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A randomized control trial for comparison among Nalbuphine, Tramadol and placebo for treating post anesthetic shivering undergoing spinal anesthesia in Cessarian section

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Abstract:

Back ground

Post-anesthetic shivering for patients may induce a variety of complications. In this prospective, randomized control trail study, we evaluated the anti -shivering effect of nalbuphine, compared with tramadol and placebo, for treating Post- anesthetic shivering after spinal anesthesia in Cessarian section.

Methodology

Sixty adult patients were included in the study. Group 1 (*n* 20) received Nalbuphine **0. 28 mg/kg**, Group 2 (*n* 20) received Tramadol 0.25mg/kg, and Group 3 (*n* 20) received saline.

Results

Treatment that stopped shivering was considered to have been statistically significant. The results demonstrated that, 5 min after treatment, both nalbuphine and tramadol provided a rapid and potent anti-shivering effect on Post-anesthetic anti-shivering effect, with high response rates of 85% and 95%, compared with those of saline (0%) (*P* , 0.01).

Conclusion

We evaluated nalbuphine versus tramadol and saline for treating post-anesthetic shivering in regional anesthesia patients undergoing spinal anesthesia in Cessarian section. Our results demonstrate that both nalbuphine and tramadol provide similar rapid and potent anti-shivering effect.

INTRODUCTION

Humans have two distinct subsystems of regulating body temperature namely behavior thermoregulation and physiological (Boris R.M. Kingma et al 2016). Behavioral thermoregulation through the use of shelter space heating, air conditioning and clothing, enables human to live most extreme climate in the world but it does not provide fine control of body heat balance (Delia SS et al 2018)

Afferent thermal sensing, central regulation and efferent pathways are three components of thermoregulatory response via C fibers (Bhattacharya PK et al; 2003), pre optic anterior hypothalamic neurons (De Wette J et al 2002) and multiple inputs that are integrated into a common afferent signals to the effector systems (Bhattacharya PK et al; 2003 & Dhimar AA et al; 2007) respectively. The principle defenses against hypothalamia in human includes skin vasomotor activity, non-shivering thermogenesis, shivering and sweating (William GR et al 2018 & Bilotta F et al 2002). Shivering is an involuntary oscillatory muscular activity that augments metabolic heat production up to 600% above basal level, 40% of unwarmed patients after receiving general anesthesia (Bhattacharya PK et al;2003 & Chaturvedi S et al 2002), 45-85% of after receiving spinal anesthesia (Techanivate A et al;2005) and 40-60% patients receiving general anesthesia (Dhimar AA et al ;2007 & Bilotta et al 2002). Based on monoamine theory of thermoregulation (Feldberg and Myer's, 1963) balance between epinephrine and serotonin is required to modulate central thermoregulatory control mechanisms (Andrej A.R, Maria C.A. et al 2009). Pharmacological agents like Tramadol, Pethidine and Nefopam have been used to modulate central thermoregulatory controls mechanisms that includes post-operative shivering cause discomfort to the patients (Bhatanagar et al 2001, Wang et al 1999, Zahedi H 2005, Kranke P et al 2002 & 2003).

The present study has been planned to compare the relative effectiveness of anti-shivering action of Tramadol and Nalbuphine after spinal anesthesia in Cessarian section.

METHODOLOGY :-

After obtaining informed consent and approval from the local ethics committee, the study was conducted in the department of Anaesthesiology and Intensive Care, Govt. Medical College, Jammu, on sixty (60) patients above the age of 14 years of either sex belonging to ASA Grade I and ASA Grade II. Exclusion criteria was patients with known history of alcohol and substance abuse. Patients with contraindication for spinal anesthesia were excluded from this study. Detailed history of the patients, physical examination, systemic examination and relevant investigations were carried out as mentioned in the proscribed proforma (Sangeeta T., Ashutosh C. et al 2013).

Patients were divided randomly into 3 groups of 20 each. Group I received Nalbuphine 0.3 mg/kg (Sajedi P, Nazemroaya B 2006), Group II- received Tramadol 0.25mg/kg (Sajedi P, Nazemroaya B 2006) and Group III-received a Placebo.

PRE-ANESTHETIC PREPARATION

Patients were prepared by 6 hrs preoperative fasting and overnight sedation with Alprazolam in the dose of 0.25 to 0.5 mg. premedication with Inj. Glycopyrrolate 0.01mg/kg

intramuscular and Inj. Diclofenac sodium 1-2mg/kg was given half an hour before surgery (Zambouri A et al 2007).
Pre anesthetic evaluation and basic laboratory investigations were done in the patients and they were explained in detail about the Grading of Shivering (No Shivering(0),(i)Pilorection or peripheral vasoconstriction but no visible shivering (ii)Muscular activity involving one muscle group, (iii)Muscular activity in more than one muscle group, but no generalized shivering, (iv) Shivering involving the whole body, Crossley and Mahajan (1994).
Shivering of grade II-IV was treated with injection Nalbuphine, tramadol or placebo. After giving the drugs intravenously the following parameters were observed a)Time between drug injection and stopping of shivering (treatment time), b)Time between the treatment and a new shivering (Relapse interval), c) Restore rate (The number of patients who stopped shivering after intravenous treatment) (Tonny S L, Richard N. K. et al 2016).

ANAESTHETIC PROCEDURE

In the operating room, baseline blood pressure (BP) (Systolic diastolic and mean). Heart rate respiratory rate and peripheral oxygen saturation (SpO_2) were recorded after attaching pautine monitors (electrocardiogram, non-invasive BP and pulse oxometer). Intravenous access was secured with the IV cannula no. 22G and standard monitors like NIBP, ECG and oximeter attached to the patient. The patients under study received spinal anesthesia
Spinal anesthesia was done by injecting 2.8 ml bupivacaine (0.5%) at L3-L4 levels with 26 number Spinal needle under aseptic precautions. After the end of the surgery the patients were shifted to the recovery room and they were observed for shivering (Anita K, Ruchi G et al 2014)
Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) Version 16 (SPSS Inc, Chicago, IIIinois, USA) and Statistical significant difference in relapse time among groups was assesses by the use of unpaired t-test. P-value of <0.05 was considered significant. The complications of both the drug were recorded and analysis was conducted with the help of computer software Microsoft excel and EPI-INFO version 60.1 for windows. Percentage was conducted for quantitative outcome variable (shivering grades). Chi square test was used to evaluate significant difference among the study groups.

RESULTS

All the three groups were comparable with respect to age weight, sex and ASA physical status as shown in Table I.
As shown in Table II, the patients experienced shivering at grade II and III in all the groups. More than 55% patients have experienced shivering at grade III. There were no significant differences among the groups in shivering severity. Statistically, the comparison among the three groups was insignificant.
In Group I the mean treatment time was 2.00±1.01 and in Group II the mean treatment time was 3.00±1.87, statistically the result was insignificant with p value of more than 0.05. Group III only patient responded to placebo after 30 minutes.
In Group I 90% patients responded to nalbuphine, Group II 85% patients responded to Tramadol whereas only 5% patients in Group III responded to placebo. The result was statistically very significant with p value of 0.0002.
Group I had recurrence of 20%, Group II had recurrence of 25% and in Group III as almost none of the patients responded to the placebo given, recurrence is not applicable. Intergroup comparison among the Group I and II are statistically insignificant.
In Group I 2 patients develops side effects other than nausea-vomiting and vertigo. In Group II 3 patients develops nausea-vomiting and side effects. For Group – not applicable. Statistically the result was insignificant with p value more than 0.05.

Table 1:- Demographic Profile:-

			Group 1	Group II	Group III	*P*	
1	Age (years)		32 ± 10.57	30.50±9.12	34.35±10.43	0.477	NS
2	Weight (Kg)		511.95±5.25	55.60±7.25	53.40±4.73	0.11	NS
3	Sex	Male	9	9	10	0.11	NS
		Female	11	13	10		
4	ASA (Physical status) I/II		11/9	9/11	7/13	0.67	NS

Note:- ASA- American Society of Anesthesiologists

Table 2:- Shivering grade and response rate among the groups:-

			Group 1	Group II	Group III	X^2	*P*	
1	Shivering grade (0,i,ii,iii,iv)		9 (ii)	11(ii)	8(ii)	0.99	0.2	NS
			11(iii)	9(iii)	12(iii)			
			0 (iv)	0(iv)	0(iv)			
In Group I the mean treatment time was 2.00±1.01 and In Group II the mean treatment time (in min.) was 3.00±1.87, statistically the result was insignificant with *p* value of more than 0.05. In group III only one patient responded to placebo after 30 minutes.								
2	Response rate	Stopped	18(90%)	17(85%)	1(5%)	-----	0.0000	HS
		No effect	2(10%)	3(15%)	19(95%)			
3	Recurrence		4(20%)	5(25%)	----	0.33	0.56	NS

Note – X^2 means Chi square test

DISCUSSION

Post-anesthetic shivering is a common complication of modern anesthesia, affecting 5-65% of patients after general anesthesia and 40%-60% of patients during regional anesthesia. Apart from the obvious discomfort, post- anesthetic shivering is associated with number of potentially deleterious sequelae. These include increased oxygen consumption and carbon di oxide production, catecholamine release, increased cardiac output, trachycardia, hypertension and taised intraocular pressure. shivering also decrease mixed venous oxygen saturation as well as interfering with monitoring technique (ECG Pulse rate, B.P. oxygen saturation etc.). A number of physical methods have been used to reduce the incidence of shivering particularly forced air warming systems and radiant heaters, but the mainstay of treatment of postoperative shivering is pharmacological. The recent study was undertaken to compare the effect of anti-shivering action of Nalbuphine and tramadol and placebo.

The study was conducted in the Department of Anesthesiology and Intensive Care Govt. Medical college Jammu, on sixty (60) patients above the of 14years of either sex belonging to ASA Grade I and ASA Grade II who develops shivering in the recovery room. After obtaining informed consent, patients was prepared by 6hrs preoperative fasting and overnight sedation with Alprazolam in the dose of 0.25 to 0.5 mg. Premedication with Inj. Glyxopyrrolate 0.01 mg/kg intramuscular and Inj. Diclofenac sodium 1-2 mg/kg was given half as hour before surgery. These patients received regional anesthesia in Cessarian section.

After shifting the patients to the recovery room they were observed for shivering. Shivering of grade II-IV was treated with tramadol or Nalbuphine. Patients were decided randomly into 3 groups of 20 each. Group 1 received Nalbuphine 0.3mg/kg, Group II received Teramadol 0.25mg/kg and Group III received a Placebo.

The demographic data (Age sex weight and ASA physical status) among the group were comparable with *p* valve less than 0.05.

The patients in group I stopped shivering earlier than patients in group II though the result was statistically insignificant. Recurrence rate was more in group II about 25% where as in group I it was only 20%, this also was statistically insignificant. The response rate among the group was statistically highly significant with 90% for group I , 85% for group II and only 5% for group III. The complication rate for Nalbuphine was 10% and tramadol was 15%.

The study indicates that nalbuphine in the dose of 0.3mg/kg and tramadol in the dose of 0.25mg/kg are both effective in controlling shivering after regional anesthesia. Shivering disappeared by 2.00±1.01minutes in case of pethidine and 3.00±1.87 minutes in case of tramadol. The t value is 1.98 and p value is 0.56 thus this is statistically insignificant. These findings are consistent with those of Sajedi P and Nazemroaya B (2006) where shivering disappeared in 1.33±0.66 minutes in nalbuphine group and 1.34±0.86 minutes in the tramadol group. Shivering disappeared by 1minutes in case of tramadol and 5minutes in case of nalbuphine respectively in a study conducted by Dhimar AA et al (2007) but the dose used was 1mg/kg each. The treatment time was lower in their study because of possibly higher dose used. In a study conducted by Tsai YC and Chu KS (2001) treatment time in the nalbuphine group was 4.2±2.3 and in the tramadol group was 5.1±3.6minutes respectively, thus the result of our study correlates with their findings.

The response rate in the nalbuphine group was 90% (18 patients), in whom shivering stopped after intravenous nalbuphine 0.3 mg/kg and where as in the tramadol group 85% (17patients) stopped shivering after intravenous dose 0f 0.25mg/kg of tramadol, in placebo group the response rate was only 5%. The result was statically higher significant (chi square value= 34.83, p=0.000). This shows that both the drugs have a definite role in controlling shivering. The anti-shivering action of pethidine is mainly due to drug induce reduction in the shivering threshold and stimulation of the kappa receptors. And the anti-shivering action of tramadol is by inhibiting reuptake of 5-HT , nor-epinephrine and dopamine. While placebo has no role. Kurtz et al (1997 &1995) found the special anti-shivering efficacy of nalbuphine and confirmed that it results from an uncharacteristically large reduction in the shivering threshold than from exaggerated generalized thermoregulatory inhibition. Tsai YC and Chu KS (2001) compared the anti-shivering effects of tramadol, pethidine and amitriptyline in the doses of 0.5mg/kg, 05mg/kg and 15mh respectively. The response rate was 87% and 93% for tramadol and meperidine group respectively, compared 13% in the amitriptyline group. Thus, their results were results were similar to our study where the response rate in pethidine group was 90% and in the tramadol it was 85%. Similarly, in a study by Wang JJ et al (1999), anti-shivering effects of meperidine, nalbuphine and saline was compared, and they found that after 5 minutes of injection, both Nalbuphine and Meperidine provided a rapid and potent anti-shivering effects on post-anesthetic shivering; with a response rates of 80% and 83% respectively; compared with those of Saline 0%(Gotz et al 1995). After 30 minutes of administration, the response rates of Nalphubine and Meperidine were 90% and 93% respectively; compared with 17% in the Saline group and thus concluded that Nalbuphine may be an alternative to Meperidine for treating post anesthetic shivering.

In the nalbuphine group 20% of the patient had recurrence whereas in the tramadol group it was 25%. This of the patient shows that nalbuphine group has slightly low rate of recurrence though it has no statistical significance (p=0.56). In a study conducted by Dhimar AA et al (2007), they compared the control of shivering with nalbuphine and tramadol in the dose of 1mg/kg each, and found that the recurrence rate in the pethidine was 50% where as in tramadol group it was only 10%. The probable reason for recurrence of shivering could be due to low plasma concentration of the active drug when hypothermia is still persisting and individual variation in the core temperature (Dhimar AA et al; 2007).

In our study we have found that nalbuphine caused sedation in 2 patients (10%) and tramadol caused nausea and

vomiting in 3 patients (15%). However the difference was statistically insignificant (p=0.37). No respiratory depression was observed in any of the cases. In the study Dhimar AA et al (2007) the complications occurred in 20% in the pethidine group while only 6.66% in tramadol group. In Tsai YC and Chu KS (2001) study patients also developed somnolence, the incidence was 33% in meperidine group and 7% in the tramadol group, no patients in our study develops somnolence. The slightly lower rate of side effects may be due to the lower dose of the drugs used in our study though statistically it is insignificant (chi square value 0.87, p value=0.37).

CONCLUSION

We concluded that Nalbuphine in the dose of 0.28mg/kg is slightly more efficacious that tramadol in the dose of 0.25 mg/kg and placebo has got no role in shivering.

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