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Comparative study of dexmedetomidine, butorphanol and tramadol for post-spinal anesthesia shivering

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ABSTRACT

Neuraxial anesthesia impairs thermoregulation causing shivering. This study evaluated effects of dexmedetomidine, butorphanol and tramadol on post spinal anesthesia shivering and also observed side-effects to find effective, faster and safer agent to control shivering after neuraxial blockade. Randomized, prospective study was conducted in 96 patients (divided into 3 groups) who developed shivering under spinal anesthesia. Patients received either intravenous, 0.5 mg/kg tramadol, 0.01mg/kg butorphanol, or 0.5µg/kg dexmedetomidine. Control of shivering, time taken for cessation, recurrence, hemodynamic changes, and side effects were compared. No significant difference in demographic profile. At onset of shivering, hemodynamic variables were comparable in all 3 groups. After treatment, significant bradycardia noted in dexmedetomidine group (P< 0.092).Cessation of shivering at 5^{th} min was 100%, 50%, and 96.87% for Groups D, T, and B respectively. Time taken was significantly lower (3.12 ± 0.9) in Group D than Group T (5.03 ± 1.15) and B (4.09 ± 1.57) mins. Recurrence was also significantly less in dexmedetomidine (0%) group compared with butorphanol (18.75%) and tramadol (9%). 40% cases in Group T had nausea and vomiting (p<0.000). Higher incidence of grade 3 sedation was observed in dexmedetomidine (68.8%) and butorphanol (46.875) groups compared with Tramadol (4%). Episodes of oxygen desaturation was not significant ($P > 0.5$). Although all three drugs are effective, Dexmedetomidine seems superior due to higher rates of success, earlier onset of action, lesser recurrence and removes anxiety with minimal adverse effects, as compared to butorphanol which showed higher recurrence rate and tramadol which had higher incidence of side effects and delayed onset of action.

Keywords: Post spinal shivering, dexmedetomidine, butorphanol, tramadol.

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INTRODUCTION

Shivering an involuntary, oscillatory muscular activity, is a physiological thermoregulatory response to cold. Human core temperature varies with the circadian rhythm and normally maintained within 36.5–37.0 °C[1]. Temperature regulation is mediated by pre-optic nucleus of hypothalamus. Shivering is elicited when this region is cooled. Efferent shivering pathway arises and descends from the posterior hypothalamus.

Shivering is commonly encountered after neuraxial (spinal and epidural) anesthesia[2]. An incidence of shivering of up to 55% has been reported[1,3].Neuraxialanesthesia inhibits tonic vasoconstriction and produces vasodilatation, which leads to rapid heat loss by redistribution of heat from core to periphery,due to altered afferent thermal input from the blocked region causing the core temperature to decrease. Hence , shivering threshold is reduced[4]. The main causes of intra/post-operative shivering are temperature loss, increased sympathetic tone, pain, and systemic release of pyrogen[.5].

It causes arterial hypoxemia due to 200–500% increase in oxygen consumption, a liner increase in carbon dioxide production[6].Excessive shivering creates an imbalance between body's oxygen demand and supply ratio leading to lactic acidosis[7].It also increases intraocular pressure (IOP) intracranial pressure (ICP); and interferes with pulse rate, blood pressure (BP) and electrocardiographic (ECG) monitoring[5,8].

In a patient with limited myocardial oxygen reserve or known coronary artery disease, shivering may further compromise myocardial function[9]. It may contribute to increased wound pain, delayed wound healing, and delayed discharge from post anesthetic care[7]. Although shivering is not a life-threatening process, it can be a source of patient discomfort. It is physiologically stressful for the patient undergoing surgery[10].The cold environment of operating rooms and cold infusion fluids, contributes to a fall in core body temperature [3,7].

The non-pharmacological management is by external heating like the use of forced air warming blankets, warmed fluids etc. The most frequently reported pharmacological interventions include clonidine, dexmedetomidine, pethidine, tramadol, doxapram, physostigmine, propofol, and ketamine [11,12]. No gold standard treatment is known.

Our study has compared the efficacy, hemodynamic, and adverse effects of tramadol, butorphanol and dexmedetomidine when used for the control of post-spinal anesthesia shivering.

The purpose of this study was to compare the response time, efficacy, hemodynamic, adverse effects and relapse of shivering of intravenous dexmedetomidine 0.5 µg/kg with that of butorphanol 0.01 mg/kg and tramadol 0.5 mg/kg in relief of shivering and to find more effective, faster and safer agent to control shivering after regional anesthesia.

METHODOLOGY

The study design used is Prospective, Randomized Control trial .The study was done in KMC Hospitals, Mangalore, in ASA I and II patients between 18 and 60scheduled to undergo various elective lower abdominal and lower limb surgeries under spinal anesthesia. Severe systemic disorders, Body mass index of ≥30 kg/m2, Thyroid disease, Psychiatric disorder, Pregnancy, Acute infections, Allergy to any of the study drugs and contraindications to spinal anesthesia were excluded from the study. With 95% confidence interval and 90% power with reference the sample size came to be 96.Our study was conducted after the approval of ethics and scientific committee from till September 2014 toJune2016. Written informed consent was taken from each patient. A pre-anesthetic check-up, relevant investigations were done preoperatively. Patients were randomly distributed into three groups of 32 patients each.

Group-B(Butorphanol group): In this group, each patient, who developed shivering, was given 0.01 mg/kg of inj. Butorphanol (BUTRUM)intravenously (IV)

Group-D(Dexmedetomidine group): In this group, each patient, who developed shivering, was given 0.5 µg/kg of inj. Dexmedetomidine IV

Group-T (Tramadol group): In this group, each patient, who developed shivering, was given 0.5 mg/kg of inj. tramadol IV.

Patients were administered 0.5% hyperbaric bupivacaine 2.8 to 3 ml intrathecally with 25G Quinke's spinal needle after preloading with 10 ml/kg of crystalloid infusion and after recording the baseline vital parameters, e.g. pulse rate, blood pressure (BP), ECG, oxygen saturation (SpO2) and axillary temperature. Sedatives and hypnotics inclusive of opioids were avoided. Ambient temperature of the operating room maintained at 23–25°C. Patients were observed for occurrence of shivering. On shivering patients were randomly administered 0.01 mg/kg of inj. butorphanol intravenously or, 0.5 µg/kg Dexmedetomidine IV or, 0.5 mg/kg of inj. tramadol IV. Time taken for cessation of shivering, hemodynamic status and complications until the postoperative 12 hoursperiod were observed.

Supplemental oxygen was administered to patients on shivering at the rate of 5 l/min with face mask.Patients were covered with drapes but not actively warmed. IV fluids and anesthetics administered at room temperature.Vital parameters such as HR, NIBP, and SPO2 recorded at intervals of every 5 min for first 30 min and every 15 mins for the rest of the observation period.

Shivering graded using a four point scale as per Wrench.Patients who developed either Grades 2 to 4 shivering were included in the study(Box-1). Shivering control is defined as complete when shivering score declines to 0, incomplete when the scores decreases but did not abolish the shivering completely, and failed if no change in scores was observed. The time taken for cessation of rigors and hemodynamic changes were observed at intervals of 1 min till 5 min and thereafter at 10, 20, 30, 45 and 60 min.

Pulse rate, BP, ECG, SpO2, respiratory rate and axillary temperature were noted immediately after regional anesthesia and during shivering and after drug administration. Recurrence and side effects of the study drugs were noted.

STATISTICAL ANALYSIS:

The data was analysed usingthe following tests. ANOVA Test, Turkey test, Bonferonni 't' test, Chi-square test, SPSS 17.0 and Statistical significance considered if $p < 0.05$

RESULTS

The 3 groups were demographically similar with respect to age, sex, height and weight ($p > 0.05$).The baseline parameters (Respiratory rate, temperature, blood pressure, heart rate, SpO2) were comparable ($p > 0.05$)

The time of onset of action is significantly lower for group D ($p=0.000$) compared to other groups.Implying that time of action of dexmedetomidine is much faster than butorphanoland tramadol (Table 1).

Gradual decline in diastolic BP is seen in all groups, but is not statistically significant ($p>0.05$)(Fig 1).

Table 1: Comparison of Time of Onset of Action

TOA	N	MEAN	STD. DEVIATION	ANOVA F	p
BUTORPHANOL	32	4.09	1.57	19.104	.000
DEXMEDETOMIDINE	32	3.12	0.90		HS
TRAMADOL	32	5.03	1.15		
TOTAL	96	4.08	1.46		

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Table 2: Comparison of Heart Rate

Parameter: HR

	Group	N	Mean	Std. Deviation	Median	ANOVA F	p		BUTORPHANOL VS DEXMEDETOMIDINE	BUTORPHANOL VS TRAMADOL	DEXMEDETOMIDINE VS TRAMADOL
Base line	BUTORPHANOL	32	75.72	9.302	78.00	.873	.421				
	DEXMEDETOMIDINE	28	73.11	7.213	72.00						
	TRAMADOL	32	75.72	9.302	78.00						
At5	BUTORPHANOL	32	78.28	9.219	78.00	2.051	.135				
	DEXMEDETOMIDINE	28	73.96	9.826	70.00						
	TRAMADOL	32	78.28	9.219	78.00						
At 10	BUTORPHANOL	32	71.94	9.912	70.00	1.599	.208				
	DEXMEDETOMIDINE	28	68.25	6.883	68.00						
	TRAMADOL	32	71.94	9.912	70.00						
At 15	BUTORPHANOL	32	67.56	10.245	69.00	1.009	.369				
	DEXMEDETOMIDINE	28	64.61	6.063	64.50						
	TRAMADOL	32	67.56	10.245	69.00						
At 30	BUTORPHANOL	32	65.28	7.924	66.50	3.531	.033				
	DEXMEDETOMIDINE	28	60.79	6.291	60.50			Post hoc analysis	.047	1.000	.047
	TRAMADOL	32	65.28	7.924	66.50						
At 45	BUTORPHANOL	32	64.56	5.775	64.50	6.214	.003				
	DEXMEDETOMIDINE	28	58.07	11.879	60.00				.008	1.000	.008
	TRAMADOL	32	64.56	5.775	64.50						
At 60	BUTORPHANOL	31	65.42	5.277	65.00	11.791	.000				
	DEXMEDETOMIDINE	26	58.96	6.459	60.00				.000	1.000	.000
	TRAMADOL	30	65.43	5.367	65.00						
At 1'15	BUTORPHANOL	27	65.96	5.509	68.00	14.938	.000				
	DEXMEDETOMIDINE	24	58.25	6.867	60.00				.000	1.000	.000
	TRAMADOL	28	66.29	5.332	68.00						
At 1'30	BUTORPHANOL	24	68.04	4.832	70.00	23.274	.000				
	DEXMEDETOMIDINE	22	59.00	6.340	59.50				.000	1.000	.000
	TRAMADOL	24	68.46	4.568	70.00						
At End	BUTORPHANOL	25	70.48	5.026	72.00	25.966	.000				
	DEXMEDETOMIDINE	26	57.31	10.620	60.00				.000	1.000	.000
	TRAMADOL	25	70.48	5.576	72.00						

Table 3: Comparison of Shivering Grade

	Group	N	Mean	Std. Deviation	Median(IQR)	Kruskall wallis test value	p value
AT1	BUTORPHANOL	32	3.00	.000	3(3-3)	12.669	.002
	DEXMEDETOMIDINE	32	2.88	.336	3(3-3)		HS
	TRAMADOL	32	3.19	.471	3(3-3)		
AT2	BUTORPHANOL	32	1.94	.878	2(2-2)	26.011	.000
	DEXMEDETOMIDINE	32	1.75	.842	2(2-2)		HS
	TRAMADOL	32	2.66	.545	3(2-3)		
AT3	BUTORPHANOL	30	1.13	.819	1(0-2)	22.655	.000
	DEXMEDETOMIDINE	27	.85	.818	1(0-2)		HS
	TRAMADOL	32	1.97	.822	2(2-2.75)		
AT4	BUTORPHANOL	26	.38	.571	0(0-1)	17.561	.000
	DEXMEDETOMIDINE	20	.50	.607	0(0-1)		HS
	TRAMADOL	30	1.23	.817	1(0.75-2)		
AT5	BUTORPHANOL	30	.00	.000	0(0-0)	23.706	.000
	DEXMEDETOMIDINE	9	.00	.000	0(0-0)		HS
	TRAMADOL	24	.50	.511	0.5(0-1)		
AT10	BUTORPHANOL	32	.00	.000	0(0-0)		
	DEXMEDETOMIDINE	0	.	.			
	TRAMADOL	12	.00	.000	0(0-0)		
AT20	BUTORPHANOL	32	.00	.000	0(0-0)		
	DEXMEDETOMIDINE	0	.	.			
	TRAMADOL	0	.	.			
AT30	BUTORPHANOL	32	.00	.000	0(0-0)		
	DEXMEDETOMIDINE	0	.	.			
	TRAMADOL	0	.	.	.		

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Table 4: Comparison of Recurrence of Shivering

RCC	BUTORPHANOL	DEXMEDETOMIDINE	TRAMADOL	TOTAL
RCC – COUNT	26	32	29	87
%	81.3%	100%	90.6%	90.6%
RCC + COUNT	6	0	3	9
%	18.8%	0%	9.4%	9.4%
TOTAL COUNT	32	32	32	96
%	100%	100%	100%	100%

Table 5: Comparison Of Sedation Score

SS	BUTORPHANOL	DEXMEDETOMIDINE	TRAMADOL	TOTAL
1 COUNT	2	0	14	16
%	6.3%	0%	56.0%	18%
2 COUNT	15	10	10	35
%	46.9%	31.3%	40.0%	39.3%
3 COUNT	15	22	1	38
%	46.9%	68.8%	4.0%	42.7%
TOTALCOUNT	32	32	25	89
%	100%	100%	100%	100%

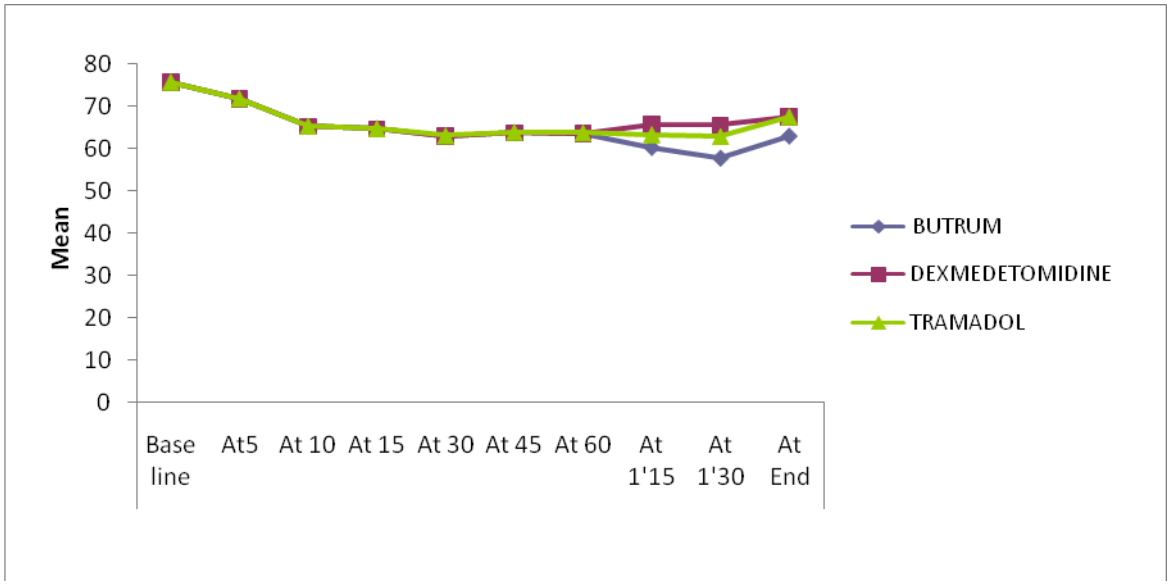

Figure 1: Comparison of Diastolic BP

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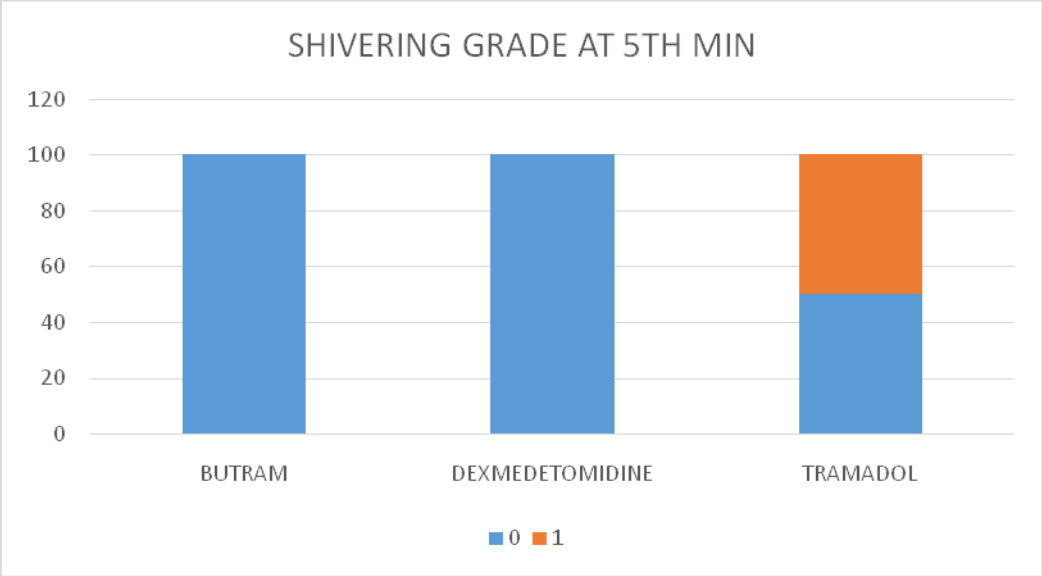

Figure 2: Comparison of Shivering Score at 5th Min

Box 1: Wrench scale of shivering.

Grades	Muscle group involved
Grade 0	No shivering observed
Grade 1	One or more of piloerection; peripheral cyanosis without other cause, but without visible muscular activity
Grade 2	Visible muscle activity confined to one muscle group
Grade 3	Visible muscle activity in more than one muscle groups
Grade 4	Gross muscular activity involving the entire body

Box 2: Ramsay sedation score

Ramsay Sedation Assessment Scale		
Awake Levels:	Patient anxious or agitated or both	1
	Patient cooperative, oriented and tranquil	2
	Patient responds to commands only	3
Asleep Levels:	A brisk response to a light glabellar tap	4
	A sluggish response to a light glabellar tap	5
	No response	6

Heart rate at baseline is comparable. At 30th min and for the remaining observation period, group D showed significantly low heart rate ($p < 0.05$) compared to other groups. Further post hoc analysis showed that fall in heart rate was more in dexmedetomidine group as compared to butorphanol and least fall was with tramadol (Table 2).

Statistically there was no significant difference in Spo2 (probably due to supplementation of oxygen to patients), axillary temperature, systolic and diastolic blood pressure between the 3 groups during the period of study ($p > 0.05$)

Cessation of shivering to grade 0 was faster in group D. And patients in group T sustained grade 3 and 2 shivering for longest time.Figure 2 shows at the 5th min after administration of drug all cases of group B and D had cessation where as 50% of group T still had grade 1 shivering (Table 3).There was significant decline in shivering grades in patients treated with dexmedetomidine.

There was recurrence (p = 0.033) in 18.8 % of patients treated with butorphanol and 9% of patients treated with tramadol.Dexmedetomidine group showed no recurrence in the study period, probably due to longer duration of action (Table 4).

All cases of group B and D had sedation asper Ramsay Sedation Scale (Box 2),whereas 78.1 % of tramadol group had sedation p=0.001. Group D showed higher grade 3 sedation score (68.8%) compared to group B (47%) and T (4%).Implying that dexmedetomidine is a more potent sedative agent compared to butorphanol and tramadol (Table 5).

Group D showed bradycardia in 15.6% cases which was more as compared to group B and T.Hypotension was not significant but comparatively more in group D 9.3%. Only group B, 2 cases had respiratory depression. Probably due to supplementation of oxygen at onset of shivering in all cases. Group T had significant nausea (10 of 32) and vomiting (1 of 32) compared to group B (1) and D (0).

DISCUSSION

Intra and post-operative shivering are often neglected.We tried to bring down the incidence of shivering by using pharmacotherapy. All treated patients had cessation of shivering. Pharmacological methods are cost effective when compared to physical methods. Many drugs possess anti-shivering properties which act on neurotransmitter pathways involved in shivering like opioids receptors, alpha -2 receptors, and serotonergic, anticholinergic receptors.

The comparability of the demographic factors such as age, weight, height, gender distribution, duration of anesthesia, and surgery in the present study has ruled out any visible or confounding bias which could have affected the results of the study. Physical factors such as operating room temperature, temperature of the recovery room, and temperature of the infused fluids are considered potential risk factors of shivering, but these factors were well controlled in our study.

In our study, we obtained satisfactory results in treatment of shivering in patients by pharmacotherapy aswe found the time interval from the commencement of treatment, to cessation of shivering is quite less with dexmedetomidine (3.12±0.90 minutes) than with butorphanol (4.09±1.57 minutes)and tramadol (5.03±1.12 minutes) which was highly significant (p=0.000) There was significant difference between butorphanol and tramadol regarding total response rate after 5 min (100% as against 50%). Bansal et al found similar difference in butorphanol (83%) and tramadol (73%) with respect to complete cessation of shivering after treatment which was not significant (p>0.05)[13].

A higher incidence of recurrence of rigors was observed in tramadol treated patients in a study of Bansal et al[13] . We found butorphanol group 18.8% recurrence which was more compared to other groups(group D 0% and group T 9%)

Bozgeyik Semsiitin etal [14] studied the effect of dexmedetomidine 0.5µg/kg in prevention of shivering. In their study 1 patient out of 30 had shivering. In the present study the incidence of shivering was zero. In our study, the incidence of sedation was 100 %. One contradictory report was by Karaman et al [15]. according to whom intra-operative dexmedetomidine infusion caused negligible sedation inspite of using a loading dose of 1 µg/kg followed by a maintenance infusion of 0.5 µg/kg/h.

The other α agonist, clonidine is associated with a high incidence of hypotension and bradycardia. Hypotension and bradycardia are known hemodynamic effects of dexmedetomidine as well [16]. In our study, three patients developed hypotension and five developed bradycardia after receiving this drug. . In our study, it was observed that the cases to which iv 0.5 µg/kg dexmedetomidine was applied, sedation could reach Ramsay three level and this level was significantly higher than that of other groups and this sedation level may

have removed anxiety in patients. The α-2 receptor agonists are known to prevent shivering to a moderate extent without any associated respiratory depression as with other anti-shivering drugs[17,18]. Nausea was also one of the adverse effects experienced, as shown in previous studies[16,19]. But in our study, none of the patients in dexmedetomidine group developed nausea or vomiting.

The results of this study indicate that dexmedetomidine takes lesser time to control shivering.

The clinically significant effect at this dose includes sedation which did not have any apparent effect on the ventilatory drive [17,20].

With 0.5 mg/kg of tramadol, the response rate reported by Shukla et al. was 92.5% and by Tsai and Chu, 87%[21,22]. We found 100% response rate in our study. Geeta Mittal et al [23]. reported similar recurrence rate with tramadol as in our study (8%) ours was 9.4%.The recurrence rate in the study by Shukla et al. was 5% [21]. In study by Chan et al[24] intravenous tramadol 0.25 mg/kg effectively controlled shivering (92%) during Caesarean delivery under neuraxial anesthesia with minimal side-effects. In studies where IV 1-2 mg/kg tramadol was given at the end of operation in post-anesthetic shivering treatment, it was reported that sedation levels were not significantly influenced[25]. In our study 78 % of patients had sedation, which was less compared to other groups. (p=0.001)

In our study, 50% patients stopped shivering within 5 minutes of receiving tramadol (0.5 mg/kg). The disadvantages of tramadol are the side- effects of nausea and vomiting. In our study 31.3% patient developed nausea and 3% had vomiting, none developed hypotension and 78% were sedated post treatment with tramadol. The results correspond with that of other studies by Tsai and Chu; Bansal and Jain [22,13].

However, in the study by Shukla et al[21]. the incidence of nausea was quite high (77.5%) .

These variations could be explained by the peculiar patient characteristics in different studies.

We have demonstrated that dexmedetomidine, butorphanol and tramadol effectively treat post-neuraxial anesthesia shivering. Dexmedetomidine appears to be more effective than butorphanol and tramadol.

LIMITATIONS:

A relatively small sample size in proportion to the burden of this perioperative problem. Our study included short duration surgeries and anti-shivering effect of dexmedetomidine needs to be seen in surgeries of longer duration where chances of developing hypothermia are more. Also in our study core temperature was not monitored. However we have monitored the surface temperature. This would not have affected study because all groups were in similar environment and also statistically similar in terms of patient characteristics and duration of surgery.

CONCLUSION

Butorphanol, dexmedetomidine and tramadol given in treatment of shivering post spinal anesthesia were found to be effective. In addition, dexmedetomidine removes anxiety with minimal adverse effects, as compared to butorphanol which showed higher recurrence rate and tramadol which had higher incidence of side effects and delayed onset of action.

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