Role of Intrathecal Nalbuphine on Prevention of Post spinal Shivering After TURP: A Randomised Control Double Blind Study

Rajeev Kumar, Anshu Pangotra*, Vinod Verma

Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, India

ABSTRACT

BACKGROUND AND AIM

Nalbuphine has been used intrathecally as an adjuvant in previous studies. The purpose of our study was to establish the effectiveness of intrathecal nalbuphine as an adjuvant to bupivacaine for prevention of shivering during spinal anesthesia in patients undergoing TURP.

MATERIALS AND METHODS

In this prospective, randomized, double-blinded, controlled study, 200 ASA class I and II patients undergoing TURP under Subarachnoid Block (SAB), were randomly allocated to two groups: C and N. Group C received 0.5% hyperbaric bupivacaine 2.5 mlintrathecally. While group N received 2.5 ml of a mixture of 400 microgram nalbuphine plus hyperbaric bupivacaine (0.5%). Haemodynamic parameters along with core tympanic temperature were recorded preoperatively then every 10 minutes till the end of surgery. The incidence and severity of shivering was recorded during the surgery and in recovery room. Shivering was graded with a scale described by Bedside Shivering Assessment Score (BSAS). A score of 0 to 3 corresponds to mild, moderate or severe shivering.

RESULTS

The incidence of shivering was less in patients belonging to group N(40) as compared to group C (5) (P>0.05).Incidence of PONV, respiratory depression, pruritis in group N was 4, 0 and 2 respectively as compared to group C it was 14, 2 and 7 respectively.

CONCLUSION

Nalbuphine used intrathecally is a useful adjuvant in SAB and, in a dose of 0.4 mg, it reduces the incident of shivering along with increasing postoperative analgesia.

KEYWORDS

Hyperbaric bupivacaine, Nalbuphine, Subarachnoid block

*Corresponding Author:
Anshu Pangotra,
Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, India
E-mail: dr.anshuroymdii@gmail.com

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INTRODUCTION

Post anaesthesia shivering is as distressing to the patient as is pain and Postoperative Nausea And Vomiting (PONV). Its incidence is estimated to be as high as 50-60% in normal population undergoing General Anesthesia (GA) [1]. Shivering may be defined as an involuntary, repetitive activity in the skeletal muscle. It occurs as a thermoregulatory response to cold, although non-thermoregulatory shivering may also occur. The core temperature in humans varies with the circadian rhythm (and with the menstrual cycle in females), but is normally maintained within the narrow range of 36.5-37.0°C [2]. The mechanism of shivering is not fully understood, it is common in patients who become hypothermic during surgery. In addition to the cold ambient temperature in the operating theatre, high flow rate of un-humidified fresh gases, the use of large volumes of un-warmed intravenous fluids, or intraoperative prolonged exposure of a large surgical wound can also be contributory [3].

Shivering is a common problem encountered after neuraxial (spinal and epidural) anaesthesia. An incidence of shivering of up to 55% has been reported. Neuraxial-anaesthesia impairs the thermoregulation system by inhibiting tonic vasoconstriction below the level of block through sympathetic and somatic neural blockade. With internal redistribution of heat from the core to the peripheral compartment, the loss of thermoregulatory vasoconstriction results in increased heat loss from body surfaces in excess of metabolic heat production [4]. Excessive shivering can result in an increased oxygen demand up to 400% of normal and induce metabolic derangements such as hypoxemia, lactic acidosis, hypercarbia and catecholamine secretion that increase cardiac output, heart rate, and blood pressure[5,6]. Therefore, shivering may cause problems in patients with low cardiac and pulmonary reserves [7]. Shivering also increases intraocular and intracranial pressure, and may contribute to increased wound pain, delayed wound healing, and delayed discharge from post-anesthetic care unit [8]. Shivering is more common in Transurethral Resection of Prostate (TURP) that may be due to absorption of large amount of irrigating fluid at room [9]. Rapid reduction in core temperature starts with bladder irrigation during TURP as unheated irrigation fluid is used and could be a significant etiological factor in production of the hemodynamic responses [10]. Thus, patients undergoing TURP are inherently more prone to develop shivering which could be discomforting as well as deleterious to them. Various methods have been used to control shivering; pharmacologic and non-pharmacologic. The non-pharmacological management is by external heating like the use of forced air warming, warming blankets, warm fluids etc.

Many pharmacological agents have been studied for the prevention or treatment of postoperative shivering. Opioids (meperidine, fentanyl, alfentanil, sufentanil, buprenorphine, nalbuphine, morphine and pentazocin) the cholinomimetic physostigmine, analgesic tramadol, adrenergic agonist clonidine and 5-Hydroxytryptamine antagonist (Ondansetron) have reduced the incidence of shivering or suppressed established shivering [11-14]. Meperidine was also tried alone or in comparison with clonidine and urapidil [15]. Magnesium sulphate, doxapram, ketanserin, nefopam, and ketamine have all been investigated for prevention or treatment of postoperative shivering [16,17]. Nalbuphine, a mixed agonist-antagonist drug, is a lipophilic semi-synthetic opioid related to both oxymorphone and naloxone, and has relatively potent mu-antagonist and kappa agonist activity.

Because of its kappa antagonist properties, nalbuphine should produce fewer μ-mediated side effects such as respiratory depression, pruritus, nausea and vomiting. It has high affinity for kappa opioid receptors in the central nervous system. Theoretically, nalbuphine may have significant effect on post anesthetic shivering. Intrathecal nalbuphine was widely used for postoperative analgesia in many studies. When nalbuphine binds to μ receptor, it serves only to competitively displace other μ agonists from the receptor without itself displaying any agonist activity similar to those of naloxone. However, when it binds to kappa receptor, it has agonist activating effect. Nalbuphine, administered intrathecally, binds to kappa receptors in the brain and spinal cord areas which are involved in nociception, producing analgesia and sedation without μ side effects.

MATERIALS AND METHODS

This study was conducted after obtaining ethical clearance from the University's Institutional Review Board (IRB 858/Acad) during the period December 2017 to November 2018. The trial was registered prior to patient enrollment with Clinical Trial Registry–India (ctri.nic.in) vide registration numberCTRI/2018/08/015223, Principal investigator: Rajeev Kumar, Date of registration: 07-08-2018. Written informed consent was obtained from all the patients before enrolling them for the study. One hundred patients admitted for TURP under spinal anaesthesia, which were willing to participate and fulfil the inclusion criteria were enrolled in this double blind randomized, controlled study.

Patients of American Society of Anesthesiologists [ASA] physical status 1 and 2, between 20-70 years of age of either sex with airway of and willing to participate were included in the study. The exclusion criteria included; patient's refusal to participate, ASA Physical status III and above, with known allergy to nalbuphine and bupivacaine, obese patient with BMI>30 kg/m^2, patient contraindicated to regional anaesthesia.

The outcome parameters were to know the incidence and severity of shivering after spinal anaesthesia in patients undergoing TURP. The secondary outcome was to look for effect of both drugs on hemodynamics.

Sample Size

Sample size was estimated considering the objective of the study i.e. there is no difference between the test and control groups. Expecting 50% decrease in shivering with intrathecal nalbuphine, the study would require a sample size of 100 for each group (i.e. a total sample size of 200, assuming equal group sizes), to achieve a power of 90%, β error <0.2 and a level of significance of 5% (two sided). Finally, 100 patients were enrolled in each group.

After enrolment in the study the patients were taken in the operating room and baseline parameters were observed and documented. A good intravenous access was secured and routine monitoring in the form of electrocardiography, pulse oximetry and noninvasive arterial pressure were instituted.

Patients were given intravenous 15 ml/kg/h of crystalloid solution (at room temperature 23°C-25°C) through an 18-gauge peripheral venous catheter. Oxygen at 5 L/min was administered through facemask and patient was covered with drapes but not actively warmed. Now patients were randomly assigned to two groups using sealed envelope based on computer generated random numbers. Spinal anaesthesia was performed in sitting position at L3-4 or L4-5 levels, midline approach by 25-gauge Quincke needle [18-20].

Group C received 2.5 ml hyperbaric bupivacaine (0.5%). Group N received 2.5 ml of a mixture of 400 microgram nalbuphine plus hyperbaric bupivacaine (0.5%).

Patients were positioned supine. Sensory levels were determined by pinprick and motor blockade was evaluated using Bromage's criteria. The Mean Arterial Pressure (MAP), Heart Rate (HR), arterial oxygen saturation (SpO_2), and core (tympanic) temperature were measured and recorded preoperatively, then every 10 min till the end of surgery. The incidence and severity of shivering were recorded during the surgery and in the recovery room. Shivering was graded using Bedside Shivering Assessment Score (BSAS). Score of 0 to 3, corresponds to no, mild, moderate and severe shivering respectively. The Injections were prepared by an independent anesthesiologist. The patient and attending anesthesiologist were unaware of the group allocation.

Statistical Analysis

To analyse quantitative data, mean and standard deviation is computed and to test significance of difference of mean t-test is performed. Test statistic it is computed as t=x1-x2/s, where x1 and x2 are sample means based on n1 and n2 observation and s2 is pooled variance obtained using formula s2=n1s1+n2s2given that n1+n2, s1 and s2 are standard deviations of both the sample. Calculated values were compared with standard table value. If calculated t-value was greater than standard table value for test size given (i.e α=5%,1% or 0.1%) level difference of mean significant otherwise means were not difference.

RESULTS

Two hundred patients were recruited for the study and there was no dropout. No significant difference was observed in any of the variables compared between nalbuphine and control groups.

Table 1 presents severity of shivering of patients in nalbuphine and control groups measured at time just after drug administration. Statistically significant difference was found of time ($p<0.05$). Figure 1 also presents the comparison of severity of shivering of patients in nalbuphine and control groups measured at time just after drug administration.

Table 2 presents severity of shivering of patients in nalbuphine and control groups measured 10 minutes after drug administration. Statistically significant difference was found ($p<0.001$). Figure 2 also presents the comparison of severity of shivering of patients in nalbuphine and control groups measured 10 minutes after drug administration.

Table 3 presents severity of shivering of patients in nalbuphine and control groups measured 60 minutes after drug administration. Statistically significant difference was found ($p<0.001$). Figure 3 also presents the comparison of severity of shivering of patients in nalbuphine and control groups measured 60 minutes after drug administration.

Shivering score	Group C	Group n	Total
0	70	83	153
1	29	17	46
2	1	0	1
Total	100	100	200

Table 1. Severity of Shivering at 0 Minutes Found to Significantly Lower in Group N X2=4.7, df=1,p<0.05, R=S

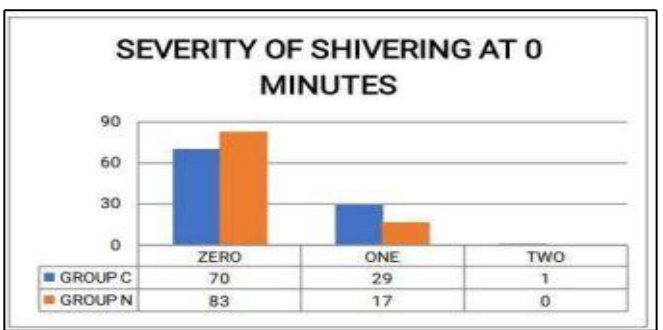

Figure 1. Graph Showing Severity of Shivering at 0 Minutes

Shivering score	Group C	Group n	Total
0	47	72	119
1	41	24	65
2	7	3	10
3	4	1	5
TOTAL	100	100	200

Table 2. Severity of Shivering at 10 Minutes Found to Significantly Lower in Group N X2=12.96, df=2,p<0.01, R=SS

Figure 2. Graph Showing Severity of Shivering at 10 Minutes

Shivering score	Group C	Group n	Total
0	53	72	125
1	4	19	23
2	10	2	12
3	33	7	40
TOTAL	100	100	200

Table 3. Severity of Shivering at 60 Minutes Found to Significantly Lower in Group N X2=21.19, df=2,p<0.001, R=SSS

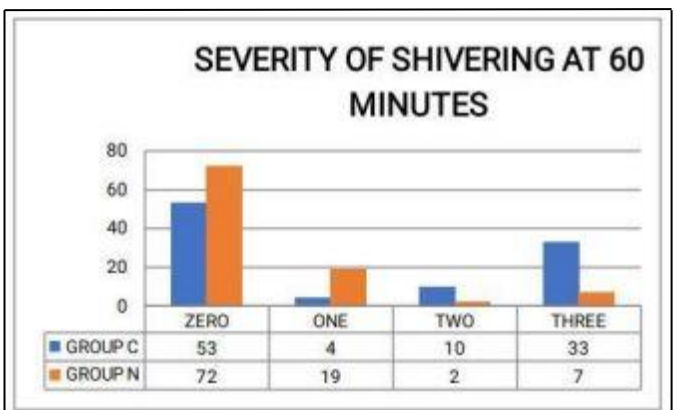

Figure 3. Graph Showing Severity of Shivering at 60 Minutes

DISCUSSION

The thermoregulatory mechanism in human body is a complex one that normally keeps the temperature within a tight range (36.5°C-37.5°C) known as "inter-threshold range". If the core temperature decreases below this range, the body responds by vasoconstriction and shivering which increases heat production two to five folds. Thus, shivering is a protective mechanism to preserve body heat but no definite linear relationship exists between body temperature and occurrence of shivering. SA induces inhibition of vasoconstriction below the level of block through sympathetic and somatic blockade. Subsequent vasodilatation and increased cutaneous blood flow results in increased heat loss *via* the skin.

In contrast to these changes, vasoconstriction and shivering are restricted to the upper body during SA. Large number of animal studies has been under taken to prove that intrathecal nalbuphine was not neurotoxic. In a sheep model using histopathological methods that intrathecal nalbuphine, even at large doses 15-24 mg were not associated with histopathological changes of the spinal cord. In our study, we compared the efficacy and adverse effects of nalbuphine as an adjunct to intrathecal bupivacaine and bupivacaine alone in TURP. The severity of shivering was low in nalbuphine group as compared to only bupivacaine group. Nalbuphine also provided hemodynamic stability. None of patient had respiratory depression (respiratory rate below 10 bpm, SPO2 <90%). Since respiratory depression is predominantly μ receptor-mediated and nalbuphine is a μ receptor antagonist, respiratory depression effect is expected to be attenuated by nalbuphine.

Patients who received bupivacaine with nalbuphine had significantly longer duration for first request of analgesia when compared with patients who received bupivacaine alone. In our study, nalbuphine also exhibits analgesic ceiling effect at 0.8 mg dosage, above which there was no increase in analgesic efficacy. This analgesic ceiling effect can be a significant limitation of nalbuphine usage. Patient who received bupivacaine alone had significantly higher pain scores earlier than patients who received nalbuphine-bupivacaine combinations as assessed by VAS. In bupivacaine group, patients were wide awake whereas patients who received nalbuphine-bupivacaine combinations were sedated, calm, and easily reusable with verbal commands (Grade 2 sedation score).

CONCLUSION

We conclude that addition of nalbuphine to bupivacaine provides better prevention from shivering, prolonged analgesia, superior pain relief and better sedation with minimal side effects compared to bupivacaine alone in spinal anesthesia. Since nalbuphine reaches ceiling effect at lower intrathecal dosage, the increased drug dosage is not required and this increases the safety margin. The combination of nalbuphine and bupivacaine in spinal anesthesia has shown to be superior in terms of preventing shivering, providing prolonged analgesia, superior pain relief, and better sedation with minimal side effects compared to using bupivacaine alone. The nalbuphine has a ceiling effect at a lower intrathecal dosage, which means that increasing the drug dosage is not required, leading to a higher safety margin. However, further research is necessary to validate these findings and determine the optimal dosage and timing of nalbuphine administration in spinal anesthesia.

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