

The Comparative Efficacy of Nalbuphine and Tramadol in Controlling Postoperative Shivering in Rabbits

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Abstract

Background: Postoperative shivering is a major dilemma in most major surgeries. It is a consequence of perioperative hypothermia, attributed to the use of obsolete anesthetic regimens being used in the field of veterinary medicine. Shivering is a protective mechanism to compensate for the thermoregulatory status of the individual. This phenomenon is most aptly observed in small mammals and rodents while recovering from anesthesia induced by ketamine and xylazine combination. **Objectives:** This study used rabbits as a model to demonstrate and qualitatively analyze the comparative efficacy of nalbuphine and tramadol to control postoperative shivering. **Materials and Methods:** Twenty rabbits were randomly divided into three different groups, i.e., A, B, and C. The average values of temperature, pulse, and respiration in Group A (control) were 101.37 ± 0.99 , 112 ± 27.32 , and 80 ± 10.06 , respectively. **Results:** Similarly, the values of these parameters obtained from Group B (nalbuphine) were 102.37 ± 0.67 , 102.8 ± 29.68 , and 74.9 ± 28.72 as compared to Group C (tramadol) were 101.79 ± 0.82 , 102.3 ± 22.47 , and 66.8 ± 14.55 . The incidence of postoperative shivering was significantly lesser in Group B, whereby 80% of the individuals completely stopped shivering, whereas in case of Group C, only 65% of the individuals underwent complete cessation of shivering. **Conclusion:** administering opioids perioperatively can profoundly inhibit the incidence of postanesthetic shivering and may counteract the malicious effects of anesthesia and surgical procedure.

Keywords: Nalbuphine, opioid drugs, postoperative shivering, thermoregulation, tramadol

INTRODUCTION

Postoperative shivering is a major issue after prolonged surgeries, requiring a large volume of fluid to be infused intravenously and abdominal viscera being exposed for lengthy periods of time.^[1] It has been reported that the occurrence of perioperative shivering (i.e., tremor) is rampant in small animals and pet rodents.^[2] Nowadays, the incidence of postoperative trembling or shivering is reduced to minuscule numbers due to mitigating drugs being administered postoperatively.^[3] Furthermore, opioids administered concurrently can maintain normothermia peri- and postoperatively.^[4] Hypothermia during and after surgery is possibly a grave impediment toward smooth anesthetic recovery.^[5] Shivering after surgery can be managed by improving oxygen perfusion with the help of artificially ventilating the lungs with a 100% oxygen supply.^[6] Yet, the most effective manner to control shivering during anesthetic recovery has been attributed to the administration of opioid drugs.^[7] During the past few decades, tramadol has emerged as a revolutionary drug which can

liberate 5-hydroxyl tryptamine, responsible for triggering mu and kappa receptors and diminishing postoperative shivering.^[8] Mu and kappa are the most important among the opioid receptors. A higher affinity for mu receptor elicits a more potent opioid analgesic effect, though drugs which have a relatively higher affinity for kappa and delta receptors cause the least amount of adverse effects as well.^[9] In homeothermic species, a thermoregulatory system adjusts the internal temperature of the body.^[10] Most anesthetic mixtures adversely affect the maintenance of the body temperature consequently leading to hypothermia in patients recovering from surgery.^[11]

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Trembling is not exclusively observed in cases with postoperative hypothermia (i.e., 50%–60% afterward volatile anesthesia). The rationale of shivering is still not well understood.^[12] Trembling is a troublesome and recurrent problem in the time after the operation.^[13] Although many mechanisms have been proposed, the initiation point of trembling is poorly understood.^[12] Trembling may also be associated with hyperactivity of the muscle causing clonic or tonic convulsions.^[14]

Certain mechanisms other than loss of heat following a reduction in core temperature may also be responsible for developing shivers.^[15] Other factors responsible for postoperative shivering may be attributed to postoperative pain, uninhibited spinal reflexes, pyrogen release, decreased sympathetic activity, respiratory alkalosis, and adrenal depression.^[16] Trembling is an involuntary muscular movement that increases the metabolic production of heat. Robust trembling enhances metabolic production of heat up to 400%–600% from the basal level.^[17] When patients are transferred from operation theater to the recovery unit, if the ambient temperature is not properly controlled, patients experience a change in core body temperature.^[18] Feeble postoperative core hypothermia can enhance complications such as contamination of the wound, cardiac arrhythmia, bleeding, and an extended peri-anesthetic care unit state.^[19] Furthermore, the excellence of recovery in anesthetized patients can also be compromised due to thermal discomfort and shivering. More often than not, trembling also hinders monitoring techniques by an increase in intracranial and intraocular pressure.^[20]

Many drugs are credited with effective anti-shivering properties, among which we studied the comparative efficacy of tramadol and nalbuphine. Tramadol is an anti-shivering drug that prevents the reuptake of dopamine and norepinephrine and aids in 5-hydroxytryptamine release.^[15] Nalbuphine is a semi-synthetic, lipophilic opioid related to both naloxone and oxymorphone.^[21] Nalbuphine is widely used as postoperative analgesia; furthermore, it can have a significant effect on postanesthetic shivering.^[22]

This study was designed to investigate the comparative anti-shivering effects of nalbuphine and tramadol in rabbits postoperatively.

MATERIALS AND METHODS

Animal model

In this randomized experimental study, 60 rabbits of 1–2 kg body weight were included, on which castration was planned. All individuals were housed under comparable conditions fulfilling all their living requirements.

Groups

Animals were randomly divided into three different groups (control, Group A, and Group B) with 20 rabbits in each group. Rabbits were kept off feed before the surgery.

Study design

Castration was performed under general anesthesia induced

by administering xylazine (Xalyz[®], Farvet) at the dose rate of 5 mg/kg and ketamine HCL (Ketarol[®], Global pharmaceuticals) at a dose rate of 50 mg/kg body weight intramuscularly.

Immediately after the surgery, all rabbits from Group A were injected tramadol (T-Mod[®], Fynk) at a dose rate of 2 mg/kg, while rabbits from Group B were administered nalbuphine (Nalbin[®], Global pharmaceuticals) at a dose rate of 1 mg/kg. All animals of the control group were given a placebo (normal saline at 0.2 ml/kg). All the drugs were administered intramuscularly.

A baseline reading of vital signs (temperature, pulse, and respiration rate) was recorded immediately before the induction of anesthesia followed by observations of these parameters at every 5-min intervals for the next 30 min.

After the administration of agents in all three respective groups, the animals were monitored for the emergence of shivering by an experienced veterinary anesthesiologist. The potency of the drugs was assessed based on the effectiveness of their ability to diminish the incidence of shivering.

Patients in Group A receiving tramadol and patients in Group B getting a dose of nalbuphine were further categorized into three groups: complete cessation, partial cessation, and no cessation of the shivering.

Statistical design

One-way analysis of variance (ANOVA) was used to analyze the level of significance among the physiological parameters (temperature, pulse, and respiration rate) between different groups. Chi-square test was used to quantify and evaluate the postoperative shivering among groups.

RESULTS

The mean values of temperature, pulse, and respiration (10 values with 3-min interval each) in all groups (control, nalbuphine, and tramadol) were shown in Tables 1-3 and Figures 1-3 respectively. In Table 1, temperature variation is evident in all the three groups. The group injected with nalbuphine showed the least decrease in temperature from the normal mean values followed by tramadol-treated group. The animals from the control group treated with placebo showed the greatest temperature fall. This trend is illustrated in Figure 1.

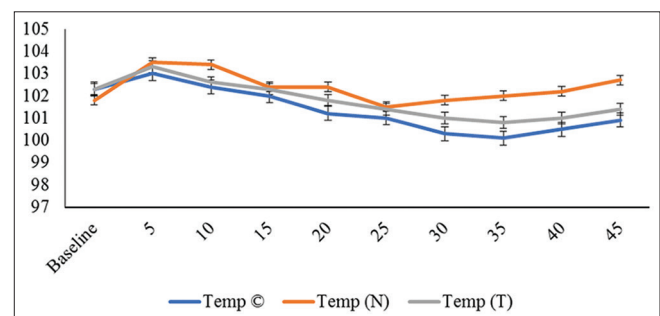


Figure 1: Line graph demonstrating the changes in temperature values postoperatively during the initial 45 min postoperative

Table 1: Presenting periodic temperature changes during the first 45-min postoperative in Group A, B, and C with average values given in the last column

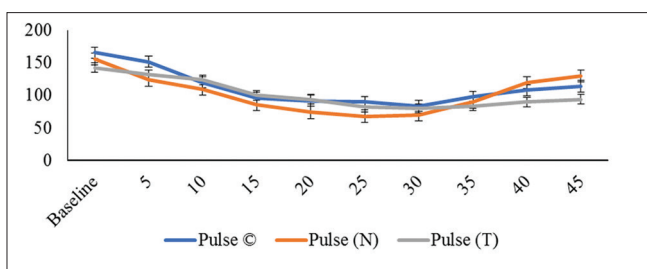
Groups	Baseline	5	10	15	20	25	30	35	40	45	Overall average
Group A ©	102.3	103	102.4	102	101.2	101	100.3	100.1	100.5	100.9	101.37 ± 0.99
Group B (N)	101.8	103.5	103.4	102.4	102.4	101.5	101.8	102	102.2	102.7	102.37 ± 0.67
Group C (T)	102.3	103.3	102.6	102.3	101.8	101.4	101	100.8	101	101.4	101.79 ± 0.82

Table 2: Presenting periodic pulse rate (per minute) changes during the first 45 min postoperative in Group A, B, and C with average values given in the last column

Groups	Baseline	5	10	15	20	25	30	35	40	45	Overall average
Group A ©	166	152	120	96	92	90	84	98	108	114	112 ± 27.32
Group B (N)	156	124	110	86	74	68	70	90	120	130	102.8 ± 29.68
Group C (T)	143	132	124	100	94	82	80	84	90	94	102.3 ± 22.47

Table 3: Presenting periodic respiration rate (per minute) changes during the first 45 min postoperative in Group A, B, and C with average values given in the last column

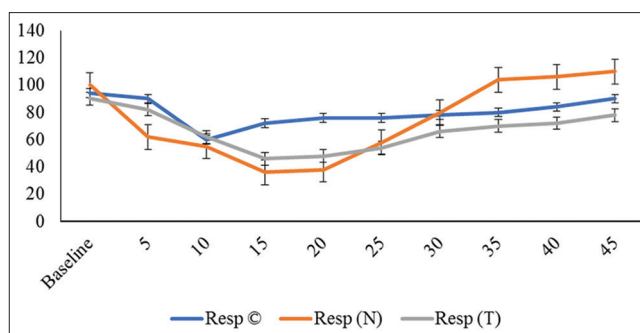
Groups	Baseline	5	10	15	20	25	30	35	40	45	Overall average
Group A ©	94	90	60	72	76	76	78	80	84	90	80 ± 10.06
Group B (N)	100	62	55	36	38	58	80	104	106	110	74.9 ± 28.72
Group C (T)	90	82	62	46	48	54	66	70	72	78	66.8 ± 14.55

**Figure 2:** Line graph demonstrating the changes in pulse rate (per minute) values postoperatively during the initial 45 min postoperative

The variation in pulse rate for all the three treated groups is given in Table 2. Group B showed a maximum decrease in pulse rate after drug administration with a gradual increase post 30 min from the baseline, achieving the lowest pulse rate among all the groups. Group A exhibited an intermediate increase in pulse rate with respect to other groups. The control group animals exhibited least decline in pulse rate. Figure 2 illustrates the pulse rate of all the groups.

The significant decrease in respiration rate was observed in Group B, followed by a steep increase up to 30 min post baseline, and afterward, this abrupt increase was normalized. The dynamic trend for respiration rate remained nonsignificantly different in Group A in comparison to Group B and C. These trends have been illustrated in Table 3 and Figure 3.

The relative extent of improvement in shivering control (complete, partial, or no improvement) in all the three groups

**Figure 3:** Line graph demonstrating the changes in respiration rate (per minute) values postoperatively during the initial 45 min postoperative

(control, nalbuphine, tramadol) has shown in Table 4. In the control group, 19 animals (19/20; 95%) showed shivering after anesthesia. During the period of 45-min postanesthetic administration of placebo (normal saline), only 1 animal (01/20; 5%) showed any signs of improvement from shivering.

In Group B, shivering stopped completely in 16 animals (16/20; 80%) within 25 min of drug administration, while 3 animals (03/20; 15%) showed partial improvement, while 1 animal (1/20; 5%) failed to display any improvement in shivering. In Group A, 13 of 20 animals (13/20; 65%) completely improved within 25 min of drug administration, 5 animals (05/20; 25%) partially improved, whereby 2 animals (02/20; 10%) exhibited no improvement in shivering whatsoever. We evaluated these data with Chi-square test, and there was a significant difference between nalbuphine- and tramadol-treated groups in postoperative shivering control Figure 4.

Table 4: Presenting percentage (%) values of cessation (no cessation, partial, and complete) postoperative in Group A, B, and C

Shivering	Control	Nalbuphine	Tramadol
Complete cessation (%)	0	80	65
Partial cessation (%)	5	15	25
No cessation (%)	95	5	10

DISCUSSION

Shivering is a consequence of most anesthetic regimens, whereby parental administration of these agents may affect vascular dilatation and distribution of blood across the circulatory system.^[23] The rabbits in our current study were considerably more hypothermic perioperatively than the humans who were previously evaluated. It has been established that in most mammals core hypothermia and on lesser instances normothermia are observed during the surgery, though it is often followed by shivering.^[24] Shivering is considered to be indirectly related to increased plasma concentrations of adrenergic agonists which may cause cardiac myopathies.^[25] Normothermia can be maintained by specialized equipment that is quite effective in negating the consequences of loss in core temperature, though such instruments are relatively expensive. Furthermore, such measures are rarely feasible in all circumstances.^[26]

In our study, the individuals injected with nalbuphine and tramadol showed a maximum decrease in pulse rate after drug administration with a gradual increase post 30 min from the baseline. However, individuals injected with placebo dose had significantly higher pulse rates which corroborates previously established precedents (Morgaz *et al.*, 2013)^[27] as hypertension and vasoconstriction are shore shot signs of mild hypothermia. It was also observed that in patients suffering from postoperative shivering, there was pronounced tachypnea which eluded to higher oxygen consumption.^[28] In our study, the individuals treated with tramadol had considerably lower respiration rates than the individuals in the control group, though respiratory values of individuals treated with nalbuphine were not that far off from the normal respiratory values in rabbits either. The relatively severe bradypnea caused by tramadol is indicative of its unique and dual mechanism of action.^[29] Tramadol exerts agonistic properties at opiate receptors and interferes with neurotransmitter reuptake.^[30] It was supported by our experimental data that tramadol has an affinity for both kappa and mu receptors evident by its profound effect on the respiratory system as compared to nalbuphine.^[31,32] Previous comparative studies with other analgesics have revealed that tramadol is equivalent in efficacy to meperidine but is five times less potent than nalbuphine as an analgesic drug.^[33]

As drugs were administered in respective groups, clinical thermometry revealed that the average body temperatures for

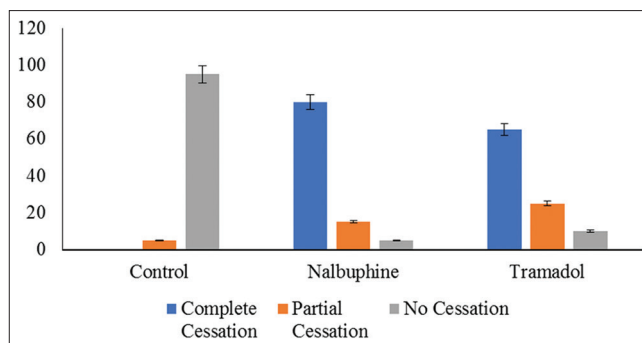


Figure 4: Line graph demonstrating percentage (%) cessation (no cessation, partial, or complete) values postoperatively during initial 45 min postoperative

individuals in the control group varied most significantly from the normal baseline during the period of anesthetic recovery, while individuals, which were administered opioids, showed no such deviation. However, individuals in Group B which were administered nalbuphine adhered much better to the normal temperature baseline than any other group.^[34] This phenomenon of postanesthetic temperature depression may be due to the pharmacodynamics and dose of an anesthetic agent which is used. Some agents may cause serotonin inhibition, which is known to have a direct effect on shivering.^[35] It was postulated that an inhibitory effect on the 5-HT₃ receptor might result from a generalized thermoregulatory inhibition at the level of the hypothalamus which may cause the redistribution of heat from the core to the peripheral parts of the body, causing a 1°C fluctuation in core temperature after the induction of anesthesia.^[36,37] Our clinical findings were concomitant with the previous data.

There is considerable evidence which suggests that shivering, unlike other thermoregulatory responses, is largely controlled by the spinal cord.^[38] Consequently, anesthetic-induced inhibition of shivering is believed to be caused by dose-dependent alterations of afferent thermal processing at the level of the spinal cord.^[39] Studies have suggested that opioids having a high affinity for kappa receptors may have a vital role in the modulation of perioperative shivering.^[40] Both nalbuphine and tramadol have a high affinity for kappa receptors; yet, in our study, nalbuphine proved to be far more efficacious in controlling anesthesia-related shivering than tramadol.^[41] This suggests that unlike tramadol, nalbuphine exerts its effects on specific receptors present in both the central nervous system and spinal cord. Geriatric and fragile patients are known to show decreased incidence and frequency of postanesthetic shivering, as it is an active physiological process requiring energy and vitality.^[42] Similarly, shivering is seldom accompanied with hypoxia because shivering is inhibited by hypoxia.^[43]

Based on the review of literature, it was postulated that there was a wide array of risk factors responsible for the development of hypothermia in patients. These factors included preoperative baseline core temperature, room temperature of operation theater, age and bodyweight of the patient, and invasiveness

of surgical incision.^[16] Several preparations have been used to mitigate shivering such as tramadol, clonidine, doxapram, propofol, physostigmine, nefopam, and ketanserin. Opioids have always been most exhaustively employed in such scenarios.^[44]

CONCLUSIONS

Most autonomic thermoregulatory defenses are easily elicited during anesthesia by enough core temperature perturbations. Our data confirm this clinical impression as shivering was observed in 95% of the individuals in the control group. About 65% of the patients receiving tramadol experienced total cessation, while nalbuphine proved to be a superior anti-shivering agent with an 80% success rate for the rectification of postoperative shivering. We, therefore, conclude that administering opioids perioperatively can profoundly inhibit the incidence of postanesthetic shivering and may counteract the malicious effects of anesthesia and surgical procedure.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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