Original Article

Indian Journal of Anaesthesia and Analgesia
Volume 3 Number 2, May - August 2016
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.3216.11

Prevention of Post-Anaesthetic Shivering After General Anaesthesia, Ondansetron Verses Butorphanol, A Randomized Double-Blinded, Placebo-Controlled Study

Sujeet Rai*, Sandeep Sahu, Apurva Agarwal***, Chitra****, Anil Verma***, H.D. Pandey******

Abstract

Background: Post-anesthetic shivering (PAS) is distressing for patients and may induce a variety of complications. The neurotransmitter pathways involved in the mechanism of post-anesthetic shivering are complex and poorly understood. We compared the effect of ondansetron (5-HT_3 antagonist) and butorphanol (agonist at "Kappa"-receptors and mixed agonist antagonist at mu opioid receptors) on intraoperative core and peripheral temperatures and PAS. *Methods:* After approval from institutional ethics committee and written informed consent 90 patients of age 18–60 years, ASA I-II, undergoing orthopedic, general or urological surgery were randomized into three groups. In this double-blinded, placebo-controlled, study: Group A (n = 30) received ondansetron 8 mg, Group B (n = 30) received Butorphanol, 25 µ gm / kg and Group C (n = 30) received saline 4 ml intravenous (IV) immediately before the anesthetic induction. Heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SPO_2), core (nasopharynx) and fingertip temperature (dorsum of middle finger) was recorded. Balanced general anaesthesia was induced by propofol 2.5 mg/kg and intubation was done with Vecuronium 0.1mg/kg. Anaesthesia was maintained with 70% N_2O in O_2 and propofol infusion. PAS was documented by persons blinded to the study and included trainees in anesthesiology who were unaware of the group assignment. *Results:* PAS occurred in 19 of 30 (63.3%) patients in Group C (saline), compared with 6 of 30 (20%) in ondansetron group (P = 0.002) and 7 of 30 (23.3%) in butorphanol group (P = 0.004). Within each group, core temperature decreased and peripheral temperature increased significantly, but there were no significant differences among the groups A and B at any time interval. *Conclusion:* We conclude that both, ondansetron (8 mg) and butorphanol (25 µ gm / kg) IV given during the induction of anesthesia prevents PAS equally without affecting the core-to-peripheral redistribution of heat during general anesthesia.

Keywords: Ondansetron; Butorphanol; Post-Anesthetic Shivering; General Anesthesia; Hypothermia.

Introduction

Incident hypothermia in homoeothermic human in intraoperative as well as early postoperative period leads to post anesthetic shivering (PAS). PAS is defined as an involuntary movement of one or several muscle groups, occurring in the early recovery phase due to general or regional anesthesia. The incidences are in between 5 to 65% and vary with age, sex, choice of drugs for induction and maintenance of anesthesia, and duration of surgery [1,2]. Besides the discomfort experienced by patients in the recovery period, shivering may increase tissue oxygen consumption (by 100–600%), cardiac output, carbon dioxide production, and circulating catecholamines, and furthermore significantly decrease the mixed venous oxygen saturation.

Although there is general agreement that it is a thermoregulatory phenomenon, a physiological response to anesthesia-induced core hypothermia leads central hypothermic and peripheral

Author's Affiliation:
*Assistant Professor, Department of Anesthesiology, Mahamaya Rajkiya Allopathic Medical college, Ambedkar Nagar. **Additional Professor, Department of Anesthesiology & Emergency Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow, UP. ***Associate Professor, ****Professor, Department of Anesthesiology, G.S.V.M. Medical College, Kanpur, UP, India.

Corresponding Author:
Sandeep Sahu, Additional Professor, Department of Anesthesiology & Emergency Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, 226014,India.
E-mail: drsandeepsahu@yahoo.co.in

vasoconstriction that may have some non-thermoregulatory component [3]. The neurotransmitter pathways conveying signals from hypothalamus to skeletal muscle are not clearly understood. But probably it involves multiple levels of information integration and numerous neurotransmitters [4,5]. There are several reports that IV administration of pharmacological agents like the opioids (meperidine, alfentanil, tramadol, nalbuphine) [6,9], clonidine [10], doxapram [11], physostigmine [12], ketanserine [13], ondansetron [14], granistron [15], dolansetron [16], ramosetron [17], ketamin [18] and dexmetomidine [19] have all reduced the incidence of shivering or suppressed established shivering. Besides pharmacological agents the non-pharmacological methods also decreases incidence of shivering [20,21].

5-HT impacts thermoregulatory responses through its action on different sites in the hypothalamus, medulla and midbrain. Buspirone, $5HT_1A$ partial agonist, acts synergistically with meperidine in reducing the threshold of shivering. In animal models, direct intra-ventricular injections of 5-HT influence body temperature and shivering [22]. All these observations suggest that the serotonergic system has a role in the control of post- anesthetic shivering. Ondansetron is a specific $5\text{-}HT_3$ antagonist has a role in neurotransmission may affect perioperative thermoregulation and PAS [14,22]. Butorphanol, an opioid agonist at 'Kappa' receptors and mixed agonist-antagonist at 'mu' opioid receptors may affect perioperative thermoregulation and PAS. Till now on reviewing literature, no study had compared ondansetron and butorphanol. Therefore, we compare the effectiveness of ondansetron and butorphanol premedication on the typical core-to-peripheral temperature redistribution evoked by general anesthesia and on the incidence of PAS, in this randomized, placebo-controlled, double-blinded study.

Material and Methods

After approval from institutional ethics committee and written informed consent 90 patients (ASA physical status I or II), scheduled for elective general, urological, orthopedic, otorhinolaryngeal and gynecological surgery were taken into the study. Exclusion criteria were allergy to ondansetron or butorphanol, surgery > 2 hr (surgeries duration more than two hrs excluded because keeping of similarities in subjects to avoid any chance of hypothermia), age <18 or > 60 yr, use of vasoconstrictors or vasodilators and pyrexial illness. All the Patients were randomly allocated by computerized randomization table into three groups (each 30 patients). Group A received ondansetron (8 mg), Group B received butorphanol (25 μ gm / kg) and Group C received IV saline, all the patients received total 4ml volume of drug or saline. These trial preparations were prepared fresh and by persons blinded to the study. The injection of trial medication was given immediately after placement of IV cannula and 5 min before induction of anaesthesia. Core temperature was recorded by using temperature probe by placing it in nasopharynx under aseptic condition and peripheral temperature was recorded by temperature probe on the dorsum of the middle finger of the hand opposite to IV infusion line. The fluid used perioperatively in all three groups was having temperature of 37^0C. Base line heart rate (HR), mean arterial pressure (MBP) and oxygen saturation were also recorded. These parameters were recorded every 10 min during surgery and postoperatively up to 1 hr. All patients were draped routinely and were not actively heated.

Analgesia was provided with injection Ketorolac 30 mg IM 1 hr before induction and after induction and injection diclofenac 75mg in 100 ml normal saline infusion run over 30 min in all three groups 30 min prior to skin closure. General anesthesia was induced with propofol 2.5 mg/kg and intubation was facilitated with vecuronium 0.1mg/kg. Anesthesia was maintained with nitrous in O_2 (70%), propofol infusion and vecuronium. PAS was documented by persons blinded to the study and included trainees in anesthesia. It was defined as readily detectable fasciculation or tremor of the face, trunk, or limb of 15 seconds duration. In the post anesthetic care unit (PACU) all the patients oxygen saturation were monitored by pulse oximetry and equipment for oxygen supplementation were kept ready bedside . All the patients who have surgeries lasting more than 2 hrs and having PAS in the post-operative period were oxygenated by nasal prongs at 3 l/min (surgeries duration more than two hrs excluded because keeping of similarities in subjects to avoid chance of hypothermia).The previous studies had found an incidence of PAS up to 40%–65%. We anticipated an incidence of 45% in the control group and took a difference of 40% in incidence of shivering between control and treated groups as being clinically meaningful. Hence, we prospectively calculated that 29 patients were required in each group for a Type I error of 0.05 and a Type II error of 0.2. One-way analysis of variance was used to analyze differences between the groups. Incidence of shivering was

analyzed by using Chi Square Test with Yates' correction and was expressed as mean ± SD, with $P < 0.05$, is considered significant.

Results

Demographic data (Table 1) and duration of anesthesia were comparable with in the groups.PAS was significantly reduced in patients receiving ondansetron compared with saline control (20% vs. 63.3% respectively, p = 0.002), and also in patients receiving butorphanol compared with saline control (23.3% vs. 63.3% respectively, p = 0.004). But there is no significant difference in the incidence of PAS between ondansetron group and butorphanol group (p = 0.754) (Table 2). Hemodynamic values, oxygen saturation (SpO2), are shown in figure 3, 4 and 5. There were no significant differences among the groups intraoperatively but MAP and HR values at recovery and in postoperative room show significant increase in control group as compared to ondansetron group or butorphanol group (p < 0.05). While oxygen saturation values in postoperative room shows significant decrease in saline group (control) as compared to ondansetron group or butorphanol group (p < 0.05), because as saline group having more incidence of PAS, so requirement of oxygen increased in this group (Figure 5). Because there is no incidence of warning hypoxia to any patient, but we continuously monitored by pulse oximetry and kept prepare the equipment for possibility of bedside oxygenation and supplementation, when saturation falls below 92% in any groups as per protocol in PACU. Core and fingertip temperature changes with the duration shown in Figures 1 and 2. Although core temperature decreased and fingertip temperature increased significantly in all groups with respect to baseline, but there were no significant temperature differences at any time among the groups.

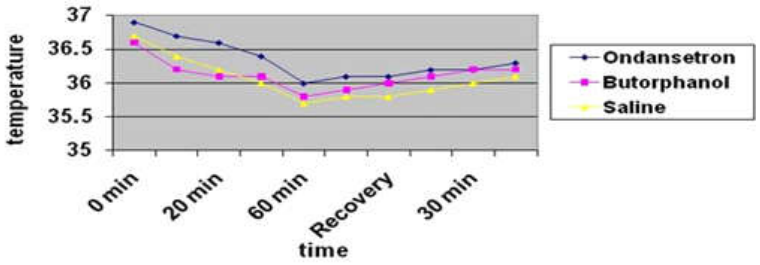

Fig. 1: Changes in core temperature: Data are expressed as mean with SD error bars. Temperature in all groups decreased significantly from baseline, but no significant differences among groups.

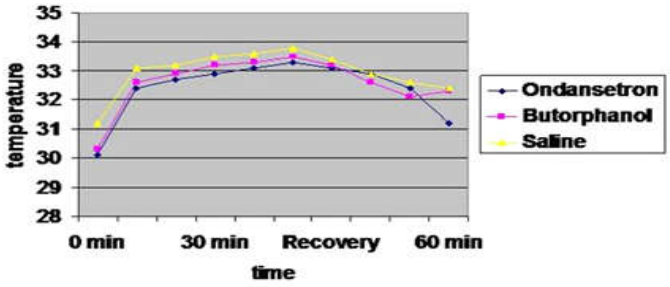

Fig. 2: Changes in peripheral temperature: Temperature in all groups increased significantly from baseline, but no significant differences among groups(mean with SD)

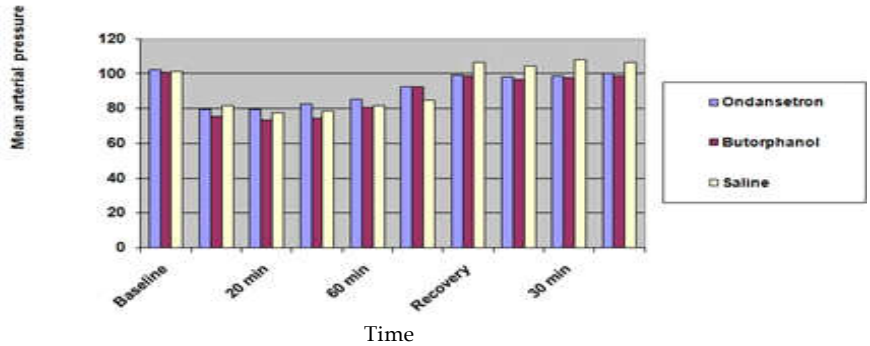

Fig. 3: Comparison of MAP in three groups

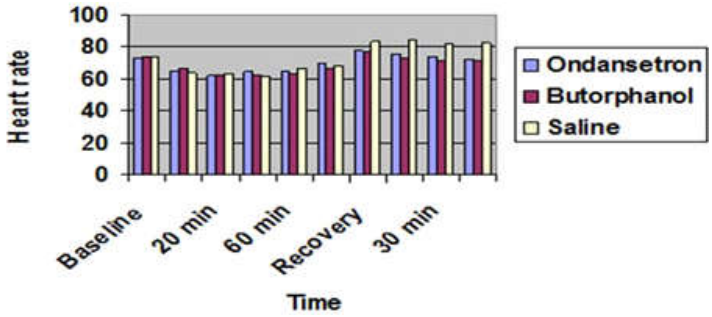

Fig. 4: Comparison of Heart Rate in three groups

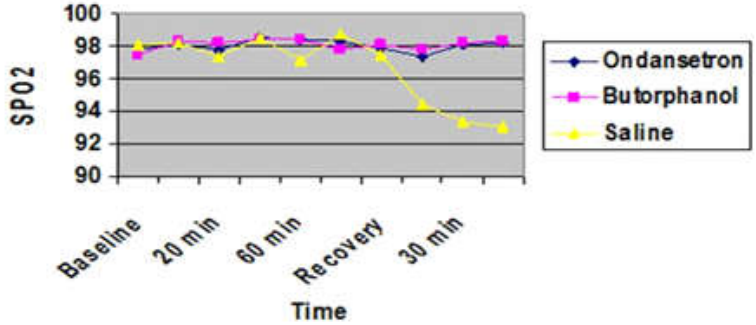

Fig. 5: Comparison of Oxygen saturation (SPo2) in all three groups

Table 1: Patients characteristics in three groups

	Ondansetron	Butorphanol	Saline
SEX(M:F)	22:8	23:7	20:10
AGE(Yrs.)	35.4±5.52	32.7±7.64	33.5±6.38
WEIGHT (Kg)	61.3±12.24	64.6±11.61	65.4±10.32

Data are mean ± SD, No group showed any significant differences in demo graphic profile among them.

Table 2: Incidence of shivering in three groups

	Ondansetron n=30	Butrophanol n=30	Saline n=30
Shivered	6(20.0%)	7(23.33%)	19(63.33%)
Did not shivered	24	23	11

p value = 0.002, control vs. ondansetron that is very significant
p value = 0.004, control vs. butorphanol that is very significant
p value = 0.754, ondansetron vs. butorphanol that is not significant

PAS was significantly reduced in patients receiving ondansetron and butorphanol as compared to saline control.

Discussion

Anesthesia induced thermoregulatory impairment and exposure to a cool environment makes most surgical patient hypothermic. Inadvertent hypothermia is associated with numerous adverse outcome PAS, is one of them in postoperative period [24,25]. We found the incidence of PAS was 63.3% in the saline group compared with 20% in the ondansetron (8 mg) group and 23.3% in the butorphanol (25 μgm / kg) group. We found that distinguishing between "mild," "moderate," and "severe" shivering on the basis of clinical observation alone will be highly subjective and of limited relevance [22].

Specific inhibition of the 5-HT_3 system by ondansetron produced statistically significant reduction in shivering. Perhaps 5-HT_3 inhibition has a specific antishivering effect, but given the variety of neurotransmitter systems known to be also involved in regulating shivering, an inhibitory effect at the 5-HT_3 receptor probably results from a generalized thermoregulatory inhibition at the level of the hypothalamus, where the bulk of thermoregulatory

control occurs [14,22].

Opoids also effects change in body temperature by acting on preoptic anterior hypothalamus,dorsal raphe nucleus,raphe magnus and locus coeruleus by increase formation of cyclic AMP, that increases thermosestivity in neuron [26]. At the same time butorphanol an agonist at 'Kappa'-receptors like meperidine and mixed agonist- antagonist at 'mu' opioid receptors like morphine (agonist) regulates its anti-shivering effect. This has been studied that for anti-PAS effect 'kappa' receptors are more important than 'mu' receptors [11]. It has a high affinity for 'kappa' -opioid receptors in the central nervous system, this was supported by the fact that meperidine also prevents shivering via kappa-opioid receptors because the anti-shivering effect of meperidine is also minimally impaired by small-dose naloxone, which blocks most μ-receptors and is diminished by large-dose naloxone, which blocks both ' mu' and 'kappa' receptors. Data suggests it may be more effective than fentanyl, morphine or even meperidine although it has not been studied in great detail [27].

These explanations are supported by our data on perioperative temperature. The anticipated core-to-peripheral redistribution of body temperature after the administration of general anesthesia is characterized by an approximate 1°C decrease in core temperature within the first 20–30 minutes after the induction, followed by an increase in fingertip temperature, measured at the skin [28]. This was unchanged in our patients who received ondansetron or butorphanol. Thus, the PAS effect of ondansetron or butorphanol is independent of intraoperative core hypothermia, suggesting that they inhibit thermoregulatory responses by a central mechanism. The extent of core hypothermia seems to be related to the degree of vasodilatation induced during anesthesia administration [28]. Ondansetron and butorphanol, both are notable for its lack of hemodynamic side effects [29] hence; their lack of effect on redistribution hypothermia is unsurprising. Ondansetron and butorphanol did not alter the hemodynamic profile of either group while it was significantly changed in control group in post-op period due to more incidence of shivering.

In contrast to some other drugs used to treat PAS like tramadol, doxapram, physostigmine, clonidine, ketamin and dexmetomidine all have unwanted cardiovascular effect. These are also commonly associated with postoperative nausea and vomiting. In contrast, ondansetron effectively relieves postoperative nausea and vomiting. Meperidine may potentially cause respiratory depression, which did not occur with butorphanol because it shows a ceiling effect on respiratory depression. So ondansetron and butorphanol, both could very plausibly be an attractive and alternative preventive treatment for PAS, especially as ondansetron has powerful antiemetic effects and a favourable cardio-respiratory profile and butorphanol has powerful analgesic effects [30].

The limitation of our study is that there are small numbers of patients in each arm.

However, the present study shows usefulness of ondansetron and butorphanol in prevention of PAS.

We have demonstrated that ondansetron 8mg and butorphanol 25μ gm / kg given before induction of anaesthesia effectively reduces the incidence of PAS equally in without effecting the core-to-peripheral redistribution of temperature that is normally observed during the administration of general anesthesia. PAS effect of ondansetron or butorphanol is independent of intraoperative core hypothermia, suggesting that they inhibit thermoregulatory responses by a central mechanism. Further studies are recommended to confirm our findings.

References

1. Oka M, Sawai T, Kajita I, Minami T. Assessment of factors leading to postanesthetic shivering in patients undergoing laparoscopic colectomy with total intravenous anesthesia using remifentanil. Masui. 2010; 59: 451-4.
2. Eberhart LH, Doderlein F, Eisenhardt G, Kranke P, Sessler DI, Torossian A, Wulf H, Morin AM.Independent risk factors for postoperative shivering. Anesth Analg. 2005; 101: 1849-57.
3. Stolwijk JAJ,Hardy JD. Regulation and control in physiology. In: Mountcastle VB, editor. Medical Physiology. 2ed.St. Louis: CV Mosby; 1974; p.1343-58.
4. M.A.Mahmood, Richard M. Zweifler. Progress in shivering control. Journal of the Neurological sciences. 2007; 261: 47-54.
5. Sessler DI. Perianesthetic thermoregulation and heat balance in humans. FASEB J. 1993; 7: 638–44.
6. Sessler DI. Thermoregulatory defense mechanisms. Crit Care Med. 2009; 37: S203-10.
7. Horn E-P, Sessler DI, Standl T, Schroeder F, Bartz H-J, Beyer J-C, Schulte am Esch J: Non-thermoregulatory shivering in patients recovering from is oflurane or desflurane anesthesia. Anesthesiology. 1998; 89: 878-86.
8. Wang JJ, Ho ST, Chun S, Liu YC. A comparison among

nalbuphine, meperidine and placebo for treating postanaesthetic shivering. Anesth Analg. 1999; 88: 686–9.

9. DeWitte J, Deloof T, DeVeylder J, Housmans PR. Tramadol in the treatment of postanaesthetic shivering. Acta Anaesthesiol Scand. 1997; 41: 506–10.
10. Buggy D, Higgins P, Moran C, O'Donovan F, McCarroll M. Clonidine at induction reduces shivering after general anaesthesia. Can J Anaesth. 1997; 44: 263–7.
11. Singh P, Dimitriou V, Mahajan RP, Crossley AW. Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. Br J Anaesth. 1993; 71: 685–8.
12. Horn EP, Standl T, Sessler DI, Von Knobelsdroff, Buchs C, Schulte am Esch J. Physostigmine prevents postanaesthetic shivering as does meperidine or clonidine. Anesthesiology. 1998; 88: 108–13.
13. Joris J, Banache M, Bonnet F, . Sessler DI, Lamy M. Clonidine and ketanserine both are effective treatment for postanaesthetic shivering. Anesthesiology. 1993; 79: 532–9.
14. Komatsu R, Orhan-Sungur M, In J, Podranski T, Bouillon T, Lauber R, Rohrbach S, Sessler D. Ondansetron does not reduce the shivering threshold in healthy volunteers. Br J Anaesth. 2006;96: 732-7.
15. Sajedi P, Yaraghi A, Moseli HA.Efficacy of granisetron in preventing postanesthetic shivering. Acta Anaesthesiol Taiwan 2008; 46: 166-70.
16. Bock M, Bauer M, Rösler L, Sinner B, Motsch J. Dolasetron and shivering. A prospective randomized placebo-controlled pharmaco-economic evaluation. Anaesthesist. 2007; 56: 63-6, 68-70.
17. Kim MS, Kim DW, Woo SH, Yon JH, Lee S. Effect of ramosetron on shivering during spinal anesthesia. Korean J Anesthesiol. 2010; 58: 256-9
18. Gecaj-Gashi A, Hashimi M, Sada F, Salihu S, Terziqi H.Prophylactic ketamine reduces incidence of postanaesthetic shivering. Niger J Med. 2010;19: 267-70.
19. Elvan EG, Oç B, Uzun S, Karabulut E, Co^{o}kun F, Aypar U. Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. Eur J Anaesthesiol. 2008; 25: 357-64
20. Butwick AJ, Lipman SS, Carvalho B. Intraoperative forced air-warming during cesarean delivery under spinal anesthesia does not prevent maternal hypothermia. Anesth Analg. 2007; 105: 1413-9
21. Galvao CM, Marck PB, Sawada NO, Clark AM. A systematic review of the effectiveness of cutaneous warming systems to prevent hypothermia. J Clin Nurs. 2009; 18: 627-36.
22. Dawson NJ, Malcolm JL. Initiation and inhibition of shivering in the rat: interaction between peripheral and central factors. Clin Exp Pharmacol Physiol. 1982; 9: 89–93.
23. Kelsaka E,Baris S,Karakaya D,Sarihasan B. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. Reg Anesth Pain Med. 2006; 31: 40–45.
24. Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. Drugs 2001; 61: 2193-205.
25. Pradeep K Bhattacharya, Lata Bhattacharya, R.K.Jain, R.C.Agarwal. Post Anaesthesia Shivering, a review. Indian Journal of Anaesthesia. 2003; 47: 88-93
26. William E. Post-operative shivering: Causes, prevention and treatment. Update in Anesthesiology. 2002: 15(3).
27. Vogelsang J, Hayes SR. Butorphanol tartrate (stadol) relieves postanesthesia shaking more effectively than meperidine (Demerol) or morphine. J Post Anesth Nurs. 1992; 7: 94-100
28. Rohm KD, Riechmann J, Boldt J, Suttner SW, Piper SN. Total intravenous anesthesia with propofol and remifentanil is associated with a nearly twofold higher incidence in postanesthetic shivering than desflurane-fentanyl anesthesia. Med Sci Monit. 2006; 12: 452-6.
29. Del Pizzo A, A double blind study on the effects of butorphanol compared with morphine in balanced anesthesia. Can Anaesth Soc J. 1978; 25: 392-7.
30. Juneja M, Ackerman III, Heine MF, Cases-Cristobal V, Urella RP, Rigor BM. Butorphanol for the relief of shivering associated with extradural anesthesia in parturients. J Clin Anaesth. 1992; 4: 390-3