

Full Length Research Paper

Analgesic effects of tramadol, paracetamol and tramadol/paracetamol combination for management of post-surgical pain in goats undergoing femoral fracture reduction fixation

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This study compared analgesic efficacy of paracetamol and tramadol alone and their combination in goats for surgical pain control. Twelve goats presented for femoral fracture management were randomly grouped into three (n=4) for the study. The first group received tramadol (3 mg/kg), the second group had paracetamol (15 mg/kg) and the third group had combination of tramadol (1.5 mg/kg)/paracetamol (7.5mg/kg) intramuscularly by a Veterinarian blinded to the treatment before induction of anaesthesia. Analgesia was evaluated by assessing vital parameters, neutrophil level and mechanical pain threshold using analgesiometer before drug administration (0hr), and at every hour for nine hours post-surgery. The combination

of 7.5 mg/kg paracetamol and 1.5 mg/kg tramadol regimen was superior to 3 mg/kg tramadol or 15 mg/kg paracetamol alone in reducing the intensity of pain during the 3rd, 4th, 5th, 6th and 7th hours of treatment as indicated by the mechanical pain threshold value. Collectively, the cardiopulmonary and thermoregulatory effects of tramadol, paracetamol and their combination were similar (p<0.05). Therefore, 7.5 mg/kg paracetamol and 1.5 mg/kg tramadol combination regimen could be used for effective postoperative pain management in goats.

Keywords: Analgesia, tramadol, paracetamol, goats, femur, fracture

INTRODUCTION

Goats in most developing countries are reared under extensive method of management with little supplement. They are mostly left to scavenge feed on the street. This system of management predisposes them to automobile

accident causing different types of fractures mostly affecting the hind limbs (Witmer, 2016; Adeyanju *et al.*, 1995; Adeyanju *et al.*, 1988). Fracture is one of the conditions that may require surgical interventions for

functional restoration (Morgan and Silverman, 1984). The surgical interventions are associated with postoperative pain (Pollock *et al.* 1991) and can cause decreased food intake and delayed wound healing (Chapman and Gavrin, 1999). Postoperative pain if not properly managed is expected for at least 24 to 72 hours (Hellyer, 2002). Hence, the need for preemptive analgesia to effectively manage postoperative pain and reducing the undesirable side effects such as irritation of the gastrointestinal mucosa and respiratory depression (Penprase *et al.*, 2015).

The ideal analgesic should have a rapid onset of action with acceptable minimal or no side effect on gastrointestinal and cardiopulmonary system (King *et al.*, 2011). Opioids and nonsteroidal anti-inflammatory drugs have been the usual choice for postoperative pain management (Lee *et al.*, 2011). However, side effects such as respiratory depression and intestinal motility disorder were reported following opioids administration (Dickenson and Kieffer, 2006). The choice of nonsteroidal anti-inflammatory drugs (NSAIDs) to avoid the side effects of opioids was also associated with side effects following cyclooxygenase (COX-I and II) inhibition (McCroory and Lindahl, 2002).

Tramadol is a synthetic opioid used to treat moderate to moderately severe pain. It has a dual mechanism of action; it binds to the μ -receptor and inhibits the monoaminergic pathway, which is responsible for noradrenaline and serotonin reuptake (KuKanich and Papich 2004). The administration of tramadol in dogs have been reported orally (Giorgi *et al.* 2009), intravenously (McMillan *et al.* 2008; Buhari *et al.*, 2012), subcutaneously (KuKanich and Papich 2004; Buhari *et al.*, 2012), intramuscularly (de Sousa *et al.* 2008) and epidurally (Guedes *et al.* 2005).

Paracetamol was discovered over 100 years ago and has been widely used in medical practice for more than half the century. In humans, paracetamol is the most commonly prescribed analgesic for the treatment of mild to moderate pain (Rawal *et al.*, 2011). Its major advantages over NSAIDs are its lack of interference with platelet function and safe administration in patients with a history of peptic ulcers or asthma (Silverfield *et al.*, 2002). The main mechanism of action of paracetamol is considered to be the inhibition of cyclooxygenase (COX) and findings suggest that it is highly selective for COX-2 (Hinz *et al.*, 2008). The tramadol and paracetamol combination are used frequently for postoperative pain management in humans (Dogar and Khan, 2017). The literature on the use of this combination in veterinary practice especially in goats is limited.

The objective of the study was to compare analgesic effect of paracetamol 15 mg/kg and of tramadol (3 mg/kg) with a combination of paracetamol 7.5 mg/kg and a lower dose of tramadol (1.5 mg/kg) administered intravenously for postoperative pain after femoral fracture reduction fixation in goats.

MATERIALS AND METHODS

This double-blind, randomized study was conducted using twelve client-owned goats' presented for the management of closed femoral diaphyseal fracture using intramedullary pinning at the Veterinary Teaching Hospital, Faculty of Veterinary Medicine of Usmanu Danfodiyo University Sokoto, Nigeria were taken into study. Age of the goats ranged from 1 year to 3 years with a mean of 1.9 years. The body weight of the goats ranged from 10 kg to 17 kg (mean= 14.3kg). Specific sex and body weight were not inclusion criteria but only goats with transverse or short oblique closed fracture of the left or right femur were considered. Exclusion criteria were open fracture, presence of signs of anaemia, lack of appetite or diarrhea. All animals were clinically evaluated and were considered fit for surgical management. The goats underwent the same anesthetic protocol: combination of ketamine/xylazine (5 mg/kg/ 0.02 mg/Kg) intravenously (IV). Normal saline (0.9% NaCl) (Braun Medical, Romania) was infused IV (10ml/kg/h) throughout the surgical procedure. All surgical procedures were conducted by the same surgeon and each procedure lasted within 30 min. The goats were randomly divided into three groups of four animals each. The first group (group T) was treated with tramadol (Tramadol^R, Ozone Laboratories Group, Romania) 3 mg/kg (intramuscularly) IM. Paracetamol 15 mg/kg was administered IM to the second group (group P). The third group (group T/P) had combination of half the dosages of tramadol/paracetamol (1.5mg/kg/7.5mg/kg) IM. The drugs were administered to the groups during pre-anaesthetic medication.

Physiologic indicators used in monitoring acute pain in animals included increased pulse rate, increased respiratory rate, rectal temperature and neutrophils (Tesfaye *et al.*, 2017). 2mls blood sample were taken before drug administration (0 hr as a baseline) and at every 1 hour for nine hours for neutrophils evaluation. All other parameters were also considered before drug administration (0 hour as a baseline) and at every 1 hour for nine hours. Mechanical pain threshold was assessed using clinical algometer (PainTestTM FPX 25 Algometer (Wagner Instruments, Greenwich, USA) for post-surgical analgesia (Murrell *et al.*, 2008; Reid *et al.*, 2007). The device was applied at four different areas 2 cm away from the site of incision (cranially, caudally, proximally, and distally). Maximum reading was set at 15N to avoid trauma to the area. The assessment was conducted before the surgery 0h, at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h and 9h post-surgery.

Statistical analysis

The results were expressed as the Mean \pm standard error of the mean (SEM). The data were analyzed using a 2-way repeated measures mixed model approach, with

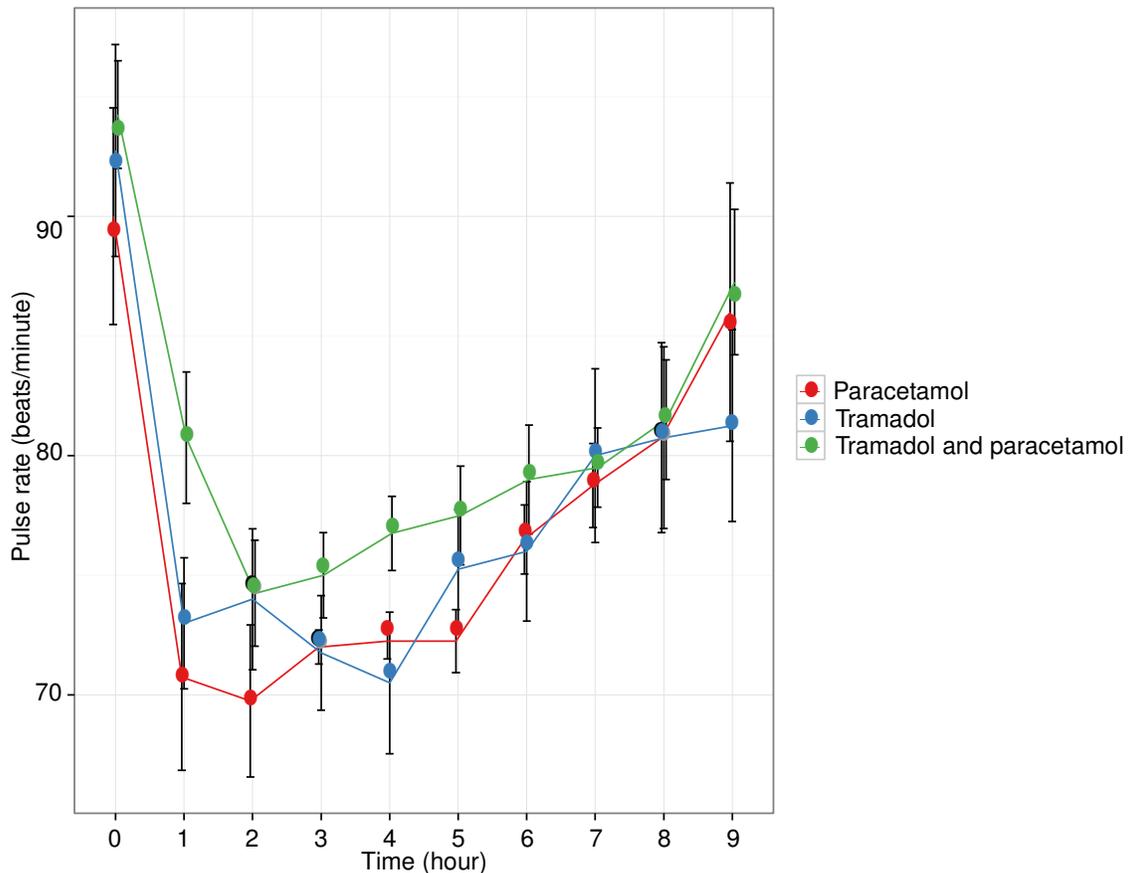


Figure 1. Mean \pm SEM pulse rate in goats following femoral fracture reduction treated with 3 mg/kg of tramadol (group T), 15mg/kg of paracetamol (group P) and 1.5 mg/kg and 7.5 mg/kg each of tramadol/paracetamol combination (group T/P) for a period of nine hours. No significant difference between the groups ($p < 0.05$).

treatment factor (treatment), repeated factor (hourly). Differences in value at $p < 0.05$ were considered statistically significant. The compound symmetric covariance structure was used to model the within-subject correlations. When using this structure, we assumed that the variability of the responses was the same at each level of time (hour) and the correlation between responses from any pair of levels of time (hour) is the same. In Vivo Stat 3.7 statistical software (2014) was used for this statistical analysis. (Bate and Clark, 2014).

RESULTS

There was no significant difference between the groups in terms of pulse rate, rectal temperature and neutrophils

values ($p > 0.05$) (Figure 1, 2 and 3). The pair wise tests at the 5% level, there is a statistically significant difference between the levels of duration (hour). The pulse rate value was significantly higher in group T/P than in group T at 1 hour after drugs administration ($p = 0.0181$) (Figure 1). Similarly, neutrophil value was significantly higher in group T/P than in group T at 2 hours ($p = 0.0009$) (Figure 3). A comparison of treatment effects on respiratory rates ($p = 0.0042$) and mechanical pain threshold ($p = 0.0002$) revealed significant differences between groups ($p > 0.05$) (Figure 4 and 5).

The respiratory rates were significantly higher in group P than both groups T and T/P at 1, 2, 3, 4 and 5 hours ($p > 0.05$) (Figure 4). On the other hand, mean values of the mechanical pain threshold were significantly higher in group T/P compare to both group T and group P at 3,4,5, 6 and 7 hours ($p > 0.05$) (Figure 5).

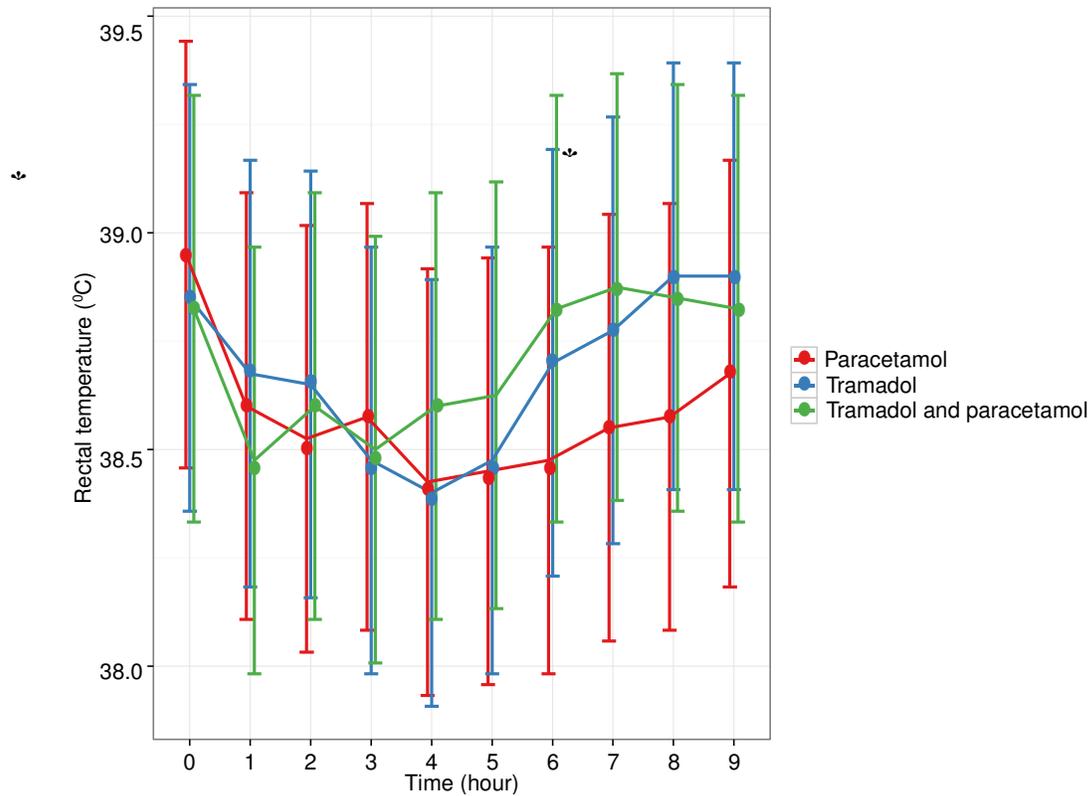


Figure 2. Mean \pm SEM rectal temperature in goats following femoral fracture reduction treated with 3 mg/kg of tramadol (group T), 15 mg/kg of paracetamol (group P) and 1.5 mg/kg and 7.5 mg/kg each of tramadol/paracetamol combination (group T/P) for a period of nine hours. No significant difference between the groups ($p < 0.05$).

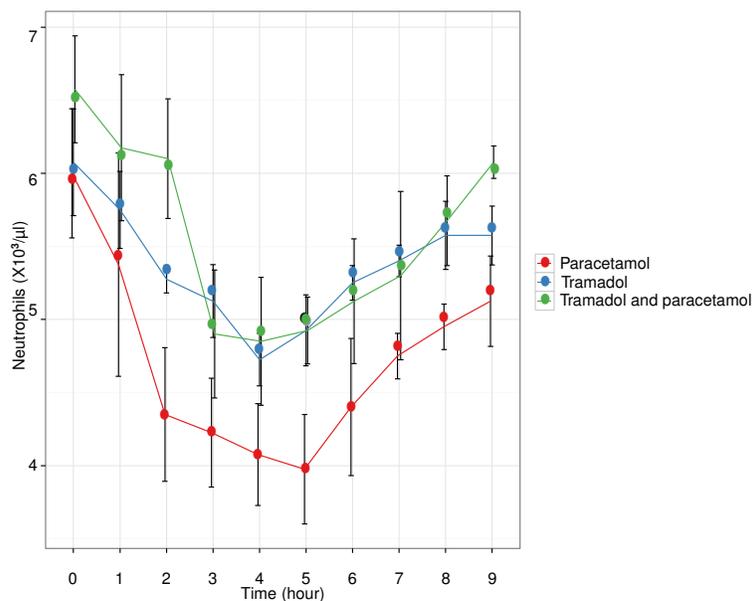


Figure 3. Mean \pm SEM neutrophils in goats following femoral fracture reduction treated with 3 mg/kg of tramadol (group T), 15 mg/kg of paracetamol (group P) and 1.5 mg/kg and 7.5 mg/kg each of tramadol/paracetamol combination (group T/P) for a period of nine hours. No significant difference was observed in the neutrophils between groups and time ($p > 0.05$).

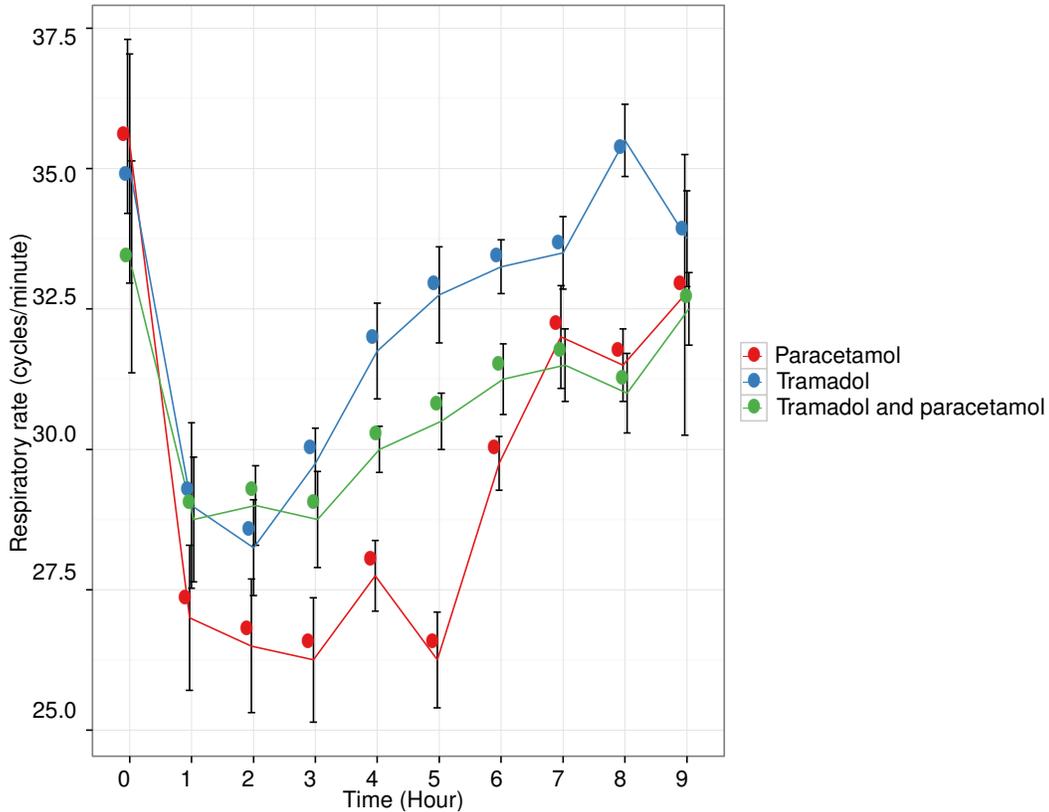


Figure 4. Mean ± SEM respiratory rate in goats following femoral fracture reduction treated with 3mg/kg of tramadol (group T), 15mg/kg of paracetamol (group P) and 1.5mg/kg and 7.5mg/kg each of tramadol/paracetamol combination (group T/P) for a period of nine hours. There was significant difference between treated with Tramadol and paracetamol at 1st, 2nd, 3rd, 4th, and 5th hour (p<0.05).

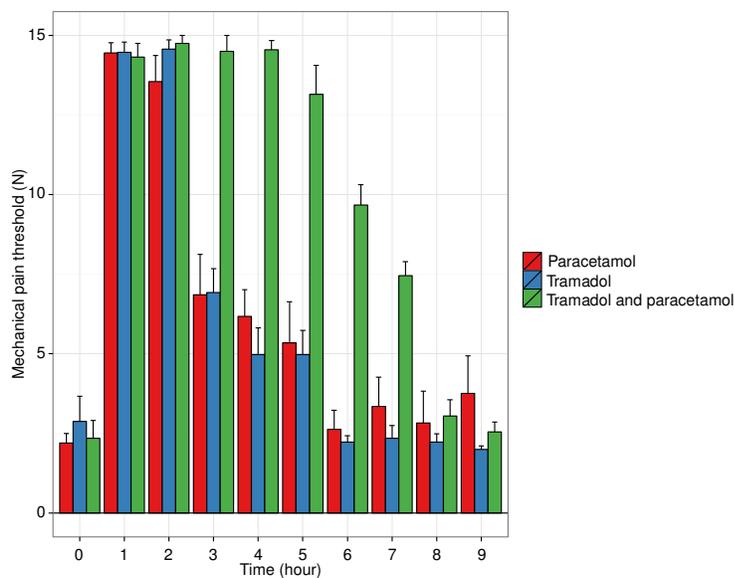


Figure 5. Mean ± SEM mechanical pain threshold (MPT) in goats following femoral fracture reduction treated with 3 mg/kg of tramadol (group T), 15mg/kg of paracetamol (group P) and 1.5 mg/kg and 7.5 mg/kg each of tramadol/paracetamol combination (group T/P) for a period of nine hours. There was significant increase in MPT in group treated with tramadol and paracetamol combination at 3rd, 4th, 5th, 6th and 7th hour (p<0.05).

DISCUSSION

Surgical wound triggers acute postoperative pain that gradually decreases with tissue healing (Yilmaz *et al.*, 2015). Several negative effects associated with postoperative pain requires effective analgesia (Emir *et al.*, 2010). Thus, effective management of postoperative pain is a global consent in providing patient comfort during wound healing (Emir *et al.*, 2010). Studies have shown the many advantages and side effect of the most commonly used opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) (Lee *et al.*, 2011; Emir *et al.*, 2010; Savarese, 2005). The dose dependent side effect of opioids limits their use, while NSAIDs are also associated with side effects following cyclooxygenase (COX-I and II) inhibition (McCrory and Lindahl, 2002; Walder *et al.*, 2001). The synergistic effect of both NSAIDs and opioids potentiate postoperative analgesia via different mechanisms and decrease the incidence of side effects associated with them when used alone (DiAx and Flood, 2006; Kissin, 2000). In humans, the treatment of postoperative mild and moderate pain was been successfully achieved with paracetamol (Yilmaz, 2015). In this study, the analgesic effects of tramadol, paracetamol and their combination for post-surgical pain management in goats following femoral fracture reduction fixation was evaluated.

Keskinbora and Aydınli, (2006) reported minimal cardiovascular effects of tramadol. Contrary to the effect caused by tramadol, therapeutic dose of paracetamol does not affect the cardiovascular system (Avellaneda *et al.*, 2000). In the present study, there were no significant differences between the three groups in terms of pulse rate, rectal temperature and neutrophils values. Although, the group treated with tramadol/paracetamol combination had a significantly higher value of pulse rate and neutrophils but within the normal range before and at first the two hours post administration, thereafter fall to lower limit. Thus, indicated rapid onset of the drugs' effect, inhibition of prostaglandin synthesis at peripheral sites of inflammation (Emir *et al.*, 2010) and inhibition of excitatory amino acids of NMDA activation thereby alleviating patient painful stress (Onsiog, 2002).

Previous studies using opioids reported low rates of respiratory depression (Momeni *et al.*, 2006; Duthie, 1998). Tramadol, which is structurally similar to opioid derivatives, has been reported to provide adequate analgesia without affecting respiratory rate. Another study reported similar postoperative pain relief provided by paracetamol and tramadol in children (Kumar, 2013). In the current study, the respiratory rates were significantly lower in both groups that received tramadol and tramadol/paracetamol combination than in group treated with paracetamol alone. This could be the effect of tramadol binding the $\mu 1$ opioid receptor and inhibiting the monoaminergic pathway, thereby acting centrally and lower the respiratory center (KuKanich and Papich 2004).

However, none of the goats developed a respiratory rate below the lower acceptable range. Thus, respiratory depression as a result of the drugs used was not observed in either group.

On the other hand, mean values of the mechanical pain threshold were significantly higher in tramadol/paracetamol group compare to both groups treated with tramadol or paracetamol alone. Thus, tramadol and paracetamol combination provide adequate analgesia over either drug used alone (Schug, 2006). Previous study reported mechanisms of action and pharmacokinetics of paracetamol and tramadol combination to complement each other hence provide more effective postoperative analgesia than the use of either drug alone (Edwards *et al.*, 2002).

In conclusion, tramadol, paracetamol and their combination were compared for the management of postoperative pain in goats following femoral fracture reduction. It was concluded that low dose tramadol-paracetamol combination decreased the amount and increased the effectiveness of postoperative analgesia. In goats, the combined 7.5mg/kg paracetamol and 1.5mg/kg tramadol regimen was superior to 3mg/kg tramadol or 15mg/kg paracetamol alone in reducing the intensity of pain during the 3rd, 4th, 5th, 6th and 7th hours of treatment as indicated by the mechanical pain threshold value. Collectively, the cardiopulmonary and thermoregulatory effects of tramadol, paracetamol and their combination were similar. Therefore, 7.5mg/kg paracetamol and 1.5mg/kg tramadol combination regimen could be used safely for postoperative pain management after femoral fracture reduction in goats.

Authors' declaration

We declared that this study is an original research by our research team and we agree to publish it in the journal.

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