Global Veterinaria 10 (6): 742-747, 2013
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2013.10.6.7493

# Sedative and Hematobiochemical Effects of Midazolam and Midazolam-Ketamine Combination in Baladi Goats

*Abu-Ahmed, Howaida*

Department of Surgery, Faculty of Veterinary Medicine,
Alexandria University, Behira Province, Rashid, Edfina, Egypt

**Abstract:** The concept of administering sedatives either alone or before general anaesthetic agents is well accepted in veterinary practice. The aim of the present study is to investigate the clinicophysiological effects of different doses of midazolam and its suitability as a preanaesthetic to ketamine in goats. Three goats received one of the following treatments, with one week interval; midazolam 0.6 mg/kg body weight, 1.2 mg/kg and 0.6 mg/kg followed by another dose of 0.3 mg/kg ten minutes later and finally combination of midazolam (0.6 mg/kg) and ketamine (4 mg/kg). Onset and duration of sedation and recumbancy, degree of sedation as well as clinical parameters were recorded. Blood samples were collected for hematobiochmical analysis. Midazolam 0.6mg/kg induced rapid onset of moderate to deep sedation for 27.67±1.45 min. Injection of another 0.3mg/kg after ten min. significantly increased the duration of sedation to 95.00±1.15min without affecting the depth of sedation. Duplication of dose to 1.2mg/kg resulted in rapid onset of deep sedation and recumbancy and the animal didn't arouse after application of painful stimuli. Midazolam/ketamine combination induced short period of general anaesthesia lasted for 24.00±2.88 min. with complete muscle relaxation and smooth recovery. In conclusion, midazolam produced dose dependent sedation in goats and its combination with ketamine produced reliable anaesthesia with good muscle relaxation.

**Key words:** Sedation · Midazolam · Ketamine · Goats

## INTRODUCTION

Sedatives are used preoperatively to induce sedation, improve the quality of induction of anaesthesia and may result in fewer drug adverse effects by reducing the amount of injectable anaesthetics required to induce and maintain general anaesthesia [1, 2]. Xylazine was commonly used in sheep and goat as sedative or an adjunct to ketamine anaesthesia [3,4]. Increasing the dose increases the central nervous system depressant effects from sedation to anaesthesia [5]. However, several side effects were reported after its use as hypoxia [6], lung edema [7] and significant decrease in heart rate and cardiac output [8]. Diazepam and Midazolam used as an alternative sedative to xylazine in sheep and goats [9-14]. Midazolam is a water soluble benzodiazepine that is considered to be fast acting with a short elimination half-life [15]. It has mild cardiovascular and respiratory effects and is commonly used as a mild tranquilizer, muscle relaxant and anticonvulsant [2]. Ketamine is classified as dissociative anaesthetic, its effect appeared rapidly after its injection and it produced profound analgesia with poor muscle relaxation [16]. The use of tranquilizers like diazepam and midazolam with ketamine anaesthesia aids in muscle relaxation and allows smoother recovery than use of ketamine alone [17]. The purpose of this study is to investigate the clinicophysiological effects of midazolam at different doses and its suitability as a preanaesthtic to ketamine anaesthesia in goats.

## MATERIALS AND METHODS

Three apparently healthy goats of both sexes weighing (23-30 kgs.) were used in this study. The animals were kept under standard management conditions for two weeks before treatment. The goats were assigned in a randomized cross-over design, with one week interval between treatments, to 4- groups; group (1) received midazolam (Midathetic®, Amoun Pharmaceutical co.) 0.6 mg/kg body weight, group (2) received midazolam

**Corresponding Author:** Abu-Ahmed, Howaida, Department of Surgery, Faculty of Veterinary Medicine, Alexandria University, Behira, Rashid, P.O. Box: 22758 Edfina, Egypt.

Table 1: Scores of sedation for behavioral changes and signs.

| Score | Behavioral changes and signs |
|---|---|
| No | No behavioral changes |
| Mild | Ataxia with lowering of head |
| Moderate | Assume sternal recumbancy |
| Deep | Lateral recumbancy and may raise the head without holding it up |

1.2 mg. /kg, group (3) received midazolam 0.6 mg. /kg followed by another dose of 0.3 mg/kg 10 min later and finally group (4) received midazolam 0.6 mg./kg as preanaesthetic to ketamine 4mg./kg. All drugs were given slowly intravenous. Heart and respiratory rates and rectal temperature were recorded both before and 15, 30, 45 and 60 minutes after injection. Blood samples were collected from jugular vein at the same previous intervals and examined for changes in RBCs, WBCs, haemoglubine (HB), haematocrit (HCT), urea, creatinine, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT). Sedation (onset and duration) and the associated behavioral changes were recorded. Degree of sedation was assessed using the scores shown in the Table (1).

Recumbancy (onset and duration) were also recorded. The depth of anaesthesia was evaluated according to eye ball rotation and presence or absence of reflexes. The quality of induction and recovery from anaesthesia were observed in all goats.

Descriptive statistical analysis for the obtained data by ANOVA test was carried out using SAS [18].

## RESULTS

Onset and duration of sedation and recumbancy after midazolam and midazolam/ketamine combination are listed in Table 2. Midazolam 0.6 mg/kg resulted in rapid onset of mild sedation within 48.33±11.67 seconds followed by moderate to deep sedation and recumbancy within 120.00±34.64 seconds. Recumbancy was sternal at first followed by lateral one with paddling with hind limbs for few seconds. The animals remained conscious and respond to any noxious stimuli. Signs of mild sedation were present after standing after 16.67±0.88 minutes. The total duration of sedation was 27.67±1.45 minutes. All goats in group (2) showed rapid onset of deep sedation and recumbancy within 30.00 ±8.66 seconds. The animals were unconscious and the head and neck were extended together with profuse salivation. The goats did not arouse after application of noxious stimuli as tail base clamping or pin pricking except moving the hind limbs toward the body (limb withdrawal reflex) with stimuli. Standing occurred after 70±2.89 min with signs of mild sedation that lasted for 90±1.73 min. The duration of sedation (95.00±1.15min.) in group (3) increased significantly than group (1) but not significantly differ from group (2). The depth of sedation was similar to that of group (1). The animals stand completely after 50.00 ±2.89 min. with ataxia and shivering of hind limbs and refused to move. Rapid onset of sedation and recumbancy and unconsciousness in group (4) occurred within 45.00±17.32 sec. post injection with absence of reflexes and downward rotation of eye ball. Short term anaesthesia was lasted for 24±2.88 min followed by smooth recovery characterized by swallowing as well as tail and head movement. Moderate to mild sedation lasted for 45.00±2.89 min. and recumbancy lasted for 35.00±2.89 min after recovery from anaeshesia. Midazolam is a good muscle relaxant; this was observed in relaxation of limbs, tail, anal sphincter and abdominal muscles in all groups. Body temperature showed non-significant decrease in all groups. Pulse and respiratory rates increased non-significantly in group (1) but increased significantly in the other three groups (Table 3). Changes in haematological parameters were within the physiological limits and returned to the pre injection values by end of the experiment (Table 4). Significant increase in creatinine, ALT and AST were observed with groups 2 and 3. While, significant decrease in both ALT and AST was observed in group 4 (Table 5).

Table 2: Means ± standard errors (Mean± SE) of onset and duration of sedation and recumbency after midazolam and midazolam/ketamine combination

| | Sedation | | Recumbency | |
|---|---|---|---|---|
| Groups | Onset (seconds) | Duration (min) | Onset (seconds) | Duration (min) |
| Midazolam(0.6mg/kg) | 48.33±11.67$^{ab}$ | 27.67±1.45$^{c}$ | 120.00±34.64$^{a}$ | 16.67±0.88$^{c}$ |
| Midazolam(1.2mg/kg) | 45.00±8.66$^{ab}$ | 90.00±1.73$^{a}$ | 30.00±8.66$^{b}$ | 70.00±2.89$^{a}$ |
| Midazolam(0.6+0.3mg/kg) | 51.67±12.02$^{ab}$ | 95.00±1.15$^{a}$ | 110.00±26.46$^{a}$ | 50.00±2.89$^{b}$ |
| Midazolam/ketamine (0.6+4mg/kg) | 45.00±17.32$^{ab}$ | 45.00±2.89$^{b}$ | 45.00±17.32$^{ab}$ | 35.00±2.89$^{b}$ |

Means within the same column of different letters are significantly different at (P□0.05).

Table 3: Means±standard errors (Mean±SE) values of temperature, pulse and respiration before and after midazolam and midazolam/ketamine combination in goats.

| Groups | Time/min | Temperature | Pulse | Respiration |
|---|---|---|---|---|
| Midazolam (0.6mg/kg) | Before | 38.60±0.06 | 64.33±0.88 | 25.00±1.73 |
| | 15 | 38.50±0.06 | 65.00±1.73 | 27.00±1.15 |
| | 30 | 38.30±0.12 | 63.00±1.15 | 29.00±1.73 |
| | 45 | 38.60±0.06 | 64.00±2.89 | 28.00±1.15 |
| | 60 | 38.70±0.17 | 65.00±0.58 | 26.00±1.15 |
| Midazolam (1.2mg/kg) | Before | 39.50±0.12$^{a}$ | 62.00±1.15 $^{c}$ | 25.00±2.89 $^{c}$ |
| | 15 | 39.30±0.12 $^{a}$ | 78.00±1.15$^{b}$ | 29.00±0.58 $^{c}$ |
| | 30 | 39.30±0.17 $^{a}$ | 80.00±1.15$^{ab}$ | 38.00±1.73$^{a}$ |
| | 45 | 38.70±0.06$^{b}$ | 85.00±2.31$^{a}$ | 36.00±2.89$^{ab}$ |
| | 60 | 38.90±0.06$^{b}$ | 83.00±1.73$^{ab}$ | 30.00±1.15$^{bc}$ |
| Midazolam (0.6+0.3mg/kg) | Before | 38.70±0.06 | 60.00±1.73$^{b}$ | 28.00±2.31 $^{c}$ |
| | 15 | 39.10±0.06 | 65.00±2.89$^{ab}$ | 36.00±0.58$^{ab}$ |
| | 30 | 38.90±0.12 | 68.00±1.15$^{a}$ | 38.00±0.58$^{a}$ |
| | 45 | 38.50±0.29 | 70.00±2.89$^{a}$ | 36.00±1.73$^{ab}$ |
| | 60 | 38.50±0.23 | 63.00±1.73$^{ab}$ | 30.00±2.89$^{b\ c}$ |
| Midazolam/ketamine (0.6+4mg/kg) | Before | 38.60±0.17$^{b}$ | 67.00±1.73d | 17.00±0.58$^{c}$ |
| | 15 | 38.90±0.12$^{ab}$ | 90.00±2.31$^{b}$ | 15.00±2.89 $^{c}$ |
| | 30 | 38.60±0.12$^{b}$ | 100.00±2.89$^{a}$ | 22.00±1.15$^{b}$ |
| | 45 | 39.00±0.06$^{ab}$ | 93.00±1.73$^{b}$ | 30.00±2.89$^{a}$ |
| | 60 | 39.20±0.12 $^{a}$ | 78.00±1.15 $^{c}$ | 22.00±1.15$^{b}$ |

Means within the same column within the same group of different letters are significantly different at (P?0.05).

Table 4: Means ± standard errors (Mean± SE) values of WBCs, RBCs, HB, HCT values before and after midazolam and midazolam/ketamine combination.

| Groups | Time/min | WBCs ($10^{3}$/UL) | RBCs (x$10^{6}$/UL) | HB (mg/dl) | HCT (%) |
|---|---|---|---|---|---|
| Midazolam (0.6mg/kg) | Before | 62.00±1.15$^{b}$ | 3.06±0.01$^{a}$ | 9.50±0.29$^{a}$ | 9.40±0.12$^{a}$ |
| | 15 | 65.20±0.12$^{a}$ | 2.96±0.01$^{a}$ | 9.60±0.17$^{a}$ | 9.10±0.06$^{ab}$ |
| | 30 | 44.10±0.06$^{d}$ | 2.70±0.12$^{b}$ | 8.50±0.29$^{b}$ | 8.20±0.12$^{c}$ |
| | 45 | 43.00±1.15$^{d}$ | 2.89±0.01$^{a}$ | 9.10±0.12$^{ab}$ | 8.80±0.06$^{b}$ |
| | 60 | 50.00±0.58$^{c}$ | 2.99±0.02$^{a}$ | 9.30±0.12$^{a}$ | 9.20±0.23$^{a}$ |
| Midazolam (1.2mg/kg) | Before | 59.70±1.73$^{a}$ | 2.23±0.02$^{b}$ | 10.20±0.12$^{b}$ | 6.60±0.06$^{b}$ |
| | 15 | 50.80±1.73$^{c}$ | 1.52±0.01$^{d}$ | 8.20±0.12$^{d}$ | 4.40±0.23$^{c}$ |
| | 30 | 45.40±1.73e | 1.54±0.02$^{d}$ | 8.30±0.12$^{d}$ | 4.50±0.29$^{c}$ |
| | 45 | 46.80±1.73$^{d}$ | 1.67±0.01$^{c}$ | 8.70±0.12$^{c}$ | 4.90±0.06$^{c}$ |
| | 60 | 56.50±1.41$^{b}$ | 2.51±0.01$^{a}$ | 10.20±0.10$^{a}$ | 6.50±0.25$^{a}$ |
| Midazolam (0.6+0.3mg/kg) | Before | 59.50±0.17$^{b}$ | 2.20±0.01$^{b}$ | 10.00±0.58$^{ab}$ | 6.50±0.29$^{a}$ |
| | 15 | 50.60±0.06$^{c}$ | 1.50±0.01$^{d}$ | 8.00±0.58$^{c}$ | 4.30±0.12$^{b}$ |
| | 30 | 45.27±0.03e | 1.51±0.01$^{d}$ | 8.10±0.58$^{c}$ | 4.40±0.12$^{b}$ |
| | 45 | 46.60±0.17$^{d}$ | 1.67±0.01$^{c}$ | 8.50±0.29$^{bc}$ | 4.80±0.12$^{b}$ |
| | 60 | 56.80±0.12$^{b}$ | 2.48±0.01$^{a}$ | 10.01±0.58$^{a}$ | 7.00±0.58$^{a}$ |
| Midazolam/ketamine (0.6+4mg/kg) | Before | 60.80±0.06$^{a}$ | 2.84±0.06$^{b}$ | 10.70±0.06$^{b}$ | 8.70±0.12$^{c}$ |
| | 15 | 26.60±0.17$^{d}$ | 1.73±0.12$^{d}$ | 8.00±0.58$^{d}$ | 5.30±0.58$^{d}$ |
| | 30 | 34.90±0.06$^{c}$ | 2.11±0.01$^{c}$ | 8.80±0.58$^{cd}$ | 6.30±0.58$^{d}$ |
| | 45 | 43.90±3.05$^{b}$ | 2.90±0.06$^{b}$ | 10.00±0.58$^{bc}$ | 7.50±0.58$^{b}$ |
| | 60 | 59.00±0.58$^{a}$ | 3.00±0.01$^{a}$ | 10.40±0.58$^{a}$ | 9.30±0.58$^{a}$ |

Means within the same column within the same group of different letters are significantly different at (P?0.05).

Table 5: Means±standard errors (Mean±SE) values of creatinine, urea,AST and ALT levels before and after midazolam and midazolam/ketamine combination.

| Groups | Time/min | Creatinine(mg/dl) | Urea(mg/dl) | AST(U/L) | ALT(U/L) |
|---|---|---|---|---|---|
| Midazolam (0.6mg/kg) | Before | 62.00±1.15[b] | 3.06±0.01[a] | 9.50±0.29[a] | 9.40±0.12[a] |
| | 15 | 65.20±0.12[a] | 2.96±0.01[a] | 9.60±0.17[a] | 9.10±0.06[ab] |
| | 30 | 44.10±0.06[d] | 2.70±0.12[b] | 8.50±0.29[b] | 8.20±0.12[c] |
| | 45 | 43.00±1.15[d] | 2.89±0.01[a] | 9.10±0.12[ab] | 8.80±0.06 [b] |
| | 60 | 50.00±0.58[c] | 2.99±0.02[a] | 9.30±0.12[a] | 9.20±0.23[a] |
| Midazolam (1.2mg/kg) | Before | 59.70±1.73[a] | 2.23±0.02[b] | 10.20±0.12[b] | 6.60±0.06[b] |
| | 15 | 50.80±1.73[c] | 1.52±0.01[d] | 8.20±0.12[d] | 4.40±0.23[c] |
| | 30 | 45.40±1.73e | 1.54±0.02[d] | 8.30±0.12[d] | 4.50±0.29[c] |
| | 45 | 46.80±1.73[d] | 1.67±0.01[c] | 8.70±0.12[c] | 4.90±0.06[c] |
| | 60 | 56.50±1.41 [b] | 2.51±0.01[a] | 10.20±0.10[a] | 6.50±0.25[a] |
| Midazolam (0.6+0.3mg/kg) | Before | 59.50±0.17 [b] | 2.20±0.01[b] | 10.00±0.58[ab] | 6.50±0.29[a] |
| | 15 | 50.60±0.06[c] | 1.50±0.01[d] | 8.00±0.58[c] | 4.30±0.12[b] |
| | 30 | 45.27±0.03e | 1.51±0.01[d] | 8.10±0.58[c] | 4.40±0.12[b] |
| | 45 | 46.60±0.17[d] | 1.67±0.01[c] | 8.50±0.29[bc] | 4.80±0.12[b] |
| | 60 | 56.80±0.12 [b] | 2.48±0.01[a] | 10.01±0.58[a] | 7.00±0.58[a] |
| Midazolam/ketamine (0.6+4mg/kg) | Before | 60.80±0.06[a] | 2.84±0.06[b] | 10.70±0.06[b] | 8.70±0.12[c] |
| | 15 | 26.60±0.17[d] | 1.73±0.12[d] | 8.00±0.58[d] | 5.30±0.58[d] |
| | 30 | 34.90±0.06[c] | 2.11±0.01[c] | 8.80±0.58[cd] | 6.30±0.58[d] |
| | 45 | 43.90±3.05 [b] | 2.90±0.06[b] | 10.00±0.58[bc] | 7.50±0.58[b] |
| | 60 | 59.00±0.58[a] | 3.00±0.01[a] | 10.40±0.58[a] | 9.30±0.58[a] |

Means within the same column within the same group of different letters are significantly different at (P?0.05).

## DISCUSSION

Ideal anaesthesia must satisfy the need for muscle relaxation for technical efficiency of the surgery [19].Using of ketamine as anaesthetic agent is usually associated with a lot of problems such as weak muscle relaxation, violent recovery and increased tonic and colonic muscle activity in most species [16,20]. In order to overcome these side effects it should be combined with sedatives like midazolam. Midazolam is classified as sedative and muscle relaxant drug of benzodiazepine derivatives [21]. In this study, goats were used as an animal model to investigate the sedative and muscle relaxant effects of midazolam. Rapid onset of sedation post midazolam injection in all groups with more comfortable and less excitement reaction could be attributed to that the midazolam as a water soluble drug has shorter half-life and thus has rapid onset and shorter recover period [11,16]. Similar finding was observed by Stegmann and Bester [22] in goats and Al-Redah [17] in sheep. Reves *et al.* [23] attributed the rapid onset to its high lipophility at physiological pH and short duration to rapid redistribution and metabolism in liver. Midazolam produced a dose dependent sedation, hypnosis and recumbancy. Increasing the dose of midazolam from 0.6 mg/kg to 1.2 mg /kg significantly increased the duration sedation from 27.67±1.45 to 90.00±73.00 min. Sedation score varied from mild to deep sedation in group (1) while the deep sedation is the major character of group (2). The duration of recumbancy also significantly increased from 16.67±0.88 to 70.00±2.89 min. The same results were reported by Stegmann [12]. Although the animals assume lateral recumbancy in group (1), they still conscious and try to stand when disturbed. On the other hand, when the dose increased to 1.6 mg /kg the animals remained unconscious and not respond to any painful stimuli except withdrawing hind limbs. This result resembled the results of Stegmann and Bester [22]. Sedation duration in the third group was significantly increased than in the first one and not differs than the second group. Combination of midazolam with ketamine resulted in rapid induction of general anaesthesia characterized by muscle relaxation, analgesia and smooth recovery, this results agreed with the result of Stegmann [12] in goats and Al-Redah [17] in sheep. The muscle relaxant activity of midazolam is thought to be associated with an increase in the inhibitory neurotransmitter glycine within spinal cord and in certain brain centers [24]. Although the depth of sedation after midazolam-ketamine combination was similar to that of midazolam (1.2mg/kg.) the animal responded to the painful stimuli with the last one because midazolam is poor analgesic in comparison

to ketamine. Melvin *et al.* [25] reported that midazolam didn't have analgesic effect in human but decrease the minimum alveolar concentration for halothane by at least 30%. Rectal temperature decreased non-significantly in all groups due to central nervous depression caused by benzodiazepins and reduced muscular activity [26, 27]. Benzodiazepines are muscle relaxant that improve the reliability and the quality of anaesthesia with minimal or no cardiovascular and respiratory comporomise [28]. Midazolam (0.6 mg./kg.) resulted in non-significant increase in respiratory rate and these results agreed with those obtained by Jangra *et al.* [29]. By contrast, respiratory rate was decreased in pig at 0.1 mg /kg [30]. Heart rate increased significantly in this investigation and those parallel with Stegmann, [12], on the other hand, decrease in heart rate was observed by Smith, *et al*. [30] in pig and by Al-Redah [17] in sheep. Ketamine stimulate the sympathetic nervous system producing an increase in heart rate [31]. HB, HCT, WBCs and RBCs were significantly decreased in all groups but returned to the pre injection values by end of the experiment. The decrease in HCT and HB during the period of sedation and anaesthesia might be attributed to the shifting of fluid from extravascular compartment to intravascular one in order to maintain the normal cardiac output [27]. All haematobiochemical parameters were within the physiological limits and returned to the pre injection values 60 minutes post injection so; there is no possibility of liver and kidney damage.

## CONCLUSION

It was concluded that, Midazolam 0.6mg/kg induced rapid onset of moderate to deep sedation. Injection of another 0.3mg/kg after ten min. significantly increased the duration without affecting the depth of sedation. Duplication of the dose to 1.2mg/kg resulted in rapid onset of deep sedation and recumbancy. Midazolam/ketamine combination induced short term anaesthesia lasted for 24.00±2.88 min. with complete muscle relaxation and smooth recovery.

## REFERENCES


1. Kojima, K.R. Nishimura, T. Mutoh, S.H. Hong, M. Mochizuki and N. Sasaki, 2002. Effects of medetomidine-midazolam, acepromazine-butophanol and midazolam-butorphanol on induction dose of thiopental and propofol and on cardiopulmonary changes in dogs. American Journal of Veterinary Research, 63: 1671-1679.
2. Lemke, K.A., 2007. Anticholinergic and sedatives. In J.C. Tranquiilli, Thurmon and K.A. rimm (eds) Lumb and Jones veterinary anaesthesia and analgesia. Blackwell publishing, Iowa, pp: 203-239.
3. Cray, P.R., 1986. Anaesthesia in goats and sheep. Part, II general anaesthesia. Compend Cont Educ, 8: 127-135.
4. Tylor, P.M., 1991. Anaesthesia in sheep and goats. In Pract., 13: 31-36.
5. Prajapathi, A.K., B.M. Jani and V.M. Mehta, 1994. Clinical and physiological effects of different intramuscular dosage of xylazine in goats. Indian Vet J., 71: 607-609.
6. Aziz, M.A. and S.S. Carlyle, 1978. Cardiovascular and respiratory effects of xylazine in sheep. Zentralbl Veterinarmed, 25: 173-180.
7. Uggla, A. and A. Lindqvist, 1983. Acute pulmonary oedema as adverse reaction to use of xylazine in sheep.Vet Recl., 113: 42.
8. Yamashita, K.T. and S. Futaoka, 2000. Cardiovascular effects of medetomidine and xylazine in horses. J. Vet. Med. Sci., 62: 1025-1032.
9. Moldenhauer, R., G. Ricker and A. Michaels, 1985. Anaesthesia of dwarf goats with a combination of atropine, diazepam and ketamine. Monatshefte Veterinarmedizin, 40: 817-820.
10. Ghurashi, M.A.H., H.I. Seri, A.H. Bakheit, E.A.M. Ashwag and J.A. Abakar, 2009. Evaluation of ketamine /diazepam anaesthesia for performing surgery in desert goats under field condition. Austarlian Journal of Basic and Applied Sciences, 3(2): 455-459.
11. Kyles, A.E., A.E. Waterman and A. Livingeston, 1995. Antinociceptive activity of midazolam in sheep. J. Vet. Pharmacol. Ther., 18: 54-60.
12. Stegmann, G.F., 1998. Observation on the use of midazolam for sedation and induction of anaesthesia in combination with ketamine in the goats. JI S. Afr. Vet. Ass., 69(3): 89-92.
13. Dizikiti, T.B., G.F. Stegmann and L.J. Hellebrekers. 2009. Sedative and cardiopulmonary effects of acepromazine, midazolam, acepromazine-butorphanol and midazolam-butorphanol on propofol anaesthesia in goats. J. S. Afr Vet Assoc., 80: 10-16.
14. Dizikiti, T.B., G.F. Stegmann, N.L. Dizikiti and L.J. Hellebrekers, 2010. Total intravenous anaesthesia (TIVA) with propofol-fentanyl and propofol-midazolam combinations in spontaneously-breathing goats. Veterinary Anaesthesia and Analgesia, 37: 519-525.

15. Cao, J.L., H.L. Ding, L.C. Zhang, S.M. Duan and Y.M. Zeng, 2002. Pretreatment with midazolam suppresses morphine withdrawal response in mice and rats. Acta Pharmacological Sinica, 23: 685-690.
16. Hall, L.W., K.W. Clarke and C.M. Trim, 2001. Veterinary anaesthesia 10th ed., W.B. Saunders Co, London.
17. Al-Redah, S.A., 2011. A comparative study between using midazolam-ketamine and diazepam-ketamine combination as anaesthetic program in sheep. AL-Qadisiya journal of Veterinary Medical Science, 10(1): 66-72.
18. SAS, 2006. Statistical Analysis System. Statistical user's Guide. INT., Cary, NC. USA.
19. Hall, L.W. and K.W. Clarke, 1992. Veterinary anaesthesia 9th ed., Bailliere Tindal. London.
20. Riebold, T.W., 1996. Ruminants: In: Lumb and Jones, Veterinary Anaesthesia, (3rd ed.) J.C. Thurmon, W.J. Tranquilli and G.J. Benson (ed). Williams and Wilkins, Baltimore, USA, pp: 610-626.
21. Muir, W.W. and J.A.E. Hubbel, 1989. Hand book of veterinary anaesthesia. The C.V. Mosby Compamy, St. Louis. Washington.
22. Stegmann, G.F. and L. Bester, 2001. Sedative-hypnotic effects of midazolam in goats after intravenous and intramuscular administration. Veterinary Anaesthesia and Analgesia, 28: 49-55.
23. Reves, J.G., R.J. Fragen and H.R. Vinik, 1985. Midazolam: Pharmacology and uses, Anaesthesiology, 62: 310-324.
24. Coleman, R.L. and J. Temo, 1997. Benzodiazepines. In P.F. White (ed.) Textbook of intravenous anaesthesia (1st edn.). William and Wilkens, Baltimore, pp: 77-92.
25. Melvin, M., B. Johnson, A. Quasha and E. Eger, 1982. Induction anaesthesia with midazolam decreases halothane MAC in humans, Aneasthesiology, 57: 238.
26. Grint, N.J. and P.J. Murison, 2007. Preoperative body temperature in isoflurane anaesthetized rabbits following ketamine-medetomidine. Vet. Anaesth. and Analg., 34: 181-189.
27. Kilic, N., 2008. Cardiopulmonary, biochemical and haematological changes after detomidine- midazolam-ketamine anaesthesia in calves. Bull Vet. Inst. Pulawy, 52: 453-456.
28. Robinson, N.E. and K.A. Spayberry, 2009. Current therapy in equine medicine, 6th eds. Saunders, Elsevier, St., Louis, Missouri.
29. Jangra, S.K., S.K. Chawla, P.K. Peshin, T. Rishi, J. Singh and S.M. Behl, 2008. Cardiopulmonary effects of midazolam in goats. Indian Journal of Veterinary Surgery, 29(1).
30. Smith, A.C., J.L. Zellner, F.G. Spinale and M.M. Swindle, 1991. Sedative and cardiovascular effects of midazolam in swine. Laboratory Animal Science, 41: 157-161.
31. Schuttler, J., E.K. Zsigmond and P.F. White, 1997. Ketamine and its isomers. In P.F. White (ed.) Textbook of intravenous anaesthesia (1st edn.). William and Wilkens, Baltimore, pp: 171-188.