Evaluation of Different Anesthetic Drugs Combination for Pain Management in Goats Undergoing Tube Cystostomy

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Abstract: The objective of this study was to evaluate the effect of multimodal analgesic drugs through cardiopulmonary, hormonal, metabolic and behavioral parameters for alleviation of pain perceived by goats during tube cystostomy. Sixteen bucks were randomly assigned into 4 groups 4 animals for each group. All bucks were received lidocaine hydrochloride 2% in a dose of 8 ml 15 minutes before surgery. Administration of meloxicam at dose of 0.5 mg/kg body weight took place before surgery on day 0 and was then repeated once daily for another 4 consecutive days postoperatively in groups Meloxicam-Butorphenol-Lidocaine (MBL), Meloxicam-Midazolam-Lidocaine (MML) and Meloxicam-Dexmedetomidine-Lidocaine (MDL). Heart rate (HR), respiratory rate (RR), rectal temperature (RT), serum concentrations of cortisol, interleukin-6 (IL-6), prostaglandin-E2 (PGE2) were determined at preset time intervals and the animals’ behavior was video recording, additionally detection of the effect of meloxicam on gastrointestinal bleeding using Hemo-Fec test was performed. Animals in MBL, MML and MDL groups showed good to excellent analgesia, a reduced vocalization and struggling. Mean HR, RR and RT were significantly reduced after dexmedetomidine treatment. Serum cortisol, IL-6 and PGE-2 levels remained significantly lower in dexmedetomidine treated animals compared to other groups. The use of dexmedetomidine and buterphanol in the analgesic protocol during tube cystostomy, alleviate stress and pain response and potentiate the analgesic effects of local analgesia. Addition of meloxicam to the analgesic protocol appears to be safe for the gastrointestinal tract and can be used for long term treatment of pain without complications.

Key words: Lidocaine • Meloxicam • Goats • Tube Cystostomy • Midazolam • Dexmedetomidine • Buterphanol

INTRODUCTION

Tube cystostomy appears currently to be the most promising procedure for obstructive urolithiasis in small ruminants intended for use as breeding animals. It appears to provide the highest rate of initial success and simplicity of the technique [1]. Tube cystostomy causes short-term pain and the associated stress may interfere with critical functions or even result in death and can severely affect animal welfare [2, 3] Pains evoked from tissue destruction as well as during wound healing, associated with tube cystostomy, inflammatory reaction are elicited this leads to activation of nociceptors [4, 5].

Multimodal analgesia is currently recommended for effective post-operative pain control, it is achieved by combining different analgesics that act by different mechanisms (opioids, non steroidal anti-inflammatory drugs (NSAIDs), g2-agonists and local anesthetics) resulting in additive or synergistic analgesia, lower total doses of analgesics and minimal side effects. The use of multimodal analgesia may decrease the recorded pain score and the requirement for postoperative analgesics in different surgical procedures [6].

Buterphanol have been used in goats to provide intraoperative and postoperative analgesia, in a dose of 0.05-0.20 mg/kg, i.m. or i.v. is useful to increase sedation.
from xylazine, acepromazine, or diazepam [7,8]. Meloxicam is widely selective NSAIDs, has greater inhibitory action against the inducible form of COX-2, which is implicated in inflammatory response, than against constitutive form of this enzyme COX-1 [9]. Meloxicam has anti-inflammatory effect better than other NSAIDs in animal models. Meloxicam has analgesic and antipyretic properties and is successfully used in goats [10].

Local analgesia in ruminants is a relatively simple, cheap and effective method of reducing both intra-and postoperative pain without the risk associated with general anesthesia. Local analgesics have routinely been used to provide analgesia during post-surgical procedures in calves. Lidocaine is a local analgesic that is commonly administered by a local or regional block technique. However, the duration of postoperative analgesia has been limited to 1-2 hours [11, 12].

Dexmedetomidine was twice as potent as mixture of medetomidine. It has sedative, analgesic, sympatholytic and anxiolytic effects without causing respiratory depression [13-15]. It is an agonist of α2-adrenergic receptors in certain parts of the brain. It is the S-enantiomer of medetomidine, used in sheep and goat [16]. Midazolam is fast acting benzodiazepine with short elimination half-life. It is unlike diazepam, can be administered by the intramuscular route as well as the intravenous route. Midazolam has mild cardiovascular and respiratory effects. It is commonly used as a mild tranquilizer, muscle relaxant and anticonvulsant. The sedative and hypnotic effects of midazolam in goats are dose dependent as well as dependent on route of administration [17, 18].

Pain perceived by animal during surgical intervention in cases of obstructive urolithiasis is highly appreciated thus; the objective of this study was to evaluate the effect of multimodal analgesic protocol in goats undergoing tube cystostomy through cardiopulmonary, hormonal, metabolic and behavioral changes for alleviation of pain.

**MATERIALS AND METHODS**

**Animals and Housing:** Sixteen apparently healthy bucks (aged 8-18 months; average body weight 15-25 kg) were used. All animals were housed in Surgery clinic and kept in individual free stalls on straw bedding and were fed a diet based on hay and concentrates. No analgesics were given within one week before the experiment. Food was withheld for 24 hours and water was for 12 hours before surgery. This study was performed in Mansoura Veterinary Teaching Hospital of Mansoura University, Mansoura, Egypt. All experiments were conducted in accordance with the Guidelines on Ethical Standards for Investigation of Experimental Pain in Animals [4]. In addition, the protocol was approved by the Mansoura Medical Research Ethics Committee (MMREC).

**Experimental Design:** Animals used in this study were randomly assigned into (4) groups, four animals for each group. All bucks were received lidocaine hydrochloride 2% (Debocaine 2%, Al-Debeiky pharmaceutical industrial co, Egypt) in a dose of 8 ml 15 mins before applying surgery. Initial administration of meloxicam (Metacam 20 mg/ml, Boehringer Ingelheim, Germany) at a dose of 0.5 mg/kg took place before surgery on day 0 and was then repeated once daily for another 4 consecutive days postoperatively in groups MBL, MML and MDL.

**Group I:** Lidocaine (L): bucks were restrained into lateral recumbency for application of linear infiltration analgesia at surgical site by lidocaine.

**Group II:** Meloxicam-Butorphenol-Lidocaine (MBL): All animals in this group were intravenously (I/V) received meloxicam then after 15 mins butorphanol (Alvegesic PH, 10 mg/ml, CP-Pharma, Germany) at a dose of 0.2 mg/kg.

**Group III:** Meloxicam-Midazolam-Lidocaine (MML): Animals in this group were I/V received meloxicam then after 15 mins midazolam (Midathetic 5mg/ml, Amoun pharmaceutical co, Egypt) at a dose of 0.5 mg/kg.

**Group IV:** Meloxicam-Dexmedetomidine-Lidocaine (MDL): Bucks of this group were I/V received meloxicam then after 15 mins dexmedetomidine (Precedex, 200 mcg/2 ml, Hospira, inc., Lakeforest, USA) at a dose of 5µg/kg.

**Monitoring**

**Cardio-Respiratory Parameters:** Heart rate (HR) was measured by using electrocardiogram (ECG, 100G, 100-240 V, 50/60 HZ, Contec Medical System Co., LTD, China [19]. The following parameters were measured from the ECG recordings:

- HR by multiplying the number of QRS (ventricular depolarization) Q (first negative deflection), R (first positive deflection) and S (negative deflection which follows the R wave) complex found over six seconds by a factor of 10 to get the number of QRS complex in minute.
• Amplitude of waves (millivolt) of P (atrial muscle depolarization), QRS complex and T (ventricular repolarization or relaxation) wave forms in Lead II.

• Duration of waves (seconds) of P, QRS complex and T wave forms and P-R (interval measured from the beginning of P wave to the beginning of QRS complex) and Q-T intervals (interval measured from the onset of the Q wave to the end of the T wave) in leads II.

• The characteristics of P and T waves: These characteristics were studied in term of positive, negative or biphasic deflations in all animals.

Behavioral Monitoring: Behavioral signs were recorded using video camera according to Alvarez et al. [12] and Graf and Senn [21]; Table 2.

Surgical Approach: Temporary para-median tube cystostomy was performed according to Van Metre [3]. Briefly, after aseptic preparation of the ventral abdomen and inguinal region. Local infiltration analgesia was performed using lidocaine 1% in a dose of 8 ml. A routine paramedian celitomy was performed. The bladder was identified; urine aspirated and packed off from the rest of viscera. The bladder was incised 0.5-1 cm long. A stab incision in the body wall was performed parallel to the bladder incision. The tip of a foley catheter (10-18 fr) was gently placed into jaw of large forceps and pulled into the abdomen. The tip of the Foley catheter including the deflated balloon was placed the bladder incision and into the bladder lumen. The purse string suture using chronic cat gut was placed in the bladder wall to secure the catheter in place and prevent urine leakage. Non absorbable suture was used in purse string suture pattern to secure the catheter to the skin surrounding the stab incision in the body wall (Figure 1).

Hemo-Fec Test: Fecal samples were collected after measurement of body temperature on day 1 to 4 and on day 7 postsurgery and were tested for occult blood using a guaiac fecal test (hemo FEC test; Roche Diagnostics GmbH, Munich, Germany) according to the manufacturers’ instructions.

Hormonal and Metabolic Parameters: Blood samples were centrifuged at 3000 rpm for 10 minutes and the separated sera were stored at 80°C until analysis. Cortisol (corticosterone ELISA kit, Calbiotech, USA), PGE-2 using goat PGE-2 ELISA kit and interleukin-6 levels by using goat IL-6 ELISA kit (Cusabio Biotech Co., LTD, China) were measured in goats.

Analgesia Scores: Response to stimuli was scored according to Alvarez et al. [12] and Ludbrook et al. [20] [Table 1].

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
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<tbody>
<tr>
<td>4</td>
<td>No response to palpation of surgical wound, normal interaction with environment, normal posture and movement.</td>
</tr>
<tr>
<td>3</td>
<td>Mild response to palpation of surgical wound normal interaction with environment, occasional vocalization, normal posture and movement</td>
</tr>
<tr>
<td>2</td>
<td>Moderate responsive to palpation of surgical wound, teeth grinding, vocalization, slightly hunched posture and restricted movement.</td>
</tr>
<tr>
<td>1</td>
<td>Responsive to palpation of surgical wound, vocalization and rigid posture, does not move freely</td>
</tr>
</tbody>
</table>

Table 2: Clinical description of behavioral signs recorded during the experiment modified after [12,21]

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Description</th>
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</table>
| Struggles (score) | slight or vigorous movement of legs and attempt to escape  
| 0 = no struggling | 1 = struggling with hind limbs                  |
| 2 = struggling with hind limbs and or front limbs | 3 = struggling with the whole body |
| Vocalization (n/10 min) | Emission of bleats with open or closed mouth 0= none 1= once 2= several times |
| Ear flicking (n/10 min) | Vigorous movement of one or both of the ears independent of a head shaking  
| 0= none 1= once 2= several times |
| Head shaking (n/10 min) | All exaggerated movements of the head without any discernible reason  
| 0= none 1= once 2= several times |
**Fig. 1:** A: Showed implantation of Folly Catheter in urinary bladder of a buck

a= urinary bladder b= Folly catheter

B: Showed fixation of foly catheter in the skin of a buck

**Time Table:** Baseline values were determined 15 min before drug application. Heart rate, ECG parameters, Respiratory rate and rectal body temperature were measured 15 min after administration of anesthetic agent, during surgery, at the end of surgery, 30 mins post-surgery, 1 h, 2 h and from day 1 to day 3 post operatively and endocrine-metabolic parameters during surgery, end of surgery, 2 h, 5 h and from day 1 to day 3. Clinical signs were recorded at skin incision, during surgery, end of surgery, then after 15 mins, 30 mins, 1 h, 2 h and 5 h post surgery.

**Statistical Analysis:** Data were analyzed using one-way ANOVA showed significant differences among groups. Analysis was performed with the software SPSS version 16.0 (SPSS Inc, USA). To determine which groups are different, the data were analyzed by Dunnett’s test was used to compare the experimental groups.

**RESULTS**

**Cardiopulmonary Results:** The mean average of HR in lidocaine treated animals was significantly increased ($P< 0.05$) until the end of surgery followed by gradual decreased up to 2h post-surgery. In MBL treated animals, it showed non-significant decreased after administration of butorphenol until 30 min post-surgery, followed by gradual increase compared to basal line values. In MML treated animals, it showed non-significant increased after administration of midazolam followed by gradual decreased up to 30 minutes post-surgery. A significant decrease in HR ($P < 0.05$) was shown after administration of dexmedetomidine until 1 h post-surgery compared to other groups (the lowest value was recorded at end of surgery 70 ± 5.7 (Table 3)

The mean RR were significantly decreased ($P< 0.05$) after dexmedetomidine treated animals until 15 mins post-surgery compared to other groups and baseline (Table 3), whereas it remained almost unchanged in lidocaine treated animals. RT significantly decreased in all groups throughout the whole period of anesthesia until 30 minutes post-surgery and the lowest value was recorded (37.2°C) in MDL treated animals compared to other groups (Table 3).

**ECG Results:** There were no statistically significant differences between all groups in ECG parameters (P wave, QRS complexes, T wave, P-R) compared to basal line values. No ECG abnormalities were observed after the administration of butorphenol or midazolam or lidocaine over the observation period. QT intervals were significantly increased after administration of dexmedetomidine ($P < 0.05$) until 30 minutes post-surgery compared to other groups and baseline (Table 4). P waves were recorded to be positive, QRS complexes were recorded negative in all groups and T waves were recorded to be positive while in MDL treated animals it was inverted.

**Behavioral Results:** The frequency of struggles and vocalizations was higher in the lidocaine treated animals than other groups. Administration of dexmedetomidine results in decreased activity, vocalization and struggling for 2 hour compared to butorphenol or midazolam treated...
Table 3: Heart rate (HR), respiratory rate (RR) and rectal temperature (RT) (Mean± SD) changes of goats following treatment with Lidocaine (L), meloxicam-butophenol-Lidocaine (MBL), meloxicam-midazolam-Lidocaine (MML) and meloxicam-dexmedetomidine-Lidocaine (MDL) measured at baseline, 15 min after injection of anesthesia, during surgery, at the end of surgery, 1h after surgery, 2h after surgery as well as 1 to 3 days post-surgery.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Baseline</th>
<th>+15 min</th>
<th>During</th>
<th>End</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (No of beats/ minute)</td>
<td>L</td>
<td>133.5±10.6</td>
<td>140.1±11.2</td>
<td>154.0±14.8</td>
<td>157.0±12.8</td>
<td>134.5±4.5</td>
<td>131.6±6.8</td>
<td>130.6±10.8</td>
<td>116.0±9.0</td>
<td>131.0±10.8</td>
<td>128.5±1.0</td>
</tr>
<tr>
<td>RR (breath/ minute)</td>
<td>MBL</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>QT (s)</td>
<td>L</td>
<td>.24±.04</td>
<td>.25±.05</td>
<td>.22±.02</td>
<td>.29±.01</td>
<td>.22±.06</td>
<td>.23±.05</td>
<td>.24±.04</td>
<td>.25±.05</td>
<td>.25±.05</td>
<td>.21±.05</td>
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<tr>
<td>RR (°C)</td>
<td>L</td>
<td>39.4±.05</td>
<td>39.3±.05</td>
<td>39.1±.1</td>
<td>39.0±.0</td>
<td>38.6±.0</td>
<td>38.9±.2</td>
<td>39.0±.3</td>
<td>39.7±.1</td>
<td>39.7±.0</td>
<td>39.7±.0</td>
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<tr>
<td>RR (L / min)</td>
<td>L</td>
<td>22±.6</td>
<td>20±.2</td>
<td>17±.1</td>
<td>16±.3</td>
<td>15±.6</td>
<td>19±.3</td>
<td>21±.6</td>
<td>23±.5</td>
<td>25±.6</td>
<td>26±.2</td>
</tr>
<tr>
<td>RR (MBL)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>RR (MML)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>RR (MDL)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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Corresponding means with different superscripts differ significantly (P < 0.05) among groups. Means with an asterisk (*) differ significantly (P < 0.05) from baseline.

Table 4: Duration in second of electrocardiographic waves (QT) (Mean± SD) changes of goats following treatment with Lidocaine (L), meloxicam-butophenol-Lidocaine (MBL), meloxicam-midazolam-Lidocaine (MML) and meloxicam-dexmedetomidine-Lidocaine (MDL) measured during skin incision, during surgery, at the end of surgery, 1h after surgery, 2h after surgery as well as 1 to 3 days post-surgery.

<table>
<thead>
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<th>Variables</th>
<th>Groups</th>
<th>Baseline</th>
<th>+15 min</th>
<th>During</th>
<th>End</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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<tbody>
<tr>
<td>QT (s)</td>
<td>L</td>
<td>.24±.04</td>
<td>.25±.05</td>
<td>.22±.02</td>
<td>.29±.01</td>
<td>.22±.06</td>
<td>.23±.05</td>
<td>.24±.04</td>
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<td>.25±.05</td>
<td>.21±.05</td>
</tr>
<tr>
<td>QT (MBL)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>QT (MML)</td>
<td>0.0±0.0</td>
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<tr>
<td>QT (MDL)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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Corresponding means with different superscripts differ significantly (P < 0.05) among groups. Means with an asterisk (*) differ significantly (P < 0.05) from baseline.

Table 5: Score of analgesia and behavioral (Mean± SD) changes of goats following treatment with Lidocaine (L), meloxicam-butophenol-Lidocaine (MBL), meloxicam-midazolam-Lidocaine (MML) and meloxicam-dexmedetomidine-Lidocaine (MDL) measured during skin incision, during surgery, at the end of surgery, 15 min, 30 min, 1h, 2h and 5h after surgery.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Skin incision</th>
<th>During</th>
<th>End</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia (score)</td>
<td>L</td>
<td>2.0±0.0</td>
<td>1.5±0.5</td>
<td>1.0±0.0</td>
<td>1.0±0.0</td>
<td>1.0±0.0</td>
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<td>1.0±0.0</td>
<td>1.0±0.0</td>
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<tr>
<td>Struggling (n / 10 min)</td>
<td>L</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
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<tr>
<td>Vocalization (n / 10 min)</td>
<td>L</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
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<td>2.0±0.0</td>
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<tr>
<td>Head shaking (n / 10 min)</td>
<td>L</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
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<tr>
<td>Ear flicking (n / 10 min)</td>
<td>L</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
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</table>

Corresponding means with different superscripts differ significantly (P < 0.05) among groups.
Fig. 2: Cortisol (A), interleukin-6 (B) and prostaglandin E2 (C) (Mean± SD) following treatment with Lidocaine (L), meloxicam-butorphenol-Lidocaine (MBL), meloxicam-midazolam-Lidocaine (MML) and meloxicam-dexmedetomidine-Lidocaine (MDL) measured at baseline, 15 min after injection of anesthesia, during surgery, at the end of surgery, 1h after surgery, 2h after surgery as well as 1 to 3 days post-surgery.

Endocrine and Metabolic Results: Mean serum cortisol concentration were significantly ($P < 0.05$) higher in lidocaine treated animals compared to other groups. The concentrations of cortisol were significantly lower in MDL compared to lidocaine treated animals. Cortisol concentrations of lidocaine treated animals increased rapidly reaching an initial peak of 224.3 ±5.6 ng/mL during surgery preemptive administration of buprenorphine or midazolam or dexmedetomidine before...
surgical procedures decreasing initial peak during surgery to $82\pm20.1$ ng/mL, $115.7\pm8.5$ ng/mL and $38.9\pm9.5$ ng/mL respectively (Figure 2).

Serum IL-6 and PGE-2 levels remained significantly lower in dexmedetomidine treated animals ($P < 0.05$) compared to other groups. The concentrations of IL-6 were significantly lower in MDL followed by MBL and MML compared to lidocaine treated animals (Figure 2). While post-operative period, they were significantly higher in lidocaine treated animals ($P < 0.05$) compared to other groups.

Fecal Occult Blood Results: Animals in MBL, MML and MDL groups had a negative result of a fecal occult blood test at day 4 and day 7 post-surgery.

**DISCUSSION**

In the current study, dexmedetomidine treated animals showed significantly reduced HR and RR as well as excellent analgesia. Additionally, serum cortisol, IL-6 and PGE-2 levels remained significantly lower in dexmedetomidine treated animals compared to other groups. The use of dexmedetomidine in the analgesic protocol during surgical intervention in cases of tube cystostomy in goats can alleviates surgical stress and pain response.

HR in lidocaine treated animals significantly increased until the end of surgery. This result could be attributed to the sympathetic nerve block and vasodilatation induced by the lidocaine [22, 23]. In this study, there was an initial increase of HR followed by gradual decrease in MML treated animals. This was coincided with the result obtained by Stegmann [18] Who mentioned that HR significantly increased after midazolam administration followed by gradual decrease in goats. The decrease in HR may have been the result of hypnosis, although it is expected that the heart rate would also decrease immediately after its administration. The increase in heart rate following midazolam was in agreement with previous observations in the goat [17].

In spite of, HR non-significantly decreased in MBL treated animals until 30 min post-surgery. This reduction in HR may be resulted from cardiovascular and respiratory depressants effect of butorphenol [11]. HR significantly increased following administration of butorphenol in goats by relaxing vascular musculature [7].

In our study, a significant bradycardia was shown in MDL treated animals until 1 h post-surgery. These observations correspond with the findings of Kastner et al. [14] and Singh et al. [15]. The Alpha2 agonist induced bradycardia which include decreased sympathetic outflow from the CNS, inhibition of norepinephrine release from sympathetic nerve terminals, direct depression of cardiac pacemaker and conduction tissue, increased vagal tone and a direct increase in the release of acetylcholine from parasympathetic nerves in heart [16, 24].

In the present study, RR significantly increased after lidocaine administration during surgical intervention. A similar increase in RR has been reported in lambs [23] Lidocaine increase RR through sympathetic nerve block and vasodilatation [22]. A decrease in RR was recorded in all MBL, MML and MDL treated animals during sedation. Respiratory depression associated with alpha-2 agonists might be secondary to the CNS depression produced by alpha-2 adrenoceptor stimulation [16] or to the result of direct depression of the respiratory centers by pre-anesthetics [7]. A similar decrease in RR has been reported after medetomidine administration in sheep [14]. This reduction in RR resulted from direct depressant effect of midazolam and butorphenol on central nervous system [25].

A significant decrease in RT was recorded in all treated animals up to 30 minutes post-surgery. This might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rates and muscle relaxation, along with depression of thermoregulatory centers [26]. Alpha-2 agonists have been reported to induce prolonged depression of thermoregulation [14]. Hypothermia tends to be the most common response, particularly when opioids, lidocaine and midazolam are used [11, 17].

ECG findings, in this study, showed that dexmedetomidine administration induced marked bradycardia in goats and prolongation of Q-T intervals. This could be attributed to decreased sympathetic outflow from the central nervous system and increased vagal tone. Similarly, the ECG changes in goats administered with medetomidine produced bradycardia and prolongation of R-R and Q-T intervals [27]. The P wave, QRS and T amplitude, in this study, did not change by dexmedetomidine injection, which indicated that the atrial depolarization, ventricular depolarization and ventricular repolarization were not affected after the injection, a result that coincided with Kinjanvdekar et al. [13] and Singh et al. [28].

In our study, quality of analgesia was ranged from good to excellent in MBL, MML and MDL treated animals up to 1 h post-surgery. It is well documented that alpha-2 agonists produce analgesia by blocking receptors at
increased until 3 h after dehorning in calves. Results agreed with the finding of Fransson et al. who found that lidocaine inhibits the cortisol prevention of cytokines induced hyperalgesia. Our results differ from the findings of Sutherland et al. in kids. Midazolam produce additional analgesic effect to opioids and G2 adrenoceptor agonists.

The behavioral alterations found in this study (less frequent struggles, vocalizations, ear flicking and head shaking) during surgery in MBL, MML and MDL treated animals indicate less pain perception and improved well-being of dexmedetomidine treated goat. This results agreed with Kastner et al. and Kinjavdekar et al. in sheep and goats. Meloxicam reduced the physiological stress response to dehorning until 24 h postoperative. In lidocaine treated animals, most of goats emitted high intensity behaviours, indicating that the anesthesia did not reduce the impact of the surgical stress and lidocaine did not significantly reduce the immediate expression of pain during surgery. These findings are consistent with previous studies in lambs.

Serum cortisol concentration increased significantly after tube cystostomy, indicating an important alteration in animal welfare and perception of pain. The stress response is reflected by a rise in serum cortisol during surgery in all groups. Addition of meloxicam to MBL, MML and MDL groups reduce the perioperative levels of stress-related hormones and decrease cortisol level. Serum cortisol concentrations were significantly higher in lidocaine treated animals during surgery compared to other groups. This finding agreed with Alvarez, Ricardo and Gutierrez who reported that, the infiltration of 2% Lidocaine did not prevent the increase in cortisol secretion in kids. Our results differ from the findings of Sutherland et al. who found that lidocaine inhibits the cortisol increase until 3 h after dehorning in calves.

In this study, the concentrations of cortisol were significantly lower in MDL treated animals. This may be due to alpha-2 agonists influence the pituitary response and may decrease adrenocorticotropic hormone output and reduce the perioperative levels of stress-related hormones. Thus, MDL is regarded as the most effective analgesic regime in tube cystostomy in goats. Although, the potent analgesic effect of dexmedetomidine and meloxicam. The surgical stress response cannot be completely suppressed by the synergistic effect of lidocaine, meloxicam and dexmedetomidine. This finding agreed with Stafford et al.

Addition of meloxicam to MBL, MML and MDL groups reduce serum cortisol concentration from 1 to 4 day post operatively. This could be attributed to adequate analgesic effect of meloxicam. This result agreed with Larsson et al. who mentioned that, the meloxicam treated kids showed less pain response compared to control for a day after disbudding through a significant decrease in serum cortisol level. In another study, plasma cortisol level were significantly reduced in post-surgery in meloxicam treated cows undergoing resection of septic joint compared to controls.

IL-6, works as a mediator in the cascade of pain, is secreted by a wide range of cells including immune cells, fibroblasts, endothelial cells and neurons. IL-6 is one of most common cytokines that induce the hyperalgesia. Preemptive lidocaine treatment has no significant effect to attenuate IL-6. These results agreed with Doherty et al. who found that lidocaine does not abolish the pain associated with surgery and the strong stimulation of nociceptors during the surgical treatment leads to a direct release of cytokines into the bloodstream which subsequently triggers an endocrine stress response. Additionally, IL-6 cause production of small mediators (cyclooxygenase 2) which generates PGE-2, which causes vasodilatation and enhances perception of pain. In the present study, addition of meloxicam had a significant attenuation of serum IL-6 during surgery and post operatively in MBL, MML and MDL groups. This may be due to decrease inflammatory cells production that responsible for IL-6 secretion after surgical incision.

The preemptive combination of dexmedetomidine-meloxicam results in highest attenuation of serum IL-6 and PGE2 than other groups. Dexmedetomidine was able to increase ability of meloxicam to inhibit prostaglandin synthesis via the blockage of cyclooxygenase and the prevention of cytokines induced hyperalgesia. This result agreed with the finding of Fransson et al. who reported that stimulation of serotonergic descending inhibitory system resulted in decreased stimulation of lymphocyte proliferation and decrease of IL-6 production.

PGE2 plays an important role in the development of acute inflammation. Meloxicam was a potent inhibitor of serum PGE2 generation and had greater selectivity for COX-2 inhibition. It had antipyretic, analgesic and anti-inflammatory action. In the present study PGE-2 level were significantly elevated in MBL, MML and MDL.
groups compared to lidocaine treated animals. This could be attributed to the effect of meloxicam which induce inhibition of cyclooxygenase which convert arachadonic acid into prostaglandins, prostacyclin and thromboxane [9].

The administration of 0.5 mg of meloxicam/ kg of BW as a preferential COX-2 inhibitor [41, 42] over a period of 4 days revealed no adverse effects on the gastrointestinal tract in the current study, as demonstrated by consistently negative test results for occult blood in feces.

CONCLUSIONS

Pre-emptive treatment with dexmedetomidine (5 ug/kg BW) combined with meloxicam (0.5 mg/ kg BW) appears to be the best combination for alleviation of surgical stress and pain perception in goats undergoing tube cystostomy.

REFERENCES


