



Effect of Meloxicam in Management of Post-Laparotomy Pain and Inflammation with Reference to Certain physiological, Hematological and Behavioural Parameters in Local Breed Sheep

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Abstract

This study was conducted from November 2013 to May 2014, with the objective of evaluating the effect of meloxicam a non steroidal anti-inflammatory drug to decrease postoperative pain and inflammation with reference to certain physiological, hematological and behavioural parameters in sheep. A total of 20 sheep were equally allocated into control and treatment groups. This experimental study was conducted for 5 days of study period. The baseline values for physiological, hematological and behavioural parameters were measured and recorded on day 0. Laparotomy was performed on day 1 in both groups using standard surgical protocol. A dose of 0.5 mg/kg of meloxicam was administered in treatment group of sheep for 3 consecutive postoperative days. All study parameters were measured and recorded on day 2, 3 and 4 postoperatively. The collected data was statistically expressed as mean \pm SD. The result obtained in this study showed that there were no significant changes in the mean post-operative quantitative measures in treatment group compared to its baseline value. The mean physiological parameters like rectal temperature, heart rate and respiratory rate were significantly lower ($p < 0.05$) in treatment group compared to the control group. The mean values of these parameters were significantly reduced from day 2 to 4 post-operatively. There was a significantly ($p < 0.05$) lower mean percentage of hematological parameters such as total and differential leukocyte count. The major constitute of total leukocyte count in this study were neutrophil followed by lymphocyte and monocyte. The beneficial effect of administering meloxicam had significantly maintained normal behavioural parameters like feed and water intake in treatment group. The results of this study showed that meloxicam had reduced postoperative pain and inflammation in sheep.

Keywords: Hematological; Inflammation; Meloxicam; Post laparotomy pain; Sheep

Introduction

The recognition of pain in sheep and other farm animals has lagged behind that of companion animals, horses and humans. However, pain research in sheep has been increasing over the

past 15-20 years (Hudson *et al.*, 2008). As part of good animal welfare, the freedom from pain, injury and disease is just one of the 5 freedoms outlined by the Farm Animal Welfare Council

(2009). Pain is defined as an unpleasant sensory and/or an emotional experience, which can range from mild, localized discomfort to agony, caused by actual or possible tissue damage or described in terms of such damage (Flecknell, 2000). Surgical pain may arise from surgical incision on a variety of muscle tissue types. According to Fonda (2009), pain is classified as acute, inflammatory, chronic and neuropathic pain. Looking for the scope of this study, it is restricted to inflammatory and acute pain. Animals depend on ability to respond to challenges coming from injury and pain; the only way available to receive and convey this information to the central nervous system (CNS) is through sensory organs distributed all over the body. Neurons have evolved specialized properties that allow receiving information, process and transmitting it into other cells. Nociception is the unconscious afferent activity produced in the peripheral and CNS by stimuli that have the potential to tissues damage (Julius and Basbaum, 2001).

Pain assessment method in animals can generally be categorized into objective and subjective methods. Objective method is instrumental and more reliable than subjective method. This method is to measure certain physiological, hematological and behavioural parameters. Physiological parameters include heart rate, respiratory rate and rectal temperature. Behavioural parameters are feed intake and water intake. Hematological parameters include total leukocyte count (TLC) and differential leukocyte count (DLC). Subjective methods are observations and categorizations of behaviours and can be measured in the form of scales, such as gait scoring scale for locomotion. It is more prone to poor reliability because it is non instrumental and the evaluation differs between individual observers (Weary *et al.*, 2006). Behavioral subjective methods can become a form of objective measure if used in a quantifiable way that is repeatable and reliable, especially with experience and training of the observers. A combination of objective and subjective methods may be optimal to gain more insight on what the animal is experiencing (Dobromylskyj *et al.*, 2005).

Post-laparotomy pain assessment and management in sheep has been challenging perhaps due to stoic nature, as an adaptation selected to skin their signs of pain or discomfort without complaint. Since sheep can be relatively undemonstrative when hurt (Anil *et al.*, 2005; Dobromylskyj *et al.*, 2005; Hudson *et al.*, 2008). The visible and more easily detected clinical signs in ruminants may be an indication of severe pain caused by advanced progression of tissue damage. Surgical incisions would be the most common trigger of inflammation and pain (Catalano, 2002). Effective management of pain in sheep using non-steroidal anti-inflammatory drugs (NSAIDs) has combining result for reduction of inflammatory pain and acute pain with the prevention of secondary hypersensitivity and chronic pain (Nolan, 2000).

Meloxicam is analgesic NSAID with anti-inflammatory, analgesic, anti-exudative and antipyretic effect. The analgesic and anti-inflammatory effects of meloxicam are the most essential for post-operative pain management in sheep. The effect is related to the primary action of meloxicam on cyclo-oxygenase-2 enzyme inhibition, reduction of inflammation and surgical pain by decreasing the production of prostaglandins, tromboxane A₂ and other inflammatory mediators (Nolan, 2000; Lees *et al.*, 2004). It is used in humans, horses, dogs and other farm animals for the relief of inflammation and pain in both acute and chronic musculo-skeletal disorders. There is a beneficial effect of administering meloxicam post-laparotomy to improve normal feed intake and body weight gain. Certain physiological and hematological parameters including heart rate, respiratory rate, rectal temperature, total and differential leukocyte count are normal in animal treated with meloxicam. Every surgical procedure is performed safely and efficiently in sheep using a combination of physical restraint and 2% lidocaine as local anaesthesia (Englhardt *et al.*, 1995).

To date, there are no works done related to the effect of meloxicam in animals' pain relief within the country. Several surgical procedures may severely affect the welfare of farm animals. These

procedures generally influence welfare by causing short or long term pain which is underestimated by veterinarians and practitioners. Therefore, it is essential to evaluate how deep and prolonged surgical pain is caused by painful routine interventions performed under field conditions; how post-operative pain can be accurately assessed in sheep and how these pain can be minimized is needed to ensure good welfare. There are three main reasons for this study. The first is a practical reason: this is painful procedure consistently performed at experimental level and so easily provides 20 numbers to do a thorough comprehensive study of pain management protocols. The second is an ethical reason: this means that no animal has to be submitted to additional suffering. Finally, a utilitarian motive: shown that how pain can be controlled and increase in human concern hopefully leading to the implementation of adequate guidelines and codes of practice for these procedures thus improving the welfare of millions of sheep. It hypothesis as the post-operative administering of meloxicam in sheep might have essential analgesic effect to maintain normal feed and water intake; it may prevent increase of heart rate, rectal temperature, respiratory rate, TLC and DLC.

Therefore, the overall objective of this study is:

➤ To evaluate the effect of meloxicam to decrease postoperative pain in local sheep.

The specific objectives of this study are:

✓ To evaluate the effect of meloxicam on change vital signs of heart rate, rectal temperature and respiratory rate postoperatively in local sheep.

✓ To investigate postoperative administration of meloxicam on serial changes in circulating total and differential leukocyte counts in local sheep.

✓ To observe the effect of postoperative administration of meloxicam on feed and water intake in local sheep.

Materials and Methods

Study Area

The study was conducted from November 2013 to May 2014 in Kombolcha Animal Diseases

Survey, Research and Diagnosis Laboratory. The operational area of the laboratory was eastern Amhara region comprising Waghamera, North Wollo, South Wollo, North Shoa and Ormoia Zone. A total of 50 districts are known to exist in these five zones(CSA, 2005).

Study Animals

Twenty sheep of Wollo breed at the age of 1 year old were included in this study. The average body weight was between 18-20 Kg. All experimental sheep were males, of the same age and had almost similar body conditions in order to get similar response. This category of age was chosen to standardize the group of experimental animals and at this age the sheep become mature and muscle also become strong. Each study sheep had received almost the same dose of meloxicam as analgesics drug (Meloxicam, 0.5 mg/kg, IM, once a day for three postoperative days). All study sheep were observed for physiological and behavioural parameters, body condition, health status, stress and disease condition, if any, for 1 month. The sheep didn't receive any medication for 1 week prior to the surgery. All sheep were kept under the same nutrition and managerial condition.

Study Design

Concerning effect of meloxicam, a NSAID, in management of post-laparotomy pain and inflammation with reference to certain physiological, hematological and behavioural parameters in sheep was conducted in this study. This drug was not so far studied in farm animals of Ethiopia and this was the driving force to assess its experimental effect in the current study. A randomized complete experimental study was conducted with 20 healthy wollo breed sheep, which underwent laparotomy surgery in Kombolcha regional laboratory clinic. The study sheep were assigned into treatment and control groups. Both groups of sheep were studied for 5 days (day 0, day of preoperatively used as baseline for treatment group; day 1, day of laparotomy surgery and day 2, 3 and 4,

postoperative days). On day 0, the measuring and recording of physiological, behavioural and hematological parameters were properly performed. On this day, neither the treatment nor control groups were given any drugs. On day 1, there was no measuring and recording of these parameters. However, sheep in both groups received antibiotics prophylaxis on this day to prevent post-operative infection and wound complication. In addition to antibiotic prophylaxis, sheep allocated in treatment group had received meloxicam for 3 post-operative days. The dose of this analgesic drug for sheep was preferred according to Sinclair *et al.* (2006) expressed as: Meloxicam (Metacam®), 0.5 mg/kg, IM, once a day for 3 consecutive postoperative days. Similar to day 0, post-operative measuring and recording of all parameters were performed in both groups from day 2 to 4 of the study periods. The whole blood was drawn from each sheep in treatment and control group for total and differential leukocyte count on day 0 (preoperatively) and on days 2, 3 and 4 (postoperatively). The blood sample was drawn from the jugular vein of both groups and added into vacutainer tubes containing EDTA.

Manual counting of total leukocytes was performed using haemocytometer according to Closes (1986). For total white blood cells count, blood sample was diluted 1:20 using WBC diluting solution in WBC diluting pipette (0.5 ml blood + 0.6 ml WBC diluting fluid) and then gently mixed and allowed to drop 0.1 ml blood, which assumed that properly unmixed. About 1 ml diluted blood was allowed to flow under the cover slip by capillary action for total white blood cells count. Differential leukocyte count (DLC) was also performed according to Closes (1986) briefly, a small drop of blood was spread on clean slide, air dried, fixed with in absolute methanol and stained in 10% geimsa stain solution. The absolute counts of individual cells were calculated after obtaining the relative leukocyte count. Time schedule and study parameters are explain in Annex I. The detailed experimental designs of all parameters were expressing the following subchapters.

Physiological parameters

The physiological parameters of sheep such as respiratory rate, heart rate and rectal temperature were measured and recorded in this study. This measuring and recording was performed during the regular visit for 4 days of the study period. The respiratory rate and heart rate were measured by instrument known as stethoscope. The rectal temperature was also measured using digital thermometer.

Leukocyte count

The leukocyte count of sheep including total leukocyte and differential leukocyte count were measured and recorded in this study. The total leukocyte count was measured by manual counting of leukocyte cells $\times 10^3$ per mm^3 of diluted white blood cells. The differential leukocyte count was measured in percentage during the study period. The measuring and recording of total and differential leukocyte count were performed during regular visit time for 4 days. The total and differential leukocyte counts were performed in laboratory within 10 hours of blood collection.

Behavioural parameters

Behavioural parameters in this study included were feed intake and water intake. The assessments of these parameters were done during pre-surgical and each post-surgical visit for 3 consecutive postoperative days. During study, the feed intake of experimental sheep was measured by provision of feed in kilogram per minutes of time. A fresh food of 4 kg was provided per 30 minutes for each study sheep during all study period. Following 30 minute, the remaining feed was measured and subtracted from the amount of first provision of feed to each study sheep. The water intake of each study sheep was measured by providing 5 liters of water for 10 minutes during study period. After 10 minute, the remaining water was measured and subtracted from the amount of first provision of water to each sheep.

Surgical Procedures

Preoperative preparation

Food for 24 hours and water for 8-12 hours was withheld depending on environmental temperatures and the animals' state of health. The skin of left flank was washed, cleaned, shaved and scrubbing for surgery. Tincture Iodine (2%) was used as antiseptic for skin pre and post-surgery. Ethanol (70%) was also used for disinfection of skin pre and post-injection of meloxicam.

Anaesthesia and surgery

Inverted L-block was carried out by infiltrating 15 ml of 2% lidocaine for each sheep in the left flank. All sheep were operated on day 1 only, to equalize the influence of anaesthesia on the

measurements during subsequent days. Each sheep received almost equal amount of anaesthesia. Surgery was performed on left flank with right lateral recumbence and all sheep were operated with one surgeon in order to avoid different response which arises from individual skill variations. Vertical incision about 8 cm long was made on left flank about 3cm below the level of lumbar transverse process. The abdominal muscles and parietal peritoneum were transverse by a direct incision corresponding to the skin incision. After exploring the abdominal cavity, the wound was closed. The parietal peritoneum was closed by continuous suture with chromic catgut. The incised muscles were brought into opposition by continuous suture with 2/0 chromic catgut. Finally, the skin incision was closed by horizontal mattress suture with non absorbable suture material known as silk.

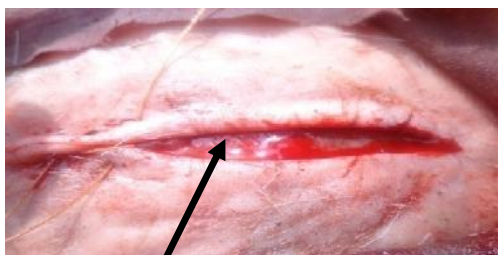


Figure 6: Layer by layer incision



Figure 7: Complete suturing of all layers

Postoperative medication

Meloxicam was administered only in treatment group for three days post operatively such as day 2, 3 and 4 during postoperative visit. The treatment group received medication in the afternoon throughout the study period i.e.

Meloxicam, 0.5 mg/kg, IM every 24 hours for maximum of 3 days post operatively (Sinclair *et al.*, 2006). Surgical prophylaxis like Sefalozin, 20 mg/kg, IV, for one day was given to both groups of sheep to prevent infection during post-laparotomy.

Data Collection

A comparative experimental study was conducted to evaluate the effect of meloxicam in the management of post-laparotomy pain and inflammation in sheep. All study sheep were visited two times a day from the beginning to the end of the study period. The study sheep in treatment and control group were around 1 year old, which were observed for 5 days. The main activities accomplished during the regular visit were measuring and recording of physical parameters in sheep such as heart rate, rectal temperature and respiratory rate; taking whole blood for leukocyte and behavioural parameters including feed intake and water intake. The finding and recording of data was kept carefully for statistical analyses.

Statistical Analysis

The two groups of sheep do not have any systematic difference except for the meloxicam applied in treatment group because it was randomly assigned to either the treatment or control group. The experimental study on heart rate, respiratory rate, rectal temperature, total leukocyte count, differential leukocyte count, feed and water intake in treatment and control group were conducted for 5 days. The experimental data was collected from both groups of sheep on day 0 preoperatively as a baseline value and day 2, 3, and 4 post-operatively. However, there was no data collection on day 1 because it was the day of surgery. Data was transferred to Microsoft Excel (2003) and the statistical analysis was performed using STATA version 11.0 statistical software. Each parameter was statistically calculated as mean \pm SD using independent and paired sample t-test in STATA and these tests were used to compare the mean of two samples. In this study, each parameter sample during post-operative days of treatment sheep and its baseline value on day 0 were analysed using paired t-test. The paired t-test examines the mean of individual differences of paired measurements and thus, it is appropriate for pre-post situations. However, the parameters between treatment and control groups were analysed using independent t-test. It is important

to evaluate the mean of individual difference between treatment and control groups.

Differences between data was considered significant when $P < 0.05$. Finally, the results were expressed in tables and sentences to compare both groups.

Ethical Considerations

The reason why farm animals' pain should be properly controlled can be grouped in the following three sets: ethical reasons, health reasons and performance reasons. There are no real differences in pain mechanisms between humans and animals that pain causes not only physical suffering but also long lasting mental distress. In this study, enough amount of feed and good housing was provided to all sheep from the beginning to the end of the study period. A surgical procedure on sheep was performed under anaesthetics without suffering to the animals. All activities such as taking blood sample from jugular vein, measuring and recording of physiological parameters, leukocyte count and behavioural parameters were performed under ethical considerations. The animal welfare was observed during the study period for all procedures and treatments until the sheep completely recovered and returned to their original place to continue its normal life. The proposal of this study was approved and ethical clearance was obtained from Tigray Regional State Science and Technology Agency Capacity Building, Research and Technology Development Directorate Regional Research Ethics Committee.

Results

Physiological Parameters

The rectal temperature ($^{\circ}\text{C}$), heart rate (beat/min) and respiratory rate (breath/min) of control and treatment groups of sheep from 0 to 4 days are presented in Table 1. There was no significant difference ($p > 0.05$) in rectal temperature, heart rate and respiratory rate between control and treatment group on day 0 preoperatively. The respective mean values of these parameters and

corresponding p-values are expressed in Table 1. The relative maximum mean rectal temperature of the treatment group was 37.83 ± 0.377 which was strongly significant ($p = 0.000$) when compared to control group (39.37 ± 0.624) on day 2 postoperatively. However, the mean rectal temperature was significantly reduced from day 2 to 4 postoperatively in treatment group compared to control group.

The mean heart rate of the treatment group was significantly different ($p < 0.002$) from day 2 to 4

of postoperatively. The relative minimum mean heart rate of treatment group was 72.2 ± 2.394 which was significantly lower ($p = 0.011$) than control group (74.8 ± 1.686) on day 3 postoperatively. The mean respiratory rate was significantly different between control and treatment groups from 2 to 4 days of study. The heart rate and respiratory rate of control and treatment groups of sheep from 0 to 4 days are expressed in Table 1.

Table 1: Effects of meloxicam on physiological parameters in control and treatment group.

Physiological parameters	Days of Study	Study groups		
		Control	Treatment	p-value
		Mean \pm S D	Mean \pm S D	
Rectal temperature ($^{\circ}$ C)	0	37.65 ± 0.324	37.68 ± 0.361	0.847**
	2	39.37 ± 0.623	37.83 ± 0.377	0.000*
	3	39.15 ± 0.643	37.79 ± 0.378	0.000*
	4	38.76 ± 0.636	37.64 ± 0.416	0.002*
Heart rate (beat/min)	0	70.4 ± 1.837	70.2 ± 3.047	0.860**
	2	75.2 ± 1.032	73.0 ± 1.943	0.005*
	3	74.8 ± 1.686	72.2 ± 2.394	0.011*
	4	75.6 ± 0.843	72.8 ± 2.347	0.002*
Respiratory rate (breath/min)	0	22.2 ± 1.131	22.4 ± 1.837	0.773**
	2	25.2 ± 1.032	22.8 ± 1.032	0.001*
	3	24.8 ± 1.398	22.6 ± 0.966	0.007*
	4	24.2 ± 1.475	22.4 ± 1.264	0.009*

** Not significant and * significant

The respective values of the mean rectal temperature, heart rate and respiratory rate and corresponding p-value of baseline (day 0) and three postoperative treatment days (day 2, 3 and 4) are expressed in Table 2. The mean rectal

temperature, heart rate and respiratory rate from 2 to 4 days of postoperative study showed no significant difference ($p > 0.05$) between day 0 and postoperative days in treatment group of sheep.

Table 2: Effects of meloxicam on physiological parameters on day 0 and postoperative days in treatment group of sheep.

Physiological parameters	Treatment group				
	Day 0		Postoperative days		p-value
	Mean \pm S D	Mean \pm S D	Mean \pm S D	Mean \pm S D	
Rectal temperature ($^{\circ}$ C)	37.48 ± 0.18	37.54 ± 0.28	37.48 ± 0.18	37.64 ± 0.42	0.555**
	37.48 ± 0.18	37.54 ± 0.28	37.48 ± 0.18	37.64 ± 0.42	0.266**
	37.48 ± 0.18	37.54 ± 0.28	37.48 ± 0.18	37.64 ± 0.42	0.071**
Heart rate (beat/min)	71.4 ± 1.89	71.6 ± 1.58	71.4 ± 1.89	72.8 ± 2.34	0.822**
	71.4 ± 1.89	71.6 ± 1.58	71.4 ± 1.89	72.8 ± 2.34	0.172**
	71.4 ± 1.89	71.6 ± 1.58	71.4 ± 1.89	72.8 ± 2.34	0.373**
Respiratory rate (breath/min)	22.0 ± 0.94	22.8 ± 1.03	22.0 ± 0.94	22.6 ± 1.35	0.103**
	22.0 ± 0.94	22.8 ± 1.03	22.0 ± 0.94	22.6 ± 1.35	0.081**
	22.0 ± 0.94	22.8 ± 1.03	22.0 ± 0.94	22.6 ± 1.35	0.081**

** Not significant

Leukocyte Count

Total leukocyte count

The total leukocyte count x 10 cells per mm³ of control and treatment group of sheep from 0 to 4 day is expressed as follow. There was no significant difference in mean of total leukocyte count between control and treatment groups on day 0 of the experiment. The TLC from day 2 to 4 showed significantly lower values in treatment group compared to control group. The relative

maximum mean TLC of the treatment group was 6.92 ± 0.456 which was significantly lower (p = 0.003) than control group (7.8 ± 0.423) on day 2 postoperatively. The relative minimum mean TLC of treatment group was 6.70 ± 0.2494 which was significantly reduced (p = 0.001) than control group (7.28 ± 0.4158) on day 4 of the study period. The respective values of the mean total leukocyte count and corresponding p-values of control and treatment groups are expressed in Table 3.

Table 3: Effect of meloxicam on TLC changes in control and treatment group of sheep.

Parameters	Days of s	S t u d y g r o u p s				
		C o n t r o l		T r e a t m e n t		p-value
		M e a n	± S D	M e a n	± S D	
TLC x 10/mm ³	0	6.53 ± 0.38	6.0	6.52 ± 0.44	1.7	0.957 **
	2	7.80 ± 0.41	3.6	6.92 ± 0.45	6.5	0.003 *
	3	7.58 ± 0.20	4.4	6.76 ± 0.29	1.4	0.000 *
	4	7.28 ± 0.41	5.8	6.70 ± 0.24	9.4	0.001 *

** Not significant and * significant

The respective values of the mean TLC and corresponding p-values of baseline (day 0) and three postoperative treatment days (day 2, 3 and 4) are expressed in Table 4. The mean TLC from

2 to 4 days of study showed no significant difference (p = 0.05) between day 0 and postoperative days in treatment group of sheep.

Table 4: Effect of meloxicam on TLC changes on day 0 and post-operative days in treatment group of sheep.

Parameter	T r e a t m e n t g r o u p				
	D a y 0		P O s t o p e r a t i v e d a y s		p-value
	M e a n	± S D	M e a n	± S D	
TLC X 10 ³ /mm ³	6.56 ± 0.26	6.61 ± 0.30	6.56 ± 0.26	6.70 ± 0.25	0.667 **
	6.56 ± 0.26	6.76 ± 0.29	6.56 ± 0.26	6.76 ± 0.29	0.200 **
	6.56 ± 0.26	6.76 ± 0.29	6.56 ± 0.26	6.76 ± 0.29	0.148 **

** Not significant

Differential leukocyte count

The respective values of mean percentage of neutrophil and corresponding p-values in all the study periods are expressed in Table 5. The mean neutrophil count of treatment and control groups showed no significant difference (p = 0.476) on day 0 preoperatively. However, a significant difference was observed in the mean neutrophil count between control and treatment group from

day 2 to 4 postoperatively. The relative maximum mean neutrophil count of the treatment group was 53.3 ± 0.850 which was significantly lower (p = 0.000) than control group (60.2 ± 3.327) on day 2 postoperatively. The relative minimum mean neutrophil count of treatment group was 51.5 ± 0.849 which was significantly lower (p = 0.006) than control group (54.3 ± 1.946) on day 4 of the study.

The mean percentage of lymphocyte count of control and treatment groups of sheep from day 0 to 4 is presented in Table 5. The mean lymphocyte count of treatment group was 34.9 ± 1.595 which was not significantly different ($p = 0.674$) compared to control group (35.2 ± 1.549) on day 0 of study period. However, the mean lymphocyte count of treatment group was significantly increased from day 2 to 4 postoperatively. The relative maximum mean lymphocyte count of the treatment group was 35.6 ± 1.43 which was significantly lower ($p = 0.012$) than control group (37.2 ± 1.135) on day 4 postoperatively. The relative minimum mean lymphocyte count of treatment group was 34.5 ± 1.581 which was significantly reduced ($p = 0.028$)

compared to control group (36.2 ± 1.619) on day 2 of study period.

On day 0, there was no significant difference ($p = 0.05$) of mean monocyte count between treatment and control group. However, a significant difference ($p = 0.05$) between these two groups was observed from day 2 to 4 of postoperative period. The mean percentage of basophil and eosinophil count from 0 to 4 days of study showed no significant difference ($p = 0.05$) between control and treatment groups. The respective values of mean monocyte, basophil and eosinophil count and corresponding p-values are expressed in Table 5.

Table 5: Effect of meloxicam on DLC changes in control and treatment group of sheep.

Parameters (%)	Days of s	S t u d y g r o u p s				p-value
		C o n t r o l		T r e a t m e n t		
		M e a n	± S D	M e a n	± S D	
Neutrophil	0	48.1	± 1.100	48.4	± 0.699	0.476**
	2	60.2	± 3.326	53.3	± 0.488	0.000*
	3	56.1	± 1.663	52.5	± 0.849	0.000*
	4	54.3	± 1.946	51.5	± 0.849	0.000*
Lymphocyte	0	35.2	± 1.549	34.9	± 1.595	0.674**
	2	36.2	± 1.619	34.5	± 1.581	0.028*
	3	36.5	± 1.581	35.1	± 0.875	0.024*
	4	37.2	± 1.135	35.6	± 1.429	0.012*
Monocyte	0	2.2	± 0.632	2.3	± 0.483	0.696**
	2	2.5	± 0.527	1.9	± 0.568	0.0248*
	3	2.8	± 0.789	2.2	± 0.422	0.0480*
	4	2.6	± 0.516	2.1	± 0.316	0.017*
Basophil	0	0.9	± 0.875	0.9	± 0.875	1.000**
	2	± 0.875		1.0	± 0.816	0.794**
	3	0.9	± 0.875	0.8	± 0.789	0.791**
	4	0.9	± 0.875	0.8	± 0.789	0.791**
Eosinophil	0	1.7	± 0.823	1.8	± 0.789	0.784**
	2	1.6	± 0.699	1.6	± 0.699	1.000**
	3	1.8	± 0.789	1.6	± 0.823	0.764**
	4	1.7	± 0.823	1.5	± 0.527	0.525**

** Not significant and * significant

The respective values of the mean DLC and corresponding p-value of day 0 used as a baseline and three postoperative treatment days (day 2, 3 and 4) are expressed in Table 6. The mean DLC

from 2 to 4 days of postoperative study in treatment group of sheep showed no significant difference ($p = 0.05$) compared to preoperative value on day 0.

Table 6: Effect of meloxicam on DLC changes on day 0 and postoperative days in treatment group of sheep.

Parameters	T r e a t m e n t g r o u p					
	M e a n ± S D					p-value
	D a y	0	P O	d a y s		
Neutrophil (%)	50.7 ± 1.25	51.5 ± 0.71	0.086	**		
	50.7 ± 1.25	51.3 ± 0.85	0.222	**		
	50.7 ± 1.25	51.4 ± 1.35	0.256	**		
Lymphocyte (%)	34.0 ± 1.3	34.1 ± 0.87	0.797	**		
	34.0 ± 1.3	34.5 ± 1.58	0.413	**		
	34.0 ± 1.3	35.1 ± 0.88	0.119	**		
Monocyte (%)	2.3 ± 0.48	1.9 ± 0.58	0.104	**		
	2.3 ± 0.48	2.2 ± 0.42	0.243	**		
	2.3 ± 0.48	2.1 ± 0.32	0.343	**		
Basophil (%)	0.7 ± 0.67	0.6 ± 0.70	0.343	**		
	0.7 ± 0.67	0.8 ± 0.79	0.343	**		
	0.7 ± 0.67	0.5 ± 0.71	0.443	**		
Eosinophil (%)	1.7 ± 0.67	1.9 ± 0.74	0.343	**		
	1.7 ± 0.67	1.5 ± 0.53	0.343	**		
	1.7 ± 0.67	1.7 ± 0.68	1.000	**		

** Not significant

Behavioural Parameters

The feed intake and water intake assessment between control and treatment groups were not significantly different (p 0.05) on day 0 of the study period. The mean value of fresh feed intake of treatment group was significantly higher (p

0.05) from day 2 to 4 postoperatively compared to control group. The mean value of water intake of treatment group was significantly lower (p 0.05) compared to control group from 2 to 4 days postoperatively. The respective values of mean feed intake and water intake and corresponding p-values are expressed in Table 7.

Table 7: Effect of meloxicam on certain behavioural parameters in control and treatment group of sheep.

Parameters	Days of s	S t u d y g r o u p s				
		C o n t r o l		T r e a t m e n t		p-value
		M e a n	± S D	M e a n	± S D	
Feed intake (kg)	0	2.5 ± 0.527	0	2.68 ± 0.4773	0.4321	**
	2	1.5 ± 0.527	2	2.4 ± 0.5164	0.0012	*
	3	1.4 ± 0.5264	3	2.6 ± 0.5164	0.0001	*
	4	1.6 ± 0.5163	4	2.7 ± 0.483	0.0001	*
Water intake (L)	0	2.7 ± 0.483	0	2.6 ± 0.5164	0.6601	**
	2	3.5 ± 0.527	2	2.8 ± 0.6325	0.0150	*
	3	3.6 ± 0.5164	3	2.7 ± 0.6749	0.0036	*
	4	3.1 ± 0.5676	4	2.5 ± 0.527	0.0248	*

** Not significant and * significant

The respective values of the mean feed intake and water intake and corresponding p-value of baseline (day 0) and three postoperative treatment days (day 2, 3 and 4) are expressed in Table 8. The mean feed intake and water intake from 2 to

4 days of postoperative study showed no significant difference (p 0.05) compared to the mean values of day 0 as a baseline in treatment group of sheep.

Table 8: Effect of meloxicam on certain behavioural parameters on day 0 and postoperative days in treatment group of sheep.

Parameters	T r e a t m e n t g r o u p									
	M e a n ± S D					p-value				
	D a y	0	P O	d a y s						
Feed intake (kg)	2 . 7 ± 0 . 6 7	2 . 5 ± 0 . 5 3	0 . 5	0 . 8						
	2 . 7 ± 0 . 6 7	2 . 6 ± 0 . 9 9	0 . 7	5 . 7						
	2 . 7 ± 0 . 6 7	2 . 4 ± 0 . 5 2	0 . 1	9 . 3						
Water intake (L)	2 . 8 ± 0 . 6 3	2 . 7 ± 0 . 6 7	0 . 6	7 . 8						
	2 . 8 ± 0 . 6 3	2 . 5 ± 0 . 5 3	0 . 2	7 . 8						
	2 . 8 ± 0 . 6 3	2 . 4 ± 0 . 6 4	0 . 2	8 . 3						

** Not significant

Discussion

Pain relief is an important aspect of treatment during pain and inflammatory processes for the well-being of the animal. Meloxicam is currently one of the most important NSAIDs approved in Canada for lactating dairy cows and has a label claim for pain in dairy cattle with no milk withdrawal period (Rang *et al.*, 2003a). Therefore, meloxicam is a drug of choice for veterinarians to administer for analgesia to sheep and other farm animals following musculoskeletal and orthopedic surgery. However, up to now, there are no works done related to the effect of meloxicam in animals' pain relief within the country. Collectively the results of all parameters of this study showed that meloxicam had prevented the abnormal increase of physiological parameters like rectal temperature, heart rate and respiratory rate and hematological parameters like total and differential leukocyte count. It had significantly maintained the quantitative measures of behavioural parameters such as normal feed intake and water intake. There was no significant difference in the results of all parameters between day 0 and post-operative days in treatment group of sheep. This is due to post-operative administration of meloxicam reduce pain and inflammatory process in sheep by reduced synthesis of inflammatory mediators such as prostaglandins, which play an important role in stimulating pain receptors, in treatment group of sheep. The results in this study are in agreement with Rinder *et al.* (2002).

The acute effects of laparotomy surgery resulted increase in physiological parameters like heart

rate, respiratory rate and rectal temperature. Laparotomy surgery arguably resulted in pain as defined by the International Association for the Study of Pain (IASP) (1994): an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is generally accepted that visceral pain in cattle is characterized by total or partial inappetence, increased rectal temperature, respiratory and heart rates. This study has shown that physiological parameters can detect acute responses that may be due to the inflammation and/or pain associated with surgery in sheep. However, it was rapidly reduced to normal range in the treatment group post-operatively. The mean value of each physiological parameter was significantly lower in treatment group compared to control group post-operatively. The rectal temperature, heart rate and respiratory rate which observed during post-operative days were not significantly different in treatment group compared to its baseline values on day 0 (Table 2). This is due to post-operative administration of meloxicam in sheep to prevent the abnormal ascending of physiological parameters by reducing pain and inflammation. The results in this study corroborates with the findings of Raekallio *et al.* (2007a)

In this study, the mean value of rectal temperature was significantly lower in treatment group compared to the control group post-operatively. The maximum mean rectal temperature reading on the first postoperative day could have corresponded to the severity of pain and inflammatory processes around the surgical site in

treatment group. It was significantly reduced from day 2 to 4 post-operatively. Therefore, the minimum mean value of rectal temperature was observed on the last post-operative day/day 4. This indicated that the treatment group of sheep rapidly returned to its normal rectal temperature/its baseline value (Table 1). This lowering rectal temperature in treatment group might be due to the reduction of inflammatory mediators which is triggered by cell injury during laparotomy surgery. Pain and inflammation is highest on the first three post-operative days. This study is in agreement with the studies reported by Groubner (2011) in sheep; Rohde *et al.* (2000) in pigs and Firth and Haldane (1999) in dogs. Postoperative administration of meloxicam in animals markedly reduced inflammation and pain to avoid abnormal ascending of rectal temperature (Kajikawa *et al.*, 1999).

The results of heart rate in this study showed that the mean value of heart rate in treatment group were significantly dropped to its baseline values from 2 to 4 post-operative days. The maximum mean heart rate was observed on the first post-operative days. This study indicated that heart rate reduced when postoperative days were increased (Table 1). In treatment group, the postoperative mean value of heart rate was almost similar the baselines mean value on day 0. Therefore, the observations of normal mean heart rate of treatment group were associated with the positive impacts of postoperative administration of meloxicam. The results obtained in this study was comparable with the previous studies done by Bunsberg (2008); Dobromylskyj *et al.* (2005) in dairy cows; Rietmann *et al.* (2004) in sheep and Pritchett *et al.* (2002) in horse.

The results of this study showed that following rectal temperature and heart rate, the respiratory rate was an important indicator of post-operative pain in sheep. The mean respiratory rate was significantly lower in treatment group compare to the control group post-operatively. The mean value of respiratory rate on post-operative days in treatment group of sheep was almost similar to its baseline value on day 0 (Table 1). The results are in agreement with the studies reported by Raekallio *et al.* (2007a) and Stock *et al.* (2001).

The sheep respond to increased rectal temperature; it has an increased respiratory rate and alters depth of respiration, in a response known as panting (Graubner, 2011).

The results of TLC in this study showed that the mean TLC was significantly lower in treatment group compared to the control group post-operatively. It was significantly higher on the first post-operative day. Gradually, it was significantly reduced from day 2 to 4 post-operatively in treatment group. Based on the results of this study, the maximum and minimum mean TLC was observed on first and third postoperative days respectively. The TLC returned to normal range rapidly in treatment group postoperatively (Table 3). This might be due to decreased adhesions of leukocytes around the site of incision, reduced inflammatory mediators and pain due to post-operative administration of meloxicam in treatment group of sheep. Neutrophil is the main components of TLC. It has the short life and its response to inflammation and pain is also highest during the first 3 post-operative days. However, the results of TLC in this study indicated that the TLC on all post-operative days did not significant difference in treatment group compared to its baseline value on day 0 (Table 4). This might be due to reduction of pain and inflammation by post-operative administration of meloxicam in treatment group of sheep. The results obtained in this study are in agreement with the studies reported by Schlam *et al.* (2005); Stock *et al.* (2001) and Churchill *et al.* (1996) reported that meloxicam reduces leukocyte infiltration into the inflamed tissue in order to reduced pain in animals.

The results of DLC in this study showed that the mean DLC was not significantly different in the post-operative days in treatment group of sheep compared to its baseline values on day 0 (Table 6). The result of DLC like neutrophil, lymphocyte and monocyte count were significantly lower in the treatment group compared to the control group on all post-operative days (Table 5). The lower mean percentage of neutrophil count was significantly observed in treatment group during all post-operative days of study. The mean percentage of neutrophil was highest in the first

postoperative days in treatment group. It was significantly decreased from day 2 to 4 post-operatively. This result showed that the mean maximum and minimum percentage of neutrophil count in treatment group was significantly observed on the first and last post-operative days respectively. This might be due to acute and inflammatory pain is the most severe during the first post-operative days. Severity of pain and inflammation has inversely proportional to postoperative days. Its severity reduced when increased postoperative days. The low response of neutrophil on day 4 might be due to a short life of neutrophil. The low response of neutrophil count in treatment group is due to post-operative administration of meloxicam reduced severity of pain and inflammation by preventing adhesion of neutrophil at the site of incision. The observations in the present study are in agreement with the studies reported by Thomas *et al.* (2005) and Wheeler *et al.* (2004) stated that neutrophil is a short-lived and produced in increased numbers during early an immune response.

In the current study, the mean percentage of lymphocyte count was significantly lower in treatment group compared to control group of sheep post-operatively. It was significantly increased in number from day 2 to 4 post-operatively. On day 2 post-operatively, the mean value lymphocyte count was significantly reduced compared to other post-operative days. Therefore, the maximum value of mean lymphocyte count was significantly observed on third post-operative day. This showed that lymphocyte is gradually increased from the first to last post-operative days and develop the immunity to prevent the re-inflammation and infection. The lower lymphocyte count in treatment group is due to postoperative administration of meloxicam. The findings in the present experiment are in agreement with other studies reported by Lees *et al.* (2004). Surgical incision and biological compounds have been reported to stimulate the immune functions and development of lymphocytosis at the site of injury which improves wound healing. It is normal for lymphocytes to be abundant in circulation, as a large population of memory cells and thus key in

prevention of re-infection and inflammation (Schalm *et al.*, 2005).

In this study, the mean percentage of monocyte was significantly lower in treatment group compared to the control group post-operatively. However, there was no significant difference between post operative days its baseline value on day 0 in treatment group of sheep. This finding corroborates the findings reported by Lees *et al.* (2004) stated that tissue injury leads to degranulation of mast cells resulting in histamine release. This elevated histamine level attracts monocyte from the bone marrow into circulation, which leaves to the sites of incision. However, Price and Nolan (2001) reported that monocytosis could occur post-operatively due to acute pain and loading of foreign body like suture materials in the tissue. In this study, the mean percentage of eosinophil and basophil count was not significantly different (Table 5). The findings are in agreement with the finding of Catalano (2002).

The observations of past research indicated that sheep exposed to acute surgical pain have reduced food intake, which will decrease heat production associated with rumen fermentation and metabolism. There is reduced feed intake and blood flow to tissue of the ruminal digestion tract, including the rumen, small intestine and large intestine, resulting reduced digestive function, reduced ruminal activity and motility (Christopherson, 2006; Johnson, 2007). In this study, the mean value of fresh feed intake and water intake did no significantly different during post-operative days of treatment group compared to its baseline value on day 0 (Table 8). There was no significant difference in both groups of sheep on day 0 preoperatively. However, the mean value of fresh feed intake was significantly higher in treatment group from day 2 to 4 post-operatively (Table 7). This might be due to the effects of post-operative administration of meloxicam in sheep to reduced pain and inflammatory mediators at the sites of incision. The results of current study in agreement with Sinclair *et al.* (2006) who reported that meloxicam treated calves with chemical disbudding consumed more milk as well as consumed calf starter earlier and at a faster rate

compared to control calves with chemical disbudding. Similarly, Heinrich *et al.* (2010) are observed a trend for meloxicam-treated calves to consume more feed following dehorning cautery compared to control calves.

In this study, no significant difference in water intake in treatment and control group was observed on day 0 preoperatively. However, the mean value of water intake was significantly reduced in treatment group of sheep during the study period. This increased water intake enables the control group to maintain body fluid homeostasis by replenishing fluid loss from the body (Table 7). In treatment group the water intake is comparable to its baseline value on day 0 because effective reductions of pain and fever by meloxicam drugs. This finding is in agreement with Nicholas *et al.* (2002); McKinley and Johnson (2004) and Turgeon *et al.* (2006).

Conclusion and Recommendations

Meloxicam is an important aspect of treatment during pain and inflammatory processes for the well-being of the animal. The results obtained in this study showed that post-operative pain had significant changes between treatment and control group postoperatively. The mean values of all study parameters post laparotomy remained same to its mean baseline values in meloxicam treated group. Again, there was no significant difference in these parameters between post-operative days and its baseline value on day 0 in treatment group of sheep. However, all parameters showed insignificant changes from its baseline values in control group of sheep where meloxicam was not administered postoperatively. These insignificant changes are attributed to pain and inflammation post-laparotomy in control group. Thus administration of meloxicam showed beneficial effect to maintained behavioural parameters such as feed and water intake. It was also responsible to avoid post-operative increase of physiological parameters like rectal temperature, heart rate and respiratory rate and control the abnormal increase of total and differential leukocyte counts in treatment group. The results of the present study showed that postoperative administration of meloxicam had been reduced pain and

inflammation in sheep. Based on the above conclusions, the following recommendations are forwarded: post-operative administration of meloxicam should be practiced in all types of surgery in sheep to maintain physiological, hematological and behavioural parameters; awareness should be created among veterinarians to practice administration of meloxicam a NSAID in management of pain and severe inflammation in sheep and adequate guidelines for postoperative pain management should be distributed to improve the welfare of millions of sheep.

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ANNEX I

Time schedule and parameters used for measurements

D a y	0	:	A r r i v a l	a t	t h e	c l i n i c
7 : 2 0	a m		H e a r t	r a t e		
7 : 5 0	a m		R e s p i r a t o r y	r a t e		
8 : 4 0	a m		R e c t a l	t e m p e r a t u r e		
9 : 3 0	a m		B o d y	w e i g h t	c h a n g e	
1 0 : 0 0	a m		F e e d	i n t a k e		
1 0 : 5 0	a m		W a t e r	i n t a k e		
1 1 : 2 0	a m		B l o o d	s a m p l e	f o r	T L C a n d D L C
D a y	1	:	D a y	o f	L a p a r o t o m y	
7 : 3 0	a m		L a p a r o t o m y	w a s	s t a r t i n g	
			All sheep	w a s	o p e r a t e d	i n
			Following	s u r g e r y,	o b s e r v e d	a l l
			In j e c t i o n	o f	M e l o x i c a m	

Day 2 : First day of post-operative	
7 : 2 0	am Heart rate
7 : 5 0	am Respiratory rate
8 : 4 0	am Rectal temperature
9 : 3 0	am Body weight change
10 : 0 0	am Feed intake
10 : 5 0	am Water intake
11 : 2 0	am Blood sample for TLC and DLC Im injection of Meloxicam

Day 3 : Second day of post-operative	
7 : 2 0	am Heart rate
7 : 5 0	am Respiratory rate
8 : 4 0	am Rectal temperature
9 : 3 0	am Body weight change
10 : 0 0	am Feed intake
10 : 5 0	am Water intake
11 : 2 0	am Blood sample for TLC and DLC Im injection of Meloxicam

Day 4 : Third day of post-operative	
7 : 2 0	am Heart rate
7 : 5 0	am Respiratory rate
8 : 4 0	am Rectal temperature
9 : 3 0	am Body weight change
10 : 0 0	am Feed intake
10 : 5 0	am Water intake
11 : 2 0	am Blood sample for TLC and DLC

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