

## Comparative Evaluation of Clonidine and Nalbuphine for Control of Post-Spinal Anaesthesia Shivering

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### Abstract

The aim of this study was to evaluate the efficacy, potency and side effects of clonidine and nalbuphine in postspinal anesthesia shivering. In this prospective double-blind randomized controlled clinical trial, 60 American Society of ASA Grade I and II patients aged between 18 and 60 years scheduled for various surgical procedures under spinal anesthesia, who developed shivering were selected. The patients were divided into Two Groups: Group C ( $n = 30$ ) comprised of patients who received clonidine 1 mcg/kg intravenously (IV) and Group N patients who received nalbuphine 0.05 mg/kg IV. Grade of shivering, disappearance of shivering, hemodynamic and side effects were observed at scheduled intervals. Disappearance of shivering was significantly earlier in Group C ( $2.75 \pm 1.35$ ) than in Group N ( $3.58 \pm 1.19$ ) ( $p = 0.01704$ ). Bradycardia is seen more in Group C than Group N ( $p = < 0.001$ ). Whereas, sedation is seen in Group N after drug administration but patient remain hemodynamically stable in Group N. We conclude that both the drugs are effective but nalbuphine controls shivering with more hemodynamic stability.

**Keywords:** Spinalanesthesia; Shivering; Clonidine; Nalbuphine.

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### Introduction

Spinal anesthesia is a safe technique indicated mainly in abdominal and lower limb surgeries in both emergency and elective settings. Shivering which is an involuntary muscular activity occurs approximately in 40–50% of patients after spinal anesthesia.<sup>1,2</sup> Shivering causes mismatch between oxygen demand and supply which can lead to side effects like hypoxemia, hypercarbia and lactic acidosis. It also causes rough recovery from anesthesia.<sup>5</sup> Shivering causes serious side effects in patients having less cardiac reserves and those

having increased intracranial pressure and in elderly and apprehensive patients.<sup>6,7</sup>

Spinal anesthesia does not affect thermoregulation by hypothalamus but it causes decrease in core body temperature. Heat loss occurs due to inhibition of vasoconstriction leading to vasodilation. Rapid infusion of cold IV fluids, cold temperature of operative room, direct contact of skin surface with cold scrubbing solutions, all these factors play an important role in occurrence of hypothermia and shivering in patients after spinal anesthesia.<sup>3,4</sup> There are various nonpharmacological as well as pharmacological methods that could help in

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controlling shivering. Use of gamgi pads and blankets to wrap the exposed body of patients, use of warmer to increase the temperature, use of warm IV fluid, intravenous fluid warmers, keeping operative room temperature adequate are some of nonpharmacological methods that could help. Pharmacological method includes use of various drugs like tramadol, clonidine, dexmedetomidine, nalbuphine, pethidine, ketamine are some of them.<sup>8</sup>

Unfortunately, drugs administered for control of shivering have got many side effects associated with them.

Nalbuphine is a semisynthetic, mixed agonist antagonist opioid that has characteristics of  $\mu$ -antagonist and  $\kappa$  agonist activities. It has a high affinity for opioid receptors in central nervous system.<sup>9</sup> A clinically important contribution of  $\kappa$  receptors for the treatment of shivering is supported by the observation that meperidine which is a  $\mu$  and  $\kappa$  receptor agonist and reduces the intensity of the cold induced shivering even in moderate dose of naloxone. Naloxone blocks  $\mu$ -receptor and have little effect on  $\kappa$ -receptor. Nalbuphine also has high affinity for  $\kappa$ -opioid receptors in the central nervous system.

Clonidine, a highly selective  $\alpha_2$  adrenoreceptor agonist. Its antishivering action is at level of hypothalamus, locus coeruleus and spinal cord.<sup>10,11</sup> It does not produce side effects like vomiting but it causes bradycardia and hypotension. Clonidine has high specificity towards the presynaptic alpha-2 receptors present in vasomotor center located in brainstem of our body. It decreases presynaptic calcium level and therefore, subsequent release of norepinephrine resulting in decrease in sympathetic tone and blood pressure.

## Materials and Methods

Institutional Ethics Committee approval was obtained along with written informed consent from each patient, sixty patients of American Society of Anesthesiologists (ASA) physical status I to II of both genders, aged 18–60 years, scheduled for surgery under spinal anesthesia were selected for this prospective, randomized double-blind study. Patient who refused for the study or the procedure, or patients with clinically significant coagulopathy, infection at the injection site, allergy to local anesthetics or the study drugs, severe cardiovascular or pulmonary disease, renal or hepatic disorder, patients on any other opioids or any sedative medications in the week prior to the surgery were also excluded from the study.

A written and informed consent was obtained from each subject.

The patients were divided into 2 Equal Groups: Group C and Group N.

Group C - 30 cases (Injection Clonidine 1 mcg/kg IV);

Group N - 30 cases (Injection Nalbuphine 0.05 mg/kg IV).

The drug preparation was done by an anesthesiologist who was not involved in administration of anesthesia, patient care or data collection. Further, intervention and monitoring were done by an investigator blinded to the group allocation.

All patients were thoroughly reevaluated preoperatively. In the preoperative room, the patient's pulse, blood pressure and temperature were taken, with the patient lying comfortably in supine position.

All the patients were kept nil by mouth for at least 6 hours prior to surgery to avoid risk of aspiration and any other anesthesia related complications.

IV access was secured with 20-gauge cannula. Basic monitoring devices were attached (these included heart rate, pulse oximeter, ECG, noninvasive BP). Baseline vitals were recorded. All the patients were preloaded with 10 ml/kg Ringer's Lactate fluid and maintained on IV fluids throughout the surgery.

In the sitting position under all aseptic precautions spinal anesthesia was given. After painting and draping of lumbar area with 26G Quincke's spinal needle was introduced in L3-L4 intervertebral space. Free flow of CSF confirmed the subarachnoid space. 0.5% bupivacaine heavy (3/3.5 ml) given to achieve desired level of block according to surgical procedure. All operation theatres were maintained at an optimum temperature of around 22°C–24°C. Supplemental oxygen was administered with the Hudson's face mask to all the patients at the rate of 2 l/min and patients were covered with drapes but not actively warmed. IV fluids and drugs were administered at room temperature.

After induction of spinal anesthesia, patients were observed for the occurrence of shivering until the postoperative period. Shivering was graded according to the Wrench Grade of Shivering.<sup>12</sup> In which 0 is No shivering, 1 is One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity, 2 is Visible muscle activity confined to one muscle group, 3 is Visible muscle activity in more

than 1 muscle group, 4 is Gross muscle activity involving the whole body.

Patients who develop either Grade 3 or 4 shivering will be included in the study. Injection Clonidine 1.0 mcg/kg or Injection Nalbuphine 0.05 mg/kg were diluted to a volume of 10 ml in a 10 ml syringe. And the syringe presented as coded syringes as per randomization list by an anesthesiologist who was unaware of the group allocation. This was then administered to the patient as a slow IV injection over a period of 10 minutes.<sup>13</sup>

The attending anesthesiologist recorded the time of onset of shivering in minutes at which shivering started after spinal anesthesia, time of administration of the test drug, and time to the cessation of shivering.

Shivering control was defined as 'complete' when posttreatment, the shivering score declined to 0; 'incomplete' when the scores decreased but did not abolish the shivering completely; and 'failed' if no change in scores was observed.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation, ECG, axillary temperature and Wrench's shivering grades were recorded at 0, 1, 2, 5, 10, 15 and 30 minutes after administering the test drug.

Duration of surgery was recorded and duration of spinal anesthesia was noted by assessing spontaneous recovery of sensory block using the pinprick method and observing spontaneous movements of limbs in the postoperative period. Recurrence of shivering was also noted.

In case there was recurrence of shivering, patients were treated with an additional dose of clonidine (1 µg/kg IV) or nalbuphine (0.05 mg/kg IV) in the respective groups and/or active warming measures using convection heaters or infusing moderately warm IV fluids.

Adverse effects such as nausea, vomiting, dizziness, sedation, bradycardia (heart rate < 50 beats/minute) and hypotension (fall in systolic blood pressure > 20% of baseline) were watched for and recorded.

Nausea and vomiting were treated with injection metoclopramide 10 mg IV as and when required. Bradycardia, if it occurred, was treated with a bolus dose of Inj. Atropine 0.6 mg intravenously. Whereas, hypotension was treated with intravenous Inj. Mephenteramine 6 mg increments.

Sedation was assessed as per the modified Ramsay Sedation Scale:<sup>14</sup>

In which 1 means Patient anxious or agitated or both, 2 is Patient cooperative, oriented and tranquil, 3 is Patient responses to commands only, 4 is A brisk response to light glabellar tap, 5 is A sluggish response to a light glabellar tap and 6 is No response. Sedation score > 3 was termed as sedation.

The coding was opened after completion of the study to compile results.

### Statistical Analysis

All the cases, were completed in the stipulated time. Data was collected, compiled and tabulated. The statistical analysis was done using parametric test and the final interpretation was based on Z-test (standard normal variant) with 95% level of significance.

Quantitative data was analyzed by *Student 't'- test*.

Qualitative data was analyzed by *Chi-square test*.

### Results

A total of 60 patients were enrolled in the present study and were randomized into two groups of 30 each, 40 of whom were male and 20 were female shows in Table 1. Both the groups were comparable with respect to age, sex, weight, duration of surgery, and the duration of spinal block. The mean age of the patients in Group C was 35.4 ± 9.27 years; and patients in Group N, 36.03 ± 8.64 years ( $p = .785$ ).

Shivering disappeared in 22 (73.33%) patients who received clonidine and 22 (73.33%) who

**Table 1:** Demographic characteristics, ASA grade

		Group C	Group N	p - Value	
1	Age (yrs)	35.4 ± 9.27	36.03 ± 8.644	0.785	NS
2	Weight (kgs)	59.33 ± 10.21	58.766 ± 10.07	0.829	NS
3	Sex				
		Male	20	20	
		Female	10	10	
4	ASA I/II	19/11	18/12		

**Table 2:** Successful treatment of postspinal shivering

Control of shivering	Group N	Group C
Complete	22 (73.33%)	22 (73.33%)
Incomplete	6 (20%)	6 (20%)
Failed	2 (6.67%)	2 (6.67%)

**Table 3:** Time taken to control shivering and its significance

Time taken to control shivering	Group N	Group C
Mean	3.58929	2.75
Std dev	1.19454	1.35058
<i>p</i> - value	0.01704 (Significant)	
Inference	Shivering was controlled significantly earlier in Clonidine group	

received nalbuphine, shows in Table 2. Both the drugs were found to be effective in reducing shivering. Though, severity of shivering was not satisfactory in 6 (20%) patients of Group C and 6 (6%) patients of Group N and unchanged in 2 (6.67%) patient of Group C and 2 (6.67%) patients of Group N. No patient had any recurrence of shivering.

The time taken for control of shivering was  $2.75 \pm 1.35$  min for Group C and  $3.589 \pm 1.19$  for Group N ( $p = 0.01704$ ), shows in Table 3. Time for onset of shivering and severity of shivering were not statistically significantly different between the two groups. However, shivering was controlled significantly earlier in Group C ( $p = 0.01704$ ).

We also observed the change in the heart rate after giving study drug in both the group. Both Group C causes significant decrease in mean heart rate than Group N ( $p = < 0.001$ ).

There was no statistically significant difference with respect to mean blood pressure, axillary temperature and oxygen saturation between the two groups.

Bradycardia mostly seen with clonidine whereas, nalbuphine causes sedation as an adverse effect.

## Discussion

Spinal anesthesia is most common technique used for lower abdominal and lower limb surgeries. Its rapid onset of action and association with postoperative analgesia makes it a very popular technique. Shivering is an involuntary muscular activity experienced by almost 40-50% of patients undergoing surgeries under spinal anesthesia.<sup>1,2</sup> Shivering is a protective mechanism for hypothermia. Vigorous involuntary muscular activity generates the heat in the body in response

to hypothermia. It is very discomforting sensation to a patient. In addition, shivering causes increase in oxygen demand up to six times the normal requirement.

Mechanism of shivering under regional anesthesia though not fully understood but it appears to be mediated by norepinephrine, dopamine, neuropeptides, 5-hydroxy tryptamine as a response to hypothermia. Hypothermia occurs after spinal anesthesia as a result of peripheral vasodilation of lower part of the body causing heat loss which is not compensated by metabolic heat production of the body.

Shivering can be controlled intraoperatively by various methods. Which includes pharmacological and nonpharmacological methods.

Nonpharmacological methods include covering the exposed part of the patient with cotton and warming blankets, using intravenous fluids warmers, maintaining optimum operating room temperature are some of these. Pharmacological method includes use of various drugs like tramadol, clonidine, dexmedetomidine, nalbuphine, pethidine, ketamine are some of them.<sup>8</sup> Unfortunately, all the drugs have some or the other side effect and perfect drug is yet to be known. And studies are being performed to find the best possible drug to control the shivering.

In the present study, we compared the efficacy of clonidine and nalbuphine for treatment of shivering after spinal anesthesia in patients undergoing various elective surgeries. Clonidine is a centrally acting selective  $\alpha_2$  agonist. Clonidine exerts its antishivering effects at three levels: Hypothalamus, locus coeruleus and spinal cord. At the hypothalamic level, it decreases thermoregulatory threshold for vasoconstriction and shivering, because hypothalamus has high density of  $\alpha_2$  adenoceptors and hence is effective in

treating the established postanesthetic shivering. It also reduces spontaneous firing in locus coeruleus - a proshivering center in pons. At the spinal cord level, it activates the  $\alpha_2$  adrenoreceptors and release of dynorphine, norepinephrine and acetylcholine. The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs. Clonidine is highly lipid-soluble and easily crosses the blood-brain barrier. Due to these merits, interaction at the  $\alpha_2$  adrenoreceptors at spinal and supraspinal sites occurs within the central nervous system.

Nalbuphine is a semisynthetic, mixed agonist antagonist opioid that has characteristics of  $\mu$ -antagonist and  $\kappa$ (kappa)-agonist activities. It has a high affinity for opioid receptors in central nervous system. A clinically important contribution of  $\kappa$  receptors is supported by the observation that meperidine which is a  $\mu$  and  $\kappa$  receptor agonist, reduces the intensity of cold induced shivering even in the presence of moderate doses of naloxone. It has less ability to depress respiratory function as compared to other opioids. Nalbuphine in the dose 0.05 mg/kg IV is selected for the study.

In our study, we found out that both clonidine 1 mcg/kg IV and nalbuphine 0.05 mg/kg IV were effective in treatment of postspinal shivering. Though time taken to control the shivering is less with clonidine ( $2.75 \pm 1.35$  min) than with nalbuphine ( $3.58 \pm 1.194$  min), ( $p = 0.017$ ).

Bradycardia was significant after clonidine administration and sedation was more in nalbuphine group ( $p = < 0.001$ ). But patients in Group N were more hemodynamically stable after the drug administration.

## Conclusion

Both intravenous nalbuphine 0.05 mg/kg and clonidine 1 mcg/kg are effective in treating patients with postspinal shivering. Time taken to control shivering is lesser with clonidine than nalbuphine but clonidine causes bradycardia. We preferred Nalbuphine 0.05 mg/kg over clonidine 1mcg/kg as nalbuphine controls shivering with more hemodynamic stability.

## Limitations

1. Smaller sample size as lesser number of people willing to give consent for the study.
2. Only ASA 1 and ASA 2 patients were considered in our study. We have to conduct studies in elderly and cardiac compromised

patients for use of nalbuphine and clonidine in control of postspinal anesthesia shivering in high-risk patients.

3. We used 0.05 mg/kg of nalbuphine and 1  $\mu$ g/kg of clonidine as a dose for control of postspinal anesthesia shivering. Different studies using different dose ranges must be conducted to get ideal dose for control of postspinal anesthesia shivering.

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