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Effects of sub-anaesthetic (low) dose ketamine infusion on intra-operative and postoperative pain in goats anaesthetized with diazepam-ketamine prior to rumenotomy

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Abstract

The study evaluated the effect of sub-anaesthetic ketamine on peri-operative pain in goats anaesthesized with diazepam-ketamine prior to rumenotomy. Nine West African dwarf goats used for the study were divided into three (3) groups (n=3). Group 1 received diazepam (0.5mg/kg IV) and ketamine (5mg/kg IV), group 2 received diazepam (0.5mg/kg IV), ketamine (5mg/kg IV) and continuous IV infusion (CRI) ketamine (20µg/kg/min) 30 minutes prior to rumenotomy and group 3 received diazepam (0.5mg/kg IV), ketamine (5mg/kg IV) and CRI ketamine (20µg/kg/min) followed by rumenotomy immediately. The mean rank pain scores of CRI ketamine groups 2 and 3 were lower than that of group 1 (control) during incision of rumen and suturing of skin, muscle and rumen. There were no significant difference in mean rank pain scores during incision of skin (P=0.239), muscle (P=0.76), peritoneum (P=1.0) and rumen (P=0.083). Mean rank pain scores of the groups were not significantly different during suturing of skin (P= 0.064) and muscle (P=0.064) but significantly different during rumen suturing (P=0.004). Respiratory rate (RR) of group 1 was significantly ($p<0.05$) higher than RR of other groups at 40 and 60 minutes IOP as well as at 60 minutes POS. At 80 minutes post-surgery, there was no significant difference in the RR across the groups ($P>0.05$). On exertion of pressure on the site of incision wounds, goats in group 1 showed pain with outcry, those in group 2 showed no sign of pain while in group 3 moderate signs of pain were exhibited by goats. It was concluded that the sub-anaesthetic dose of ketamine infused (20µg/kg/min) did not effectively ameliorate intra-operative rumenotomy-induced pain in diazepam-ketamine anaesthesized goats. However less postoperative pain and hyperalgesia were recorded in the groups infused with low dose ketamine compared to the control group.

Keywords: Diazepam, Ketamine, Pain, Rumenotomy, Sub-anaesthetic

Introduction

In clinical practice, general anaesthesia in small ruminants is challenging (Ghurashi *et al*., 2009). Thus, combination of drugs for induction of anaethesia is usually advantageous over the administration of a single drug (De Rossi *et al*., 2003). The use of ketamine as an injectable anaesthethic in goats is favored since it has a wide safety margin (Thurmon, 1986). It is also cheap and

readily available (Udegbunam & Adetunji, 2007). However, its sole use is considered unsatisfactory for surgery due to its tendency to produce excitement during induction and recovery (Green *et al.,* 1981). It also increases muscle tone and causes profuse salivation (Thurmon, 1986). These side effects are usually countered by the use of sedatives such as xylazine, acepromazine and diazepam (Udegbunam & Adetunji, 2007).

Diazepam is a potent hypnotic-sedative and produces muscle relaxation (Koshy *et al.*, 2003). It is a long acting sedative due to its slow metabolism and it has relatively lesser cardiovascular effects when compared with other sedative drugs (Koshy *et al*., 2003). In combination with ketamine, diazepam alleviates the unwanted cardiovascular effects of ketamine and demonstrates anti-convulsant, amnestic and muscle relaxant effects via central mechanism (Koshy *et al*., 2003). Despite the usefulness of diazepam/ketamine combination, this when used in goats produced short duration anaesthesia and inadequate analgesia (Ghurashi *et al.*, 2009).

There are numerous analgesic drugs and techniques available to the veterinary practitioner today and a number of pain management guidelines have been published (Kukanish, 2013). However, there is no single drug or technique that will manage all pain effectively. Opiod based pharmacotherapy has long been the standard for acute pain management in trauma and surgical patients due to a perceived lack of viable alternative therapies, despite their well-known adverse effects (Ghurashi *et al*., 2009). There has been an emphasis on multimodal management of acute pain, specifically the utilization of opiod-sparing adjunct medications, including non-steroidal anti-inflammatories, gabapentinoids, antiepileptics, tramadol, and regional anaesthesia (Kukanish, 2013). Additionally, low dose ketamine has been used for the management of acute pain, particularly in patients who have demonstrated an inadequate response to conventional opioid therapy (Koshy *et al*., 2013).

Sub-anaesthetic (low) doses of ketamine have gained acceptance for acute and chronic pain management in dogs, horses and humans (Kukanish, 2013). It has also been used for perioperative analgesia in clinical veterinary patients (Muir, 2010). A recent Cochrane review concluded that ketamine administered at a sub-anaesthetic dose is effective in reducing postoperative morphine requirements as well as nausea and vomiting and these adverse effects are mild or absent (Beghdad *et al*., 2011). Ketamine has also been used to counteract opiod-induced hyperalgesia and prevented the development of opioid tolerance (Kukanish, 2013). A previous work also demonstrated the safety and utility of ketamine among opiod-tolerant patients undergoing elective operations (Kator *et al*., 2016).

Sub-anaesthetic doses of ketamine have been shown by several studies to possess analgesic effect. However, no study has been conducted in goats to ascertain the optimal sub-anaesthetic dose of ketamine that can be used for peri-operative analgesia in this species. Also, the benefit of pre-incisional/pre-emptive infusion of sub-anaesthetic dose of ketamine has not been investigated in goats. This study was therefore conducted to investigate the effect of constant rate infusion of low dose of ketamine on intra-operative and post operative pain induced by rumenotomy in goats. The benefit of pre-incisional administration of ketamine was also studied.

Materials and Methods

Animals

Nine adult West African Dwarf (WAD) goats with an average mean weight of 5.5 ± 0.5kg were used for this study. The WAD goats were procured from the market in Nsukka Local Government Area and kept in the Department of Veterinary Surgery goat pen, University of Nigeria, Nsukka. They were acclimatized for 30 days before the commencement of the experiment. They were fed with grasses, concentrate and water was provided *ad libitum.* Within this period, they were confirmed free of blood and gastrointestinal parasites through fecal floatation test and blood smear.

Ethics

Studies were performed in conformity with National institute of health (NIH) revised guidelines for laboratory animals care and use (NIH, 1985) and the University of Nigeria ethical codes and regulations for research. Ethical approval number (UNAEC/2018/204)

Experimental design

The WAD goats were assigned to three (3) groups with three (3) animals in each group designated as listed below;

Group 1: Diazepam (0.5mg/kg IV) + ketamine (5mg/kg IV) (control group)

Group2: Diazepam (0.5mg/kg IV) + ketamine(5mg/kg IV) + ketamine (20µg/kg/min, continuous IV infusion) 30 minutes prior to rumenotomy

Group 3: Diazepam (0.5mg/kg IV) + ketamine(5mg/kg IV) + ketamine (20µg/kg/min, continuous IV infusion) + rumenotomy immediately
Before anesthetic induction, the baseline parameters of goats namely weight, respiratory and heart rate were determined.

Induction of anaesthesia
Animals in all groups were injected with 0.5mg/kg diazepam (Klitch drugs, India) IV to sedate them and 5 mg/kg ketamine (Mark pharmaceuticals Ltd, Lagos, Nigeria) was administered IV to induce anaesthesia. In group 2, goats were infused with 20µg/kg/min of lactated ringers (Dana®, Nigeria) at the rate of 5ml/kg/hr 30 minutes prior to rumenotomy. A supplemental dose of 5mg/kg IV ketamine was also given to goats in this group immediately before surgery. In group 3, animals received 20µg/kg/min ketamine in lactated ringers at the rate of 5ml/kg/hr. However, rumenotomy was conducted immediately. Supplemental 5mg/kg IV ketamine was given IM to animals in this group prior to suturing of the rumen.

Rumenotomy
The abdominal area (left lateral) was properly shaved using razor blade and the animals were draped. The operating site was properly scrabbed using gauze soaked in dilute chlorhexidine solution. Also the animals were kept off feed six (6) hours before the surgery started. A 5 cm incision was made on the left flank traversing the skin, subcutaneous tissue, abdominal muscles, fascia and the peritoneum. After making the laparotomy incision, the rumen was lifted from the abdomen with Allis forceps and packed off with gauze. A Rochester-pean forceps was used to keep it in place and a stab incision was made on the rumen in an avascular area. The incision was extended with surgical blade. The incision on the rumen was closed with a double layer of Lambert inverting suture pattern using chromic cat gut (2/0). The transverse abdominis muscle and peritoneum were sutured in a simple continuous manner using chromic catgut (2/0). The remaining muscles and fascia were also closed with the simple continuous pattern using same size of catgut. Skin apposition was performed using simple interrupted pattern with silk 2/0.

Pain assessment
Pain was assessed on incision and suturing of the skin, subcutaneous tissues, peritoneum, muscle layer and the rumen. Pain scoring was done subjectively using the underlisted criteria as developed by the authors
No pain - 0
Mild pain (twitching) - 1
Moderate pain- (outcry)-2
Severe pain (Outcry+ twitching) - 3
Very severe pain (Outcry + struggling) – 4

Changes in physiologic parameters
Physiologic parameters (heart rate and respiratory rates) were determined pre-operatively at baseline and intra-operatively at times 20, 40 and 60 minutes. Also in the postoperative period, the physiologic parameters were determined at times 20, 40 and 80 minutes. Assessment of pain by palpation was done 24 hours post-surgery by palpating the wound site.

Postoperative care
The goats were injected with 20 mg/kg 20% oxytetracycline (Pantex®, Holland) IM to avoid secondary bacterial infection. The animals were kept in a quiet area and the wounds were observed for some days for post operative complications.

Data analysis
Data analysis was performed with IBM SPSS 20 software. Data on heart rate and respiratory rate were expressed as mean ± standard deviation and were compared using one way ANOVA. Post-hoc comparison of means was performed using LSD post-hoc test at $P<0.05$. Subjective pain scores of all the groups were compared using Kruskall-Wallis H test. Mean ranks of the groups were compared and significant difference was assumed at $P < 0.05$. Data on side effects were expressed as percentages.

Results
Evaluation of pain in the different groups
The mean rank pain scores of the groups are presented in Table 1. The mean rank pain score of group 1(control) was higher than mean rank of other groups at rumen incision, skin muscle suturing and rumen suturing. Comparison of the mean rank pain scores of the three groups showed that there were no significant difference in the mean rank pain scores of the groups at skin incision ($P = 0.239$), muscle incision ($P = 0.760$), peritoneum incision ($P = 1.00$), rumen incision ($P = 0.083$), skin suturing ($P = 0.064$) and muscle suturing ($P = 0.064$). Mean rank pain scores of the group 1 (10.5), group 2 (2.5) and group 3 (6.5) were however significantly ($P= 0.004$) different at rumen suturing.
Heart rate of the different groups

Heart rates (HR) of different groups as presented in table 2 showed that in the intra-operative (IOP) period, at 20 minutes, there was no significant ($p>0.05$) difference in the heart rate of the different groups. At 40 minutes IOP, heart rate of group 1 (186.0 ± 11.0) was not significantly ($p>0.05$) different from either HR of group 2 (241.0 ± 68.3) or group 3(172.0 ± 16.3). However, heart rate of group 2 was significantly ($p<0.05$) higher than that of group 3. At 60 minutes IOP, the heart rates of the different groups did not show any significant difference. At 20 minutes and 60 minutes post surgery, there was no significant ($p>0.05$) difference in the heart rates across the groups. At 80 minutes post surgery, the heart rate of group 1 (211.5 ± 26.1) was significantly ($p<0.05$) higher than that of group 2 (169.5 ± 3.0) but that of group 3 (188.0 ± 25.9) was not significantly different from either that of group 1 (211.5 ± 26.1) or group 2 (169.5 ± 3.0).

Respiratory rate of the different groups

Respiratory rate of the different groups presented in table 2 showed that at 20 minutes IOP, there was no significant ($p>0.05$) difference in the respiratory rates across the groups. At 40 minutes IOP, respiratory rate of group 1 was significantly ($p<0.05$) higher than respiratory rate of other groups. At 60 minutes IOP, there was a significant ($p<0.05$) difference in the respiratory rate across the groups with the respiratory rate of group 1 (98.5±9.0) being the highest while that of group 3 (59.0±3.8) was the least. At 20 minutes post surgery (POS), there was no significant ($p>0.05$) difference in the respiratory rate across the groups. At 60 minutes post surgery, the respiratory rate of group 1 (65.0±2.6) was significantly ($p<0.05$) higher than that of the other groups while the respiratory rate of group 2 (49.5±6.4) and 3 (49.0±8.9) did not show any significant ($p>0.05$) difference. At 80 minutes post surgery, there was no significant ($p>0.05$) difference in the respiratory rate across the groups.

Evaluation of pain by palpation 24 hours post-surgery

Results of this test are presented in table 3. On exertion of pressure on the site of incision wound, goats in group 1 and 3 showed pain with outcry, those in group 2 showed no sign of pain while moderate pain was noticed on palpation of wounds

Table 1: Mean rank pain score of the different groups during incision/suturing

Groups	Skin incison	Muscle incision	Peritoneum incision	Rumen incision	Skin suture	Muscle suture	Rumen suture
1	7.0	6.0	6.5	9.5	9.0	9.0	10.5
2	4.5	6.0	6.5	5.5	4.0	4.0	2.5
3	8.0	7.5	6.5	4.5	6.5	6.5	6.5
Chi-square (χ)	2.86	0.550	0.001	4.968	5.50	5.5	11.00
P-values	0.239	.760	1.0	0.083	0.064	0.064	0.004

Group 1= diazepam + ketamine; group 2= diazepam + ketamine + pre-emptive CRI ketamine 20µg/kg/min + rumenotomy 30 mins later; group 3= diazepam + Ketamine + CRI ketamine (20µg/kg/min) + rumenotomy immediately

Table 2: Cardiopulmonary parameters (Mean ± SD) of the different groups in the intra-operative and postoperative periods

Parameters	Grps	Baseline	Intra- operative period			Postoperative period		
		0 min	20 mins	40 mins	60 mins	20 mins	60mins	80 min
HR	1	169.0±10.4^{a}	160.0±18.0^{a}	186.0±11.0^{ab}	180.0±46.2^{a}	162.5±65.3^{a}	212.5±18.9^{a}	211.5±26.1^{b}
	2	182.0±57.3^{a}	141.5±14.5^{a}	241.0±68.3^{b}	205.0±5.0^{a}	184.0±5.2^{a}	192.5±39.6^{a}	169.5±3.0^{a}
	3	140.5±12.3^{a}	157.5±10.0^{a}	172.0±16.3^{a}	204.0±39.3^{a}	183.0±16.7^{a}	176.5±17.8^{a}	188.0±25.9^{ab}
RR	1	52.5±9.0^{a}	62.0±8.2^{a}	76.0±8.6^{b}	98.5±9.0^{c}	75.5±20.9^{a}	65.0±2.6^{b}	52.0±9.2^{a}
	2	41.0±8.7^{a}	54.0±11.4^{a}	55.5±6.4^{a}	82.0±2.8^{b}	84.0±3.7^{a}	49.5±6.4^{a}	42.0±20.8^{a}
	3	41.0±6.8^{a}	80.5±30.7^{a}	52.0±8.1^{a}	59.0±3.8^{a}	66.0±4.9^{a}	49.0±8.9^{a}	42.5±4.4^{a}

Different superscripts $^{a, b}$ in a column indicate significant difference with $p<0.05$

HR= heart rate (beats/min)., RR (breaths/min)= respiratory rate., min=minutes

Group 1= diazepam + ketamine; group 2= diazepam + ketamine + pre-emptive CRI ketamine 20µg/kg/min + rumenotomy 30 mins later; group 3= diazepam + Ketamine + CRI ketamine (20µg/kg/min) + rumenotomy immediately

Table 3: Response to mechanical induction at suturing of skin incision site 24hours post-surgery

Groups	Response to induction
1	Pain with outcry
2	No sign of pain
3	Pain

Table 4: Clinical observation in the intra-operative period in all groups expressed in percentages (%)

Clinical observation	Group 1 (n=3)	Group 2 (n=3)	Group 3 (n=3)
Grunting (%)	100	100	100
Dyspnoeic breathing (%)	100	100	100
Apneustic breathing (%)	0	0	0
Champing of jaw (%)	0	100	0
Tympany (%)	0	0	0
Salivation (%)	0	0	0

Group 1= diazepam + ketamine; group 2= diazepam + ketamine + pre-emptive CRI ketamine 20µg/kg/min + rumenotomy 30 mins later; group 3= diazepam + Ketamine + CRI ketamine (20µg/kg/min) + rumenotomy immediately

in group 3.

Clinical Observations

Clinically, it was observed that goats in groups 1 and 3 grunted and their breathing was dyspnoeic. In group 2, in addition to the clinical observations recorded in groups 1 and 3, apneustic breathing and champing of jaw were recorded (Table 4).

Discussion

Pain scores analysis showed that group 2 had lower mean rank pain score at skin incision. Pain score of this group was probably lower since supplemental 5mg/kg ketamine was administered to goats in this group just before skin incision. However in the rest of the intra-operative period (from time of rumen incision), goats in groups infused with ketamine showed mild to moderate pain while pain was moderate to severe in the control group as shown by their lower mean rank pain scores. This finding suggests that the dose of ketamine infused did not produce effective analgesia in these groups. This finding is affirmed by an earlier study by Ambros & Duke (2013), which showed that ketamine infusion (20µg/kg/min) minimally affected thermal and mechanical nociception in cats. Several studies in humans, dogs and ponies revealed that ketamine suppressed temporal stimulation of repetitive stimuli rather than a single painful stimulus (Arendt-Nielsen *et al.*, 1996). On the contrary, Branson (2001) reported that infusion of 0.4-0.8 mg/kg/hour of ketamine to horses suffering from osteomyelitis and laminitis resulted in effective pain relief. Ketamine is a non-competitive antagonist that blocks NMDA-receptor ion channel (Ambros & Duke, 2013). These NMDA receptors are not involved in the initial fast synaptic transmission of acute nociceptive processes but require intense and sustained stimulation to be activated (Davies & Lodge, 1987). This may explain why ketamine only marginally affects acute pain and appears more effective in pathologic/chronic pain states by inhibiting spinal cord wind-up and central sensitization (Kukanish, 2013).

The benefit of pre-emptive administration of low dose ketamine prior to skin incision was also evaluated in this study. The observations made in group 2 goats which were infused with ketamine for a 30 minutes period before skin incision showed that intense pain was felt by all goats on the attempts at skin incision unlike in other groups. This necessitated supplemental ketamine (5mg/kg, I.V) injection to allow skin incision. Similarly other researchers reported that pre-incisional administration of low dose ketamine did not have pre-emptive effect following caesarean section in humans (Bauchat *et al*., 2011; Ebong *et al*., 2011). In this study, the administered dose of ketamine may be the reason for the lack of analgesic effect. Low dose ketamine is defined as an intravenous or epidural administration of <1.0 mg/kg and, intramuscular bolus injection of 2.0 mg/kg and intravenous infusion of <20 µg/kg/min (Schmid *et al*., 1999). Unlike the high dose of ketamine, low doses when administered might not achieve relatively high plasma concentration to suppress NMDA receptor activation. Previously, a similar study in which diazepam/ketamine (0.5mg/kg diazepam and 4mg/kg ketamine) were combined resulted in 31.5 ± 4.4minutes surgical anaesthesia (Ghurashi *et al*.,

2009). This report suggested that the latency period of 30 minutes allowed before skin incision was too long thus the waning of the analgesic effect of ketamine.

In this study, the heart rates of all the groups were not significantly different at 20 minutes IOP. Ketamine, a dissociative anaesthetic of the phencyclidine group is a known cardiovascular stimulant (White, 1985). It causes cardiac stimulation by sympathetic effects mediated within the central nervous system (Altura *et al*., 1980). However, prior administration of benzodiazepines notably diazepam, midazolam and fluniltrazepam have been shown to be effective in blunting/preventing this cardio-stimulatory effect of ketamine (White, 1985). In this study, since diazepam was used as a premedicant, it might have obstructed the cardio-stimulatory effect of ketamine. Furthermore, this study also showed that compared to HR of control, HR of group 2 (pre-emptive CRI ketamine group) was higher at 40 minute IOP while at 60 min IOP, HR of groups 2 and 3 (CRI ketamine group) were higher. Timm *et al*. (2008) reported that low dose ketamine infusion lead to significant increase in heart rate and blood pressure. The significantly higher HR recorded in the aforementioned CRI ketamine groups can be said to be a cardiovascular side effect of low dose ketamine infusion. It is worthy to mention that goats in groups 2 received supplemental intravenous bolus ketamine (5mg/kg) injection close to the 40 minutes time point (before skin incision) while goats in group 3 were also injected with same dose of ketamine IV close to the 60 minutes time point (before rumen suturing). The higher HR recorded at 40 minutes IOP (group 2) and 60 minutes IOP (groups 2 and 3) can be due to the effect of the supplemental bolus ketamine administered. In the postoperative period however, HR of control group (DK group) was significantly higher at 60 minutes and 80 minutes time points. This finding suggests that this group of goats felt more pain at the postoperative period compared to the groups which received low dose ketamine infusion intra-operatively. Ketamine is an anti-nociceptive drug which acts by blocking the NMDA receptors. Therefore several studies have demonstrated the benefit of infusion of low dose ketamine (<20µg/kg/min) in improvement of postoperative pain following abdominal surgery (Beghdad *et al*., 2011), major visceral procedures (Argiriadou *et al*., 2004), radical prostatectomy (Snijdelaar *et al*., 2004), donor kidney transplantation and nephrectomy (Stubhaug *et al*., 1997).

Respiratory rates of goats in the three groups at all time points intra-operatively and post-operatively (at 20 and 60 minutes) were higher than the respective baseline values. Ketamine is known to cause mild respiratory depression and hypoventilation (Sanford, 1986; Wright, 1982). In horses, IV administration of diazepam over a wide range of doses (0.05-0.4 mg/kg) did not produce significant change in heart rate, cardiac output, arterial blood pressure, respiratory rate and arterial gas values (Muir, 2010). In goats no significant change in RR occurred following the use of diazepam/ketamine combination (Ghurashi *et al*., 2009). It can therefore be concluded that the observed increase in respiratory rate in the three groups in the IOP and POP may not be due to the drugs used to induce anesthesia rather RR might have increased in response to pain. In addition, the significantly higher RR recorded in the various group at different time points in the IOP and POP may be as a result of pain.

Hyperalgesia a component of postoperative pain is enhanced responsiveness to painful challenges after tissue damage caused by an incision (Weber *et al*., 2005). Ketamine hydrochlorides analgesic effect observed are attributed to its anti-hyperalgesic effect (Hansen, 2008). Pain on touch and palpation were absent by 24hrs in the CRI ketamine group 2 and mild pain in group 3. De Kock *et al*. (2001) and Ozyalcin *et al*. (2004) showed our finding which suppose that sub-anaesthetic dose of ketamine reduced wound hyperalgesia. This effect was more pronounced in group 2 in which low dose ketamine was infused for a period of 30 minutes before skin incision.

In all groups, grunting and dyspnoeic breathing were observed. Similarly, these side-effects have been reported following use of ketamine drug combinations in ruminants (Adetunji & Ogunyemi, 1998). Apneustic breathing, salivation and regurgitation were not observed in all the goats in the various groups. Earlier, similar findings were made following use of diazepam-ketamine drug combination in goats (Udegbunam & Adetunji, 2007). These authors attribute the absence of both side effects to the use of diazepam for premedication.

It can be concluded that sub-anaesthetic dose of ketamine infused (20µg/kg/min) did not ameliorated intra-operative rumenotomy-induced pain in diazepam-ketamine anaesthesized goats. Less

postoperative pain and hyperalgesia were also recorded in the groups infused with low dose ketamine compared to the control.

Conflicts of Interest

The authors declare no conflicts of interest.

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