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A COMPARISON OF NALBUPHINE AND PENTAZOCINE IN CONTROLLING POST-OPERATIVE PAIN IN DOGS

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ABSTRACT

Surgical success in most cases is governed by the quality of post-operative pain management. In Pakistan, most veterinary surgeons face a dire predicament as they fail astutely in this regard. Owing to the controlled dispensing of potent narcotics and their potential misuse, an imperative need for effective post-operative analgesic management of pain exists in dogs. 32 dogs were randomly divided into two groups. Group A was injected Nalbuphine @ 0.5 mg/kg post-operatively while Group B was injected Pentazocine @ 3mg/kg. Subjective and objective analysis of pain was conducted by unbiased observers. Vital signs (Temperature, pulse, respiration) were analyzed along with supplementation of hepatic and renal function tests. Objective and subjective analysis of both groups yielded results in the favor of pentazocine. In group A, temperature, pulse and respiration averaged 101.86±0.58°F, 83.46±2.75 per minute and 19.26±2.14 per minute respectively. Group 2 demonstrated temperature, pulse and respiration averages of 102.31±0.40°F, 83.41±2.74 per minute and 19.54±2.14 per minute respectively. Values of hepatic and renal function were also observed to be significantly higher in Nalbuphine treated group. All the results indicate that pentazocine is not only a significantly better analgesic but also has lower hepatotoxic and renal toxic effects.

KEYWORDS

Pentazocine, Nalbuphine, Analgesia, Pain assessment, Post-operative pain management.

1. INTRODUCTION

It is imperative to manage post-operative pain in dogs, as this physiological pain has far reaching pathological consequences [1]. For years narcotic agents have been considered most effective in controlling post-operative pain. But use of opiates has been repeatedly associated with sedation, dysphoria, cardiovascular and respiratory depression [2]. In Pakistan, highly potent natural opioids are considered as controlled substances and bearing in mind their lack of availability and possible misuse, synthetic opiates prove to be good alternatives [3]. As synthetic opiates have proven to be equally effective in controlling moderate pains while their affinity for mu receptors being very low causes less pronounced sedative and euphoric effects [4]. Furthermore, agents such as pentazocine and nalbuphine though being slightly addictive pose very little risk of misuse in veterinary practice settings [5].

Pentazocine is a narcotic analgesic with mixed agonist and antagonist activity. It is more potent than codeine but less effective than morphine [6]. Significant analgesia occurs within 15 to 20 minutes after IM injection in dogs [7]. It is available in both oral and injectable formulations. Pentazocine is used to control mild to moderate postoperative pain. Pentazocine is more or less tolerable in most Dogs but acute toxicity may result in sinus tachycardia, hypotension, hypoventilation and Nystagmus [8].

Similar to pentazocine, nalbuphine is also a synthetic opiate which is chemically related to oxymorphone [9]. Nalbuphine exerts its effects by binding to specific opiate receptors present in the central nervous system. It has antagonistic activity at Mu receptors and an agonist at the Kappa and

Delta receptors [10]. It is speculated that Nalbuphine is capable of altering the perception of pain as well as emotional response to it [11]. The use of Nalbuphine in veterinary practice has not been extensively reported, though the purpose of this study is to investigate Nalbuphine and compare it with Pentazocine for efficacy and adverse effects.

Both Nalbuphine and Pentazocine have been a staple part of post-operative analgesic management in human medicine for last few decades. Yet, its application in veterinary practices has faced skepticism and unilateral incoherence of research [11]. Consequently, our study focused on similarly placed analgesics on opioid scale suitable for instances where more potent opioids were either unavailable due to legal constraints or their cost was a limiting factor. Naloxone and pentazocine target kappa and delta opioid receptors more actively as compared to mu receptors. This leads to their decreased potency but also reduces the effects of withdrawal along with post-operative addictions [12]. Though, addiction to chronic pain management is rarely observed in veterinary practices but misuse by the owners and attendants is a valid concern for the pharmaceuticals as well as drug enforcement agencies [13].

2. MATERIALS AND METHODS

All animals were treated humanely. This study was conducted at Riphah College of Veterinary Sciences. The study period was from September 2017 to February 2018. 32 dogs were used in this study. All dogs were stray mongrels caught for the purpose of spaying. All dogs aged between 3-4 years and weighed approximately 15-20 kgs. Dogs were treated with pyrantel pamoate as they were brought to the clinic. These dogs were immunized for rabies as well.

2.1 Surgical procedure, anesthesia and analgesia

Female dogs were randomly assigned into two groups with each having 16 dogs (n=16). Each of these groups namely Group A and Group B were given analgesia with either Nalbuphine or Pentazocine respectively prior to initiation of surgical protocol. Consequently, Female Dogs in Group A were administered Nalbuphine at a dose rate of 0.5mg/kg bwt while Female Dogs in Group B received 3mg/kg bwt at hour 0. Before anesthetic induction all dogs were premedicated with atropine at a dose rate of 0.02mg/kg SC and sedated with Xylazine at dose rate of 0.5mg/kg IM. Anesthesia was induced with a cocktail of Diazepam at 0.5mg/kg and Ketamine at 10mg/kg Intravenously. Dogs were maintained in anesthesia with Isoflurane at MAC₅₀=1.2 and 100% Oxygen. A surgical plane of anesthesia was assessed by standard clinical monitoring techniques and closely supervised by an anesthetist.

All dogs underwent Ovariohysterectomy according to the standard procedure described in the Textbook of Small Animal Surgery by Slatter [14]. Animals were allowed to recover from anesthesia and monitored for signs of discomfort and pain. Analgesic effects of Nalbuphine and pentazocine were monitored after extubation. All dogs in Group A and Group B received pain medication at every six-hour interval for 24hours. The analgesic effect of either regiments was monitored during the 24hr period for each dog.

2.2 Analgesic Assessment

After extubating, Physiological Parameters (Temp, Pulse and Respiration), Behavioral Activities and Pain scores for all dogs were recorded every 3hours for the next 24hour period. All dogs were allowed to recover in a cage until their body temperature normalized. Then they were taken to a run 3x2.5m, where physiological parameters and playing activity was assessed. The pain scores (objective analgesic assessment) and overall efficacy scores (Subjective analgesic assessment) were analyzed separately [15].

2.3 Subjective Analgesic assessment

All dogs were analyzed based upon their degree of normalcy and comfort. They were scored based upon their responses to stimuli and overall exuberance. At the end of the study efficacy scores for Group A (Nalbuphine) and Group B (Pentazocine) were compared.

Pain Scores (objective analgesic assessment)			
Sr. No.	Signalment	Evaluation	Score
1	Vocalization	None, Intermittent or Persistent	0-2
2	Movement	Calm, Restless or thrashing	0-2
3	Respiratory Pattern	Normal or abdominal	0-2

2.4 Objective analgesic assessment

Animals were scored based upon their degree of discomfort. All dogs were scored as per their frequency of vocalization, movement and abnormally erratic respiratory patterns. With higher scores being given to poorer performances. Scores for Group A and Group B were compared and statistically analyzed.

2.5 Renal and Hepatic effects

A sample of serum was collected before surgical procedure to establish baseline values for LFT and RFT in all Female Dogs. Serum Urea, Creatinine and Alanine aminotransferase (ALT) values were evaluated post operatively at 24 and 48 hr. intervals. Change in these values for all individuals were compared with baseline values.

2.6 Statistical Analysis

All the physiological norms (temperature, pulse, respiration) were analyzed by One-Way ANOVA while subjective and objective analgesic scoring was analyzed by the use of non-parametric Kruskal-Wallis test. Moreover, parameters of serum analysis (ALT, Creatinine and Serum urine) were evaluated via One-Way ANOVA.

3. RESULTS

Physiological parameters were observed, every three hours during post-operative 24-hour period. Study revealed that temperature of animals belonging to group A and group B differed significantly during all time intervals. All the temperature values of animals belonging to group B (Pentazocine) were higher (closer to normal) in all the time intervals. Detailed values at different time durations are given in Table 1. Trend-line showed a dynamic change in temperature readings with values of group B animals averaging closer to the normal body temperature (Figure 1).

Table 1: Temperature values at different time intervals during first 24-hours post-operative.

Parameter	0 hour	3 hours	6 hours	9 hours	12 hours	15 hours	18 hours	21 hours	24 hours
Group A (Nalbuphine)	101.525±0.61 ^B	100.98±0.56 ^B	101.5±0.45 ^B	101.975±0.81 ^B	101.18±0.32 ^B	102.38±0.73 ^B	102.15±0.41 ^B	102.57±0.52 ^B	102.48±0.28 ^B
Group B (Pentazocine)	101.656±0.54 ^A	102.00±0.71 ^A	102.3±0.64 ^A	102±0.57 ^A	102.07±0.51 ^A	102.53±0.87 ^A	102.76±0.47 ^A	102.83±0.69 ^A	102.61±0.52 ^A

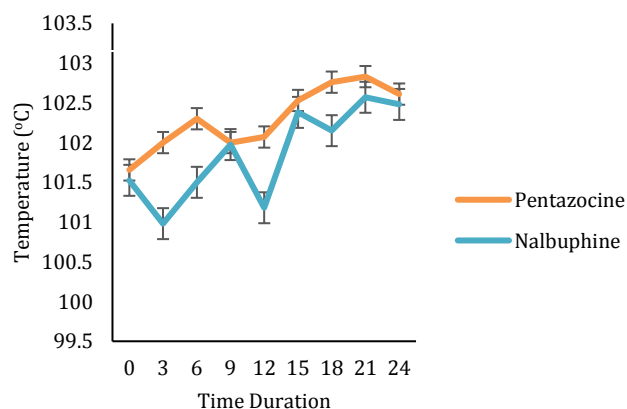


Figure 1: Line graph showing temperature (Mean ± S. E) at different time intervals during first 24 hours post-operative after injecting Pentazocine and Nalbuphine.

Pulse rate was recorded on per minute basis after every three hours post-operatively. Pulse rate at zero time, 9 and 18 hours differed insignificantly between the two groups. Moreover, pulse rate was significantly higher in group B animals during initial readings such as 3, 6 and 12 hours. On the contrary, pulse rate was recorded to be significantly higher in animals belonging to group A during last phase of the study. Readings obtained at 15, 21 and 24 hours were evident of this phenomenon. A comprehensive account of the pulse rate values is given in Table 2. Trend-line analysis demonstrated that during first few hours, pulse rate was lower in animals of group B with becoming more stable as time duration passed (Figure 2).

Table 2: Pulse Rate (Per minute) values at different time intervals during first 24-hours post-operative.

Parameter	0 hour	3 hours	6 hours	9 hours	12 hours	15 hours	18 hours	21 hours	24 hours
Group A (Nalbuphine)	82.88±2.69 ^A	87.69±2.57 ^A	81.94±2.81 ^A	82.88±2.54 ^A	79.56±2.61 ^A	83.44±2.59 ^B	88.13±2.68 ^A	82.13±2.19 ^B	82.56±2.31 ^B
Group B (Pentazocine)	84.94±2.51 ^A	84.94±2.56 ^B	80.63±2.37 ^B	80.56±2.64 ^A	79.19±2.21 ^B	86.25±2.71 ^A	85.88±2.09 ^A	84.19±1.97 ^A	84.13±2.03 ^A

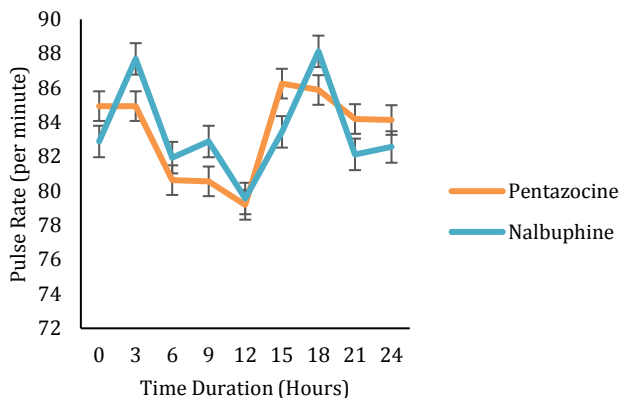


Figure 2: Line graph showing pulse rate (Mean ± S.E) at different time intervals during first 24 hours post-operative after injecting Pentazocine and Nalbuphine.

The third physiological parameter (respiration rate) showed a different trend as compared to afore-mentioned parameters. It was also recorded on per minute basis after every three hours similar to the pulse rate. Respiration rate was found to be statistically higher in group B animals at all time durations except at 18, 21 and 24 hours where respiration rate was found to be non-significantly different among two groups. A detailed analysis of the respiration rate is given in Table 3. The trend-line of respiration rate values shows that both lines come very close to each other during last three readings as the results are non-significantly different (Figure 3).

Table 3: Respiration Rate (per minute) values at different time intervals during first 24-hours post-operative.

Parameter	0 hour	3 hours	6 hours	9 hours	12 hours	15 hours	18 hours	21 hours	24 hours
Group A (Nalbuphine)	19.31±2.31 ^B	19.44±2.25 ^B	17.313±1.91 ^B	16.063±1.87 ^B	16.688±2.36 ^B	22.00±2.48 ^B	21.313±1.92 ^A	20.00±2.01 ^A	21.188±2.17 ^A
Group B (Pentazocine)	19.5±2.12 ^A	20.13±2.18 ^A	17.563±2.35 ^A	17.188±1.96 ^A	17.5±1.99 ^A	22.19±2.16 ^A	21.76±2.12 ^A	20.063±2.17 ^A	19.938±2.10 ^A

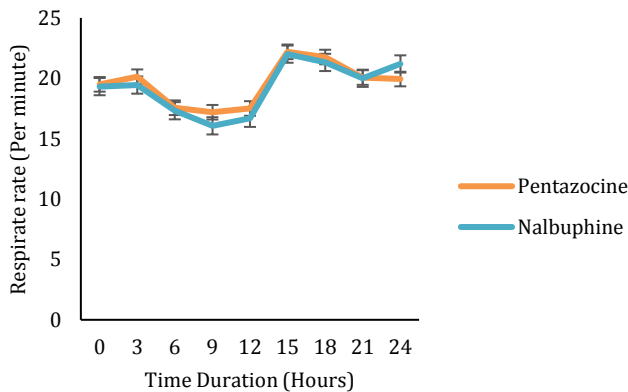


Figure 3: Line graph showing respiration rate (Mean ± S.E) at different time intervals during first 24 hours post-operative after injecting Pentazocine and Nalbuphine.

Table 4: Subjective analgesic scoring values at different time intervals during first 24-hours post-operative.

Parameter	6 hours	12 hours	18 hours	24 hours
Group A (Nalbuphine)	2 ^A	3 ^B	3 ^B	3 ^A
Group B (Pentazocine)	2 ^A	3.5 ^A	3.5 ^A	3 ^A

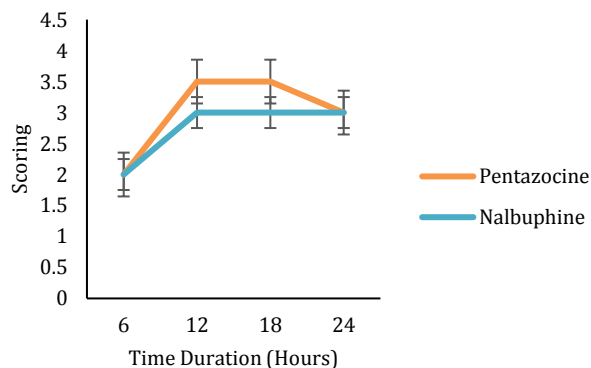


Figure 4: Line graph showing subjective analgesic scoring (Mean ± S.E) at different time intervals during first 24 hours post-operative after injecting Pentazocine and Nalbuphine.

Analgesic efficacy scoring was done subjectively and objectively. Both types of scoring were analyzed via Kruskal-Wallis statistical test. Study revealed that group B animals showed a significantly higher degree of analgesic efficacy at 12 and 18 hours post-operatively. Contrarily, analgesic efficacy scoring was non-significantly different during 6 and 24 hours (Table 4). Trend-line demonstrates overall higher degree of scoring in animals belonging to group B (Figure 4). Similarly, objective analgesic scoring revealed that the group A animals showed significantly higher degree of scoring at 6,12 and 18 hours post-operatively. On the contrary, degree of scoring at 24 hours was found to be non-significantly different (Table 5). Trend-line demonstrates that the scoring curve of group B animals was overall lower in the chart as compared to group A animals.

Table 5: Objective analgesic scoring values at different time intervals during first 24-hours post-operative.

Parameter	6 hours	12 hours	18 hours	24 hours
Pentazocine	2 ^B	2.5 ^B	2 ^B	2 ^A
Nalbuphine	3 ^A	3 ^A	3 ^A	2 ^A

Laboratory analysis demonstrated that group A animals were experiencing higher hepatorenal toxicity attributed to elevated ALT and Serum urea levels compared to animals of group B. Detailed values are given in Table 6, 7. Creatinine levels were observed to be significantly higher in group B animals receiving pentazocine. Detailed values are given in Table 8.

Table 6: ALT level at different time intervals during first 24-hours post-operative.

Parameter	Baseline	24 hours	48 hours
Pentazocine	40.25±1.25 ^B	52.31±1.11 ^B	45.31±1.19 ^B
Nalbuphine	46.19±1.09 ^A	80.25±1.47 ^A	74.25±1.54 ^A

Table 7: Serum Urea level at different time intervals during first 24-hours post-operative.

Parameter	Baseline	24 hours	48 hours
Nalbuphine	19.19±0.27 ^A	23.75±0.34 ^A	15.75±0.29 ^B
Pentazocine	16.75±0.20 ^B	19.75±0.23 ^B	18.44±0.31 ^A

Table 8. Creatinine level at different time intervals during first 24-hours post-operative.

Parameter	Baseline	24 hours	48 hours
Nalbuphine	76±1.42 ^B	83±1.41 ^B	80±1.56 ^B
Pentazocine	77±1.37 ^A	88±1.59 ^A	85±1.63 ^A

4. DISCUSSION

Since nalbuphine's approval for human use in 1979 by Federal Drug Authority (FDA) USA, it has been used to mitigate mild to slightly aggressive chronic pains during oncogenic therapies and biliary spasms [16]. Nalbuphine is pharmacodynamically related to naloxone [17]. Nalbuphine is believed to alter the pain perception thus, leading to its efficacy as an anti-depressant along with being an effective analgesic [18]. Our study reaffirmed the possible application of nalbuphine as a pre-emptive analgesic in dogs. Subjective and objective analysis of the group receiving nalbuphine presented promising results, though as stipulated by prior research in dogs, efficacy of pentazocine has always proved to be superior than other opioids of synthetic nature [19]. Pentazocine has a potency of approximately one half of that of morphine yet it has certain pharmacological characteristics which are very similar to true opioids agonist [20, 21]. In earlier studies, it has been purported that unlike other opioid agents pentazocine will not cause severe respiratory depression though a decrease in GIT motility and antitussive effects have been observed [22]. Pentazocine has also been reported to cause a transient decrease in blood pressure along with reduced cardiac output [23]. Our study verified this phenomenon when at 3, 6, 12 hours intervals, pulse rate observed in patients who were administered pentazocine were significantly lower than the subjects of group A receiving Nalbuphine. As in previous studies, slight hyper-salivation, emesis and tremors were observed post-administration [22].

Nalbuphine and Pentazocine though having similar target receptors, have affected temperature erratically during the 24-hour period of drug administration. Nalbuphine pertaining to its proprioceptive altering nature is much more prone to cause a decrease in temperature whereby, pentazocine being more closely associated to Meperidine is resistive to such adverse changes [6, 23]. Pentazocine targets only opioid receptors whereas in cases of small mammals and canine species nalbuphine is known to possess a reasonable sedative effect [24]. Sedative effects of pentazocine are not very pronounced and often referred to cause dysphoria instead of sedation [25]. However, nalbuphine is proven to affect the limbic system thereby inadvertently causing a decline in body

temperature from the normal values [26]. Such verifiable findings were corroborated in our study as well when nalbuphine caused a statistically significant decrease in values of body temperature in animals of Group A. Pertaining to aforementioned deleterious effects of nalbuphine on cognition and central nervous system, relatively more pronounced deviation from normal breathing rates were observed in groups receiving nalbuphine postoperatively.

Meaningful quantification of pain was based on previously reported methods for assessing physiologic and behavioral parameters in animals experiencing pain [27]. Moreover, we analyzed mentation as described in Table. Pain assessment considers the behavioral and physiological post-operative changes as well as degree of anthropomorphism. Our study was conducted on the presumption that the changes in responses of an animal after administration of analgesics and the degree of consistent mitigation of pain after analgesic management would prove to be reliably quantifiable parameter for assessment. In our study, this was referred to as subjective pain assessment. Pentazocine proved to significantly superior at counteracting pain in group B animals as compared to animals of group A that were administered nalbuphine. Objective assessment of group A and group B bearded similar results as mentioned earlier in subjective analysis. Vocalization, movement and breathing pattern in animals receiving pentazocine remained significantly stable while patients receiving nalbuphine exhibited higher degree of pain during initial 12 hours post-operative. Despite having comparable half-lives, bio-availability, pharmacodynamics and pharmacokinetics, pentazocine proved to be far superior in alleviating post-operative pain as compared to nalbuphine. It can be postulated that this increase in efficacy of pentazocine is attributed to a decrease in ionic nature relative to nalbuphine, which possesses three hydroxyl groups instead of having one as in pentazocine [28].

Serum analysis revealed that values of ALT and Urea were significantly increased in animals receiving nalbuphine. It is due to the fact that pharmacodynamic studies of this drug have confirmed that nalbuphine requires hepatic conjugation and involvement of cytokine enzymes for its excretion [29]. Consequently, it is empirical to assume that group A demonstrated higher levels of ALT and Serum urea. Earlier studies have indicated that though pentazocine doesn't show hepatotoxicity yet animals receiving it for prolong period of times have been known to experience alleviated creatinine levels [30]. Such renal toxicity is evident in our results as well.

5. CONCLUSION

Our study concluded that the accumulative score for subjective and objective analgesic scoring exhibited a significantly superior trend in the favor of pentazocine as compared to nalbuphine.

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