermine IV. The coding was opened after completion of the study to compile results.

STATISTICAL ANALYSIS

After completion of the study, observations obtained were tabulated and analysed using Statistical Package for Social Sciences (SPSS version 16.0; Chicago, IL). Numerical data were presented as mean±standard deviation and categorical data as proportions (%). The comparison of the mean levels of all variables between two groups was made by the unpaired t-test and Analysis of Variance (ANOVA) values was calculated and $P<0.05$ was considered to be statistically significant. The Chi square test was used to analyse the difference between the gender, ASA class, the number of patients who developed shivering and number of patients who had other complications. Friedman test was used to compare intragroup data for heart rate and mean arterial pressure.

RESULTS

There were 150 patients in both the group with no dropouts. Both the groups (Group T and group D) were comparable regarding distribution of age, duration of anaesthesia, duration of surgery, ASA grading and were non-significant on statistical comparison (Table-1).

Parameter	Group D (n=150)	Group T (n=150)	P value
Age (In years)	52±11	55±8	≥ 0.05
Duration of surgery (min)	80±12	75±10	≥ 0.05
Duration of spinal anaesthesia (min)	145±16	124±15	≥ 0.05
ASA grading (I/II/III)	12/82/6	10/80/10	≥ 0.05

Table 1: Hemodynamic parameters of both the group

p≤0.05 is considered significant

In group T in 20 out of 150 patients shivering of grade 2 was noted (13.35%); 15 out of 150 patients (10%) had grade 2

shivering in group D. None of the patients in group D had grade 3 or grade 4 shivering requiring any treatment. In group T 10 patients (6%) had grade 3 shivering, but none had shivering of grade 4. The comparison of shivering in both the groups was statistically insignificant (P value >0.05). (Table-2) The haemodynamic parameters of both groups were comparable before giving the drugs. In group D in 30 patients there was a drop of HR to less than 50 bpm, which responded with single dose of atropine (0.3mg). Out of this, 3 patients had drop of BP to less than 20% of mean value which responded well to single dose mephentermine in 2 patients and in one patient mephentermine was given twice.

Shivering Grade	Group D (n=150)(%)	Group T (n=150)(%)	P value
1	135(90%)	120(80%)	≥ 0.05
2	15(10%)	20(13.33%)	≥ 0.05
3	0	10(6%)	≥ 0.05
4	0	0	≥ 0.05

Table 2: Comparison of grade of shivering in both the group

Test done was Chi-square and ANOVA. P-value <0.05 was considered significant.

In group T nausea was seen in 70 patients (66.6%, p< 0.01), out of which 45 patients (30%, p<0.04) vomiting was seen and was statistically significant. In group D nausea and vomiting was seen in 6.6% and 3.3% respectively. Almost similar number of patients were sedated in both groups with sedation score of 2 and above. (Table 3).

Adverse Effects	Group D{n=150(%)}	Group T{n=150(%)}
Nausea	10(6.66)	70(66.6)
Vomiting	5(3.33)	45(30)
Sedation(1/2/3/4)	60, 45, 45, 0 (60% above 2)	62, 50, 33, 5 (58.7% above 2)
Hypotension	3(2)	0
Bradycardia	30(20)	0
Respiratory depression	0	0

Table 3: Comparison of adverse effects in both the group

Data expressed as percentage (Chi-square test); n=no. of patients

DISCUSSION

Intraoperative and postoperative shivering (Incidence 40-50%) is a distressing experience for the patient and uncomfortable for both surgeon and anaesthesiologists.[16] For treatment patients are often given only reassurance at most of the times or inadequate medication. Numerous drugs for treatment of shivering is being used, but no routine protocol has been established in clinical practice. Our study was planned to find out a better drug at proper dose for prevention of occurrence of shivering in patients who are more susceptible to it.

Spinal anaesthesia significantly impairs the thermoregulation system by inhibiting tonic vasoconstriction, which plays a significant role in temperature regulation.[16] Further it also causes a redistribution of core heat from the trunk to the peripheral tissue.[17] The other risk factors for shivering is old age, cold irrigating fluid, operation theatre temperature and level of sensory block.[18] The commonest age group of patients presenting for TURP surgery is 50-70 years. In this age group shivering can be very detrimental, so rather than treating shivering we should prevent its appearance.

The neurotransmitter involved in pathways of shivering is opioid, α_2 adrenergic, serotonergic and anticholinergic receptor.[16] Thus we have numerous drugs acting on these receptors opioids (Pethidine, nalbuphine or tramadol), clonidine, ketamine, nefopam, doxapram which has been utilized for anti-shivering potential. Number of clinical studies has been done to compare their efficacy at different doses for establishing best agent to prevent shivering.[11,12,13]

Tramadol exerts its anti-shivering effect by inhibiting reuptake of norepinephrine and dopamine and at the same time facilitating release of 5HT. It is the most commonly used and drug for treatment and prevention of shivering.[18]

Dexmedetomidine an α_2-adrenergic has shown to have anti-shivering effects along with other properties like sedation, analgesia and antihypertensive effect. The anti-shivering effect of Dexmedetomidine is by binding to α_2 receptor. Dexmedetomidine displays specific and selective α2-adrenoceptor agonism in the brain and spinal cord. The responses to activation of these receptors include decreased sympathetic tone with attenuation of the neuroendocrine 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 concentrations, oxygen consumption, blood pressure and heart rates. In addition to above benefits, it also has hypothalamic thermoregulatory effect. The role Dexmedetomidine as an anti-shivering agent has been evaluated at different doses 0.5μg/kg/min, 0.75μg/kg/min and 1μg/kg/min. Yong-Shin Kim compared the three doses for prophylaxis against postoperative shivering in an elective laparoscopic total hysterectomy under general anaesthesia. They concluded that dose 0.75μg/kg/min-1μg/kg/min was very effective in prevention of shivering.[9] Same was conclusion of Bajwa et al.[11] and Elvan et al.[12] who concluded in their study that Dexmedetomidine at 1μg/kg/min was very effective in preventing shivering. We used Dexmedetomidine at dose of 1μg/kg/min bolus followed by slow infusion of 0.4μg/kg/min for prevention of appearance of shivering. We got 100% result with this dose with an additional benefit of sedation during intraoperative period. Few patient had episode of bradycardia (20%) and hypotension (2%), which was managed without much clinical consequences.

The other drug which we used for the study was Tramadol in the dose of 1mg/kg body weight (bw) as in study by Maheshwari et al.[19] The result we achieved was 92% success in prevention of shivering, but with a high incidence of nausea (66%) and vomiting (30%). There are other studies, which used tramadol in lesser dose of 0.5mg/kg bw for treatment of shivering with a variable response rate (70-75%).[20,21,22] The side effect of nausea and vomiting was definitely less compared with higher dose. The exception was Dhimar et al.[23] who compared tramadol (1mg/kg bw) with pethidine (1mg/kg bw) and concluded tramadol to be more effective on shivering with better response rate, effective control, less recurrence rate and less side effects (Nausea and vomiting 6.6% with tramadol, but 20% with pethidine). The most probable cause of this exception may be less susceptible

group used in the study. Like our study Mittal et al.[3] compared Dexmedetomidine and tramadol as anti-shivering agent in 50 patients undergoing varied surgery under spinal anaesthesia and found both to have good response rate. Incidence of nausea and vomiting was seen in only tramadol group. Hypotension and bradycardia was seen in a very few patients in group Dexmedetomidine, which was managed without any untoward effect. In our study, we used a larger sample size (300 patients) and tramadol and Dexmedetomidine for prophylaxis against shivering. The result was extremely satisfying with both the drugs with Dexmedetomidine giving additional benefit of sedation (Sedation score 2 and above in 90%) during intraoperative period. The selection of patients in our study was also the patients with more susceptibility to shivering (Old age, spinal anaesthesia, TURP surgery). The only problem in tramadol group was higher incidence of nausea and vomiting (Nausea was seen in 70 patients (66.6%) and vomiting in 45 patients (30%)) when used in higher dose, but lower dose had less effective control against shivering. Thus Dexmedetomidine is a recommendable drug to be used as a prophylaxis against shivering during perioperative period. The dose we used 1μg/kg showed satisfying result with good haemodynamic control without any respiratory compromise. In our study we have taken dose 1μg/kg of Dexmedetomidine and we had a very satisfying result with it. We need more studies to compare different doses of Dexmedetomidine (0.5μg/kg body weight and 0.75μg/kg body weight) with tramadol for its effectiveness in prevention of shivering.

CONCLUSION

Both tramadol (1mg/kg) and Dexmedetomidine (1μg/kg) are effective drug for prophylaxis against shivering. Dexmedetomidine has additional benefit of having very less incidence of nausea and vomiting. Thus in Dexmedetomidine we have a good drug against very annoying perioperative shivering. We need further studies to compare different doses of Dexmedetomidine for recommending least dose for effective prophylaxis against shivering in susceptible patients.

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