

The effects of Meloxicam application on quality of life and development in calves

Los efectos de la aplicación de Meloxicam sobre la calidad de vida y el desarrollo en terneros

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ABSTRACT

Although it is stated that there is an increase in calf loss rates at the global level and especially in modern dairy farms, this issue, which is an international animal welfare issue, has not been adequately defined at the national, large farm, or small farm level in most developing Countries. The rate of calf deaths before, during, and after birth is between 2–20% in heifers and cows. Previous studies showed that 75% of deaths occur during birth or within the first hour after birth, 10% before birth, and 15% within 48 hours after birth. This study aimed to determine the effect of Meloxicam administration on the quality of life and development of calves. An experimental method was used to achieve the aim of this research. A total of 60 Holstein calves, 30 in the experimental group and 30 in the control group, were included in the study for the study group. MELOXÍCAM (0.5 mg·kg⁻¹) was administered to the mother cow and the calf immediately after birth, 2 days before the expected delivery. In this study, an 8 week process was passed to collect the data. It was concluded that Meloxicam did not affect the BHBA values of maternal cows. No calves died from pneumonia and diarrhea-related diseases after being treated with Meloxicam. From the total protein and total albumin values of the calves, it was concluded that Meloxicam did not affect the protein ratio, but did affect the albumin ratio. It was concluded that Meloxicam application increased the vital activity of calves.

Key words: Meloxicam; calves; quality of life; animal; Holstein cow

RESUMEN

Si bien se afirma que existe un aumento en las tasas de pérdida de terneros a nivel mundial y especialmente en las granjas lecheras modernas, este tema, que es un problema de bienestar animal internacional, no ha sido adecuadamente definido a nivel nacional, de granja grande o de granja pequeña. nivel en la mayoría de los países en desarrollo. La tasa de muertes de terneros antes, durante y después del parto es de 2 a 20 % en novillas y vacas. Estudios previos mostraron que el 75 % de las muertes ocurren durante el nacimiento o dentro de la primera hora después del nacimiento, el 10 % antes del nacimiento y el 15 % dentro de las 48 horas posteriores al nacimiento. Este estudio tuvo como objetivo determinar el efecto de la administración de meloxicam en la calidad de vida y desarrollo de los terneros. Se utilizó un método experimental para lograr el objetivo de esta investigación. Se incluyeron en el estudio para el grupo de estudio un total de 60 Holstein terneros, 30 en el grupo experimental y 30 en el grupo de control. Se administró MELOXÍCAM (0,5 mg·kg⁻¹) a la vaca madre y al ternero inmediatamente después del nacimiento, 2 días antes del parto esperado. En este estudio, se pasó un proceso de 8 semanas para recolectar los datos. Se concluyó que el meloxicam no afectó los valores de BHBA de las vacas maternas. Ningún ternero murió por neumonía y enfermedades relacionadas con la diarrea después de haber sido tratado con meloxicam. A partir de los valores de proteína total y albúmina total de los terneros, se concluyó que el meloxicam no afectó la relación de proteína, pero sí la relación de albúmina. Se concluyó que la aplicación de meloxicam incrementó la actividad vital de los terneros.

Palabras clave: Meloxicam; terneros; calidad de vida; animal; Holstein vaca

INTRODUCTION

As in humans, it is very important for animals to have a healthy pregnancy process and then a healthy birth [1]. The continuation of pregnancy after insemination and embryo transfer in cows (*Bos taurus*) depends on the hormonal mechanisms between CL and PGF2 α [2]. The development of the embryo and the continuation of the pregnancy are possible with the prevention of the release of PGF2 α from the uterine endometrium and the functional continuation of the luteal structure. In the same way, the elimination of hormonal irregularities in cows will ensure healthy reproduction [2, 3, 4, 5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for many purposes. It has some obvious uses for pain relief, antipyretic and anti-inflammatory effects and is therefore widely used in human and veterinary fields [6]. NSAIDs show their expected effects by inhibiting the cyclooxygenase (COX) enzyme responsible for prostaglandin synthesis. When cell damage occurs in the body for any reason, phospholipids are released from the damaged cell wall and arachidonic acid is produced. When comparing NSAIDs, Meloxicam has proven to be potent among them. Systemic Meloxicam produces analgesia largely through peripheral mechanisms. Thanks to the substances contained in it, most of its actions are said to have a direct effect on sensitized nociceptors [4, 7]. Meloxicam acts by inhibiting inducible COX-2 and prostaglandin synthesis. With this feature, it exerts anti-inflammatory, anti-exudative, analgesic, and antipyretic effects [8].

Meloxicam is an NSAID from the drug oxicam class, and Meloxicam is one of the anti-inflammatory drugs of the oxicam group and is an enolic acid derivative drug. Meloxicam is a nonsteroidal anti-inflammatory active substance from the oxicam group [9]. It has analgesic, antirheumatic, antipyretic, anti-inflammatory, and anti-exudative effects. The physical appearance of the drug is a yellow and odorless powder. Practically insoluble in water but slightly soluble in methanol. The pKa of the drug is 1.1-4.2. Its molecular weight is 351.41 and its melting point is 254°C. Its chemical name is Meloxicam with the formula C₁₄H₁₃N₃O₄S₂, which has the structure of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazyl)-2H-1,2-benzothiazine-3-carboxamide-1,1 dioxide [3, 10, 11]. COX-2, an inducible cyclooxygenase, causes the formation of pro-inflammatory prostaglandins by different effects and factors that cause inflammation. Meloxicam is excreted from the body, 50% through the urine and the remainder in the feces. Meloxicam is a selective COX-2 inhibitor with a half-life of approximately 13 hours (h) in cows. Flunixin meglumine is a nonselective COX inhibitor with a half-life of 8-12 h in cows. According to various researchers, it was reported that Meloxicam and Flunixin meglumine also prolong the survival of KL by inhibiting PGF2 α synthesis [12, 13]. The half-life of oral Meloxicam in ruminant calves was 27.54 h (19.97-43.29 h) and dose-adjusted 1.00 (0.64-1.66) [14]. These findings suggest that oral administration of Meloxicam can provide effective, long-lasting analgesia in ruminants.

It is very important in the birth process of cows. The normal birth of cows is directly proportional to their high milk production. Likewise, the normal birth of the cow also ensures that it can show fertility in the next pregnancy process. The difficult gestation period of cows and their difficult birth affect the calf's life negatively. Likewise, difficult births are a situation that reduces the milk yield of the cow. All these negativities increase the risk of animals being sent to slaughter [15, 16, 17]. As soon as the birth takes place, the breathing of the baby should be checked first. Several different methods can be applied for

the first respiratory stimulation by providing patency of the airways in calves. After birth, respiratory and cardiac examinations of calves, examinations of the mucosa, vision and eye reflexes, umbilical cord examination, measurement of body temperature, and determination of skin and hair structure should be done carefully and it should be evaluated whether there is a physical anomaly in the animal. It is necessary to reduce the mortality rates of the calves and to improve the rearing environments.

European Food Safety has made many improvement studies in this area and the risk analysis approach for this situation [18]. The first days after the birth of the cows are important periods for the calves to continue their lives. Survival of calves in the first days after birth depends on the correct intake of quality colostrum [19, 20]. The cause of calf death is known as diarrhea, pneumonia, and sepsis. Deaths related to these diseases occur as a result of bacteremia, viremia, and endotoxemia. It has been determined that approximately 31% of deaths can be prevented by changes in the colostrum feeding method and amount [18, 21, 22]. Koyuncu and Karaca [18] asserted that in the mistakes made in colostrum management, timing is in the first place and quality and quantity are in the second place. Providing the right amount of quality colostrum immediately after birth provides a good start for all calves. In calves; while a good improvement is achieved due to the decrease in the incidence and mortality rate of diarrhea and other disease cases, it has a positive effect on milk yield in the long term [21, 23, 24, 25].

Bayyit and Merhan's [17] study was to determine the levels of AFPs and oxidative stress in normal and difficult calving cows. To reach the data of this study, 15 Simmental cows with normal calving and 15 cows with difficult calving were included. Half of the blood taken from the vena jugularis of the animals after birth was put into tubes with anticoagulants, and the remaining half of the blood was placed in tubes without anticoagulants. As a result of the analyses, it was concluded that haptoglobin, malondialdehyde increased, ceruloplasmin, and albumin and reduced glutathione concentrations decreased in cows with difficulty giving birth [17]. Ucar investigated the effect of Meloxicam application on pregnancy rates in dairy heifers in his study conducted in 2014 [26]. As a result of the research, he administered Meloxicam as one or two injections at half dose on the 15th day and concluded that it had no positive effect on the pregnancy rate. It was observed that Meloxicam may have a reducing effect on P4 levels, although it was not statistically significant.

The number of studies using nonsteroidal anti-inflammatory drugs to maintain pregnancy has increased [2]. Positive results were obtained in studies using Flunixin Meglumine [13, 27]. Dursun [28] investigated the effect of nonsteroidal anti-inflammatory drugs on reducing embryonic deaths and increasing the pregnancy rate. For this purpose, Flunixin, Meglumine, and Ketoprofen, which are widely used in Veterinary Medicine, were preferred. Although the pregnancy rate increased with Ketoprofen administration, it was concluded that it did not have a significant effect on the prevention of late embryonic deaths. Flunixin, Meglumine, and Ketoprofen drugs have an important advantage over other NSAID drugs due to their long duration of action, fewer side effects, and less residue in milk [27, 29, 30].

Meloxicam application is a drug used in animals and used to solve many problems. In recent studies, positive effects of application on cows on insemination and pregnancy processes have been determined. This study aimed to determine the effect of Meloxicam on the quality of life and development of calves. It aimed to investigate

the effects of Meloxicam administration on the quality of life and development of calves after birth and facilitating delivery.

It is known that Meloxicam, which is in the non-steroidal anti-inflammatory group, has analgesic, anti-inflammatory, and antipyretic effects. In the literature review, it is seen that the use of different NSAID groups in cows is used to ensure pregnancy, fertilization, and relief of orthopedic pain. However, no study was found that evaluated the effectiveness of non-steroidal anti-inflammatory group drugs during birth and the survival of calves, especially the effect of Meloxicam.

MATERIALS AND METHODS

To reach the data of this research, an experimental study method was carried out. The animals included in the study are in two groups the experimental group and the control group. The Holstein cows included in the study were selected from the central processing, in the Village of Iskele Karpaz Buyukkonuk in North Cyprus. Necessary permissions were obtained from the Municipality of Buyukkonuk to carry out the application.

This study was approved by resolution 2021/140 of the Animal Experiments Local Ethics Committee of Near East University. In this research were included 60 Holstein cows. The mean milk yield of the cows included in the study was 23 ± 3.50 kg (mean value with standard deviation). The mean age of the cows was 5.0 ± 1.2 . All of the study was done in the same farm and fed in the same way, the feed content was given as 11 kg of milk feed pallet feed and 10 kg of roughage. Meloxicam ($0.5 \text{ mg} \cdot \text{kg}^{-1}$) was administered to the cows 2-3 days (d) before pregnancy and blood was taken from *vena jugularis* to check Betahydroxybutyric Acid values (BHBA) after calving. The time 2 or 3 d before the birth was determined from the findings described for Eutocia (decrease the body temperature; reduce the rumination, relaxation of the pelvic ligaments, vulva swelling, restlessness behaviour, reduce dry matter intake)[31]. The cows were examined three times a d and the fever measured. If the fiber was one grade below and three of the above symptoms were present, then the drug was administered. The animals all calved after 2 to 3 d. Before drinking the first colostrum, blood was taken from the calf (*v. jugularis*) and 2 L of colostrum was given. 6 L of colostrum was given to all calves in one d. Likewise, colostrum was given for two d. In order to look at the changes in colostrum, Total protein and Albumin values, blood was drawn on the following d: Total protein: first d, 1.2. and d 7; Albumin: first d, 1.2. and 7th d. The weights of the calves were weighed on the first d, 1, 2, 3, 4, 5, 6, 7 and 8 weeks. In this study, did not use the euthanasia method.

In this research, it was determined that Meloxicam administered to the mother had no effect on colostrum quality. There was no statistically significant difference between the two groups (MA^+ / MA^-) and the mean values were very close to each other. In a study comparing colostrum replacer with colostrum, it was concluded that Meloxicam applications did not increase absorption and did not affect total protein and IgG uptake. found in their study that there was no increase in IgG uptake after Meloxicam administration.

Animal material

The animal material of the study was divided into 2 equal groups. The groups were named Meloxicam administered (Meloxicam $0.5 \text{ mg} \cdot \text{kg}^{-1}$, $n=30$) and the control group (KG, $n=30$) without any application.

Meloxicam was administered to the mother Holstein cow and the calf immediately after birth 2 d before the expected delivery.

Statistical analysis

In this study, the scoring system is based on the analysis of the data developed by Apgar [32]. The reason for choosing APGAR is to determine the health scores of the calves immediately after birth and to evaluate their chances of survival [32]. The viability of newborn calves can be scored by evaluating many different criteria such as the appearance of hair cover, peripheral edema, the color of mucous membranes, response to reflex stimulation, heartbeats, rectal temperature, time to sternal position, time to stand up and start of sucking reflex [33, 34]. Statistical analyzes of the obtained data were made in SPSS 24.0 software environment. A two-way analysis of variance was used for repeated measurements for data analysis. Paired t-test was used to compare the mean values within the experimental and control groups, and the Bonferroni test was used to compare the simultaneous data of different groups. The $P < 0.05$ value was taken into account for the significant difference level of the difference between the groups and the changes according to time. The chi-square test was applied for cross-table analysis.

RESULTS AND DISCUSSIONS

Maternal cow BHBA values

Within the scope of the study, Meloxicam was administered to the Holstein cows in the experimental group ($n=30$) and not to the control group ($n=30$). Beta-hydroxybutyrate (BHBA) values of both groups were measured after birth. Independent samples t-test was applied to compare the BHBA values of the cows in the experimental and control groups, and no significant difference was found in the result ($t_{(58)} = -1.945$, $P > 0.05$).

Causes of calves death

TABLE I exhibits the mortality rate and the cause of death among calves based on this research.

TABLE I
Mortality Rates and the cause of Death among Calves

	Death at Birth	Diarrhea	Severe Diarrhea	Pneumonia	Total Death
Meloxicam (+)	2	2	1	0	5
Meloxicam (-)	2	3	1	1	7

When the findings regarding the causes of death of the control and experimental group calves during the 8-week experimental period were examined, it was found that 2 of the calves treated with Meloxicam died at birth, 2 died from diarrhea, and 1 died from severe diarrhea. It was found that the calves that were not administered Meloxicam died at birth, 2 died from diarrhea, 1 died from severe diarrhea, and 1 died from pneumonia.

When the causes and rates of death are examined, it can be concluded that Meloxicam administration reduces the mortality rate in calves. In particular, it can be said that it reduces the rate of

death from diarrhea. Likewise, it was concluded that the puppies treated with Meloxicam did not die of pneumonia. The conclusion from this finding is important. It is important to determine the causes of the death of calves and to try to eliminate these situations. Gastrointestinal and respiratory system diseases have an important place in yield and mortality losses in calves in the neonatal period. Diseases causing diarrhea from gastrointestinal diseases of calves in this period and diseases causing pneumonia such as respiratory system diseases play an important role as well [35].

Newborn calf diarrhea is common all over the world and the first 2–3 weeks after birth are critical because of the risk of diarrhea [26]. It is seen that the number of calves that died from diarrhea from Meloxicam administration was less than that of calves that did not receive Meloxicam. This is very pleasing considering that most of the causes of death of calves in the world are due to diarrhea. It can be said that the application of Meloxicam reduces the rate of death from diarrhea.

While there are 25 calves treated with Meloxicam and continuing their lives in good health, there are 23 healthy calves without Meloxicam.

Protein values of calves

Total protein levels of calves at 0, 1, 2, and 7 d after birth were examined and their mean values were calculated in TABLE II and the mean values between d were compared.

TABLE II
Time-Dependent Changes in Protein Levels of Calves (Average ± SS)

Parameter	Group	Day 0	Day 1	Day 2	Day 7
Total Protein	Experiment	6,24±0,47	6,33±0,49	6,30±0,55	6,39±0,65
	Control	6,19±0,53	6,40±0,59	6,53±0,69	6,38±0,62

Notes: Experiment (n=28): Meloxicam group, Control group (n=27)

Total protein values increased in the experimental group from Day 0 to Day 1, decreased on Day 2, and increased again on Day 7. No significant difference was observed between these ups and downs as a result of paired t-tests ($P>0.05$).

Total protein values increased from Day 0 to Day 1 in the control group, continued to increase on Day 2, and decreased on Day 7. A significant difference was observed as a result of paired t-tests between these ups and downs ($P<0.05$). A significant difference was observed between Day 0 and Day 1, Day 1 and Day 2, and Day 0 and Day 2 in the control group. There was no significant difference between Day 7 and other days ($P>0.05$).

There was no significant difference between the groups in the Bonferroni test results ($P>0.05$). In other words, as a result of comparing the total protein values for each day between the experimental and control groups, a similarity was observed. The graph obtained from the average values is given in FIG. 1.

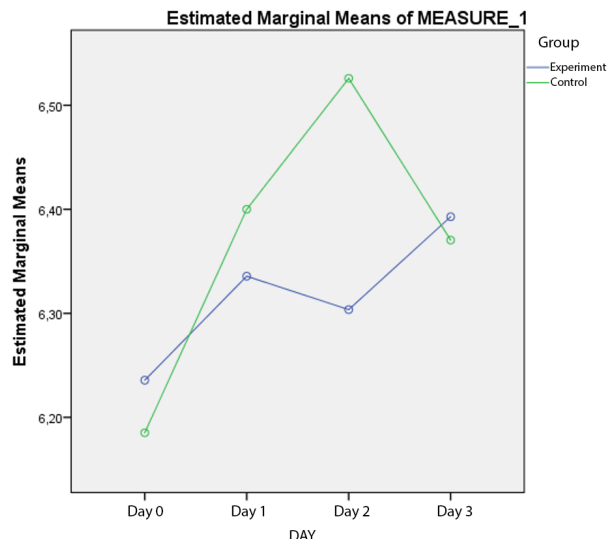


FIGURE 1. Marginal mean values of protein values in calves. Control group: green, Experimental group: blue

Albumin values of calves

Albumin levels of calves at 0, 1, 2, and 7 d after birth were examined and their average values were calculated in TABLE III and the average values between d were compared.

TABLE III
Findings on Albumin Levels of Calves at 0, 1, 2 and 7 days (Average ± SS)

Parameter	Group	Day 0	Day 1	Day 2	Day 7
Total Protein	Experiment	3,16±0,20	3,27±0,13	3,35±0,17	3,45±0,22
	Control	3,30±0,17	3,44±0,18	3,45±0,19	3,43±0,22

Notes: Experiment (n=28): Meloxicam group, Control group (n=27)

Albumin values lower in the experimental group from Day 0 to Day 1, lower on Day 2, and increased on Day 7. Significant differences were observed between these outputs as a result of paired t-tests ($P<0.05$). A significant difference was observed between Day 0 and Day 1, Day 0 and Day 2, and Day 0 and Day 7 in the experimental group. There was no significant difference between Day 1 and Day 2, Day 2 and Day 7 ($P>0.05$).

In addition, Albumin blood serum values taken from the calf were found to be lower in experimental group calves on days 0, 1 and 2). On the contrary, in the control group, the Albumin value was significantly higher ($P<0.01$ and $P<0.05$).

Meloxicam is closely bound to albumin in both humans and bovines. This connection occurs in a very sensitive part of the molecule. This compound increases both PH levels and ionic strength, and therefore increases the drug concentration. Because Meloxicam binds to the Albumin molecule, therefore in the plasma, the half-life of the drug takes a long time, i.e. more than two hours [36]. Therefore, after the Meloxicam applications, the mean value was significantly lower. It was

found in horses that the application of Meloxicam in inflammatory diseases decreased the high concentration of Albumin [37].

Albumin values increased from Day 0 to Day 1 in the control group, continued to increase on Day 2, and decreased on Day 7. A significant difference was observed as a result of paired t-tests between these ups and downs ($P < 0.05$). A significant difference was observed between Day 0 and Day 1, Day 0 and Day 2, and Day 0 and Day 7 in the control group. However, no significant difference was found between Day 1 and Day 2, Day 1 and Day 7, and Day 2 and Day 7 ($P > 0.05$).

There was a significant difference in the Bonferroni test between the groups ($P < 0.05$). In other words, as a result of the comparison of Albumin values for each day between the experimental and control groups, a significant difference was observed in favor of the experimental group. Albumin values were significantly lower in the experimental group. The graph obtained from the average values is given in FIG. 2.

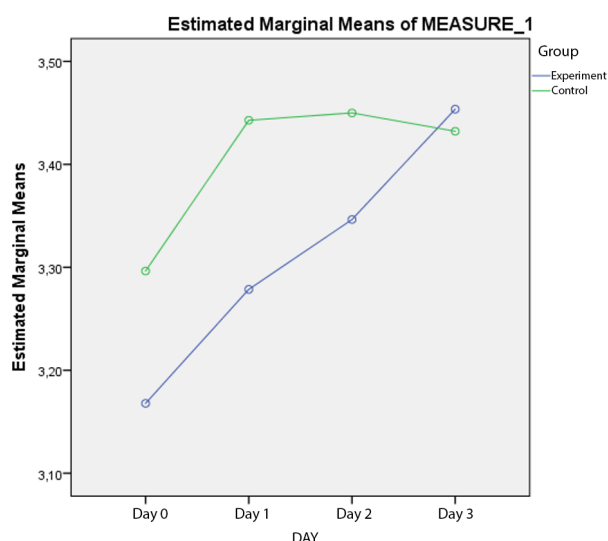


FIGURE 2. Marginal mean values of albumin values in calves. Control group: green, Experimental group: blue

APGAR findings of calves

APGAR analysis was performed in both the experimental and control groups and is given in TABLE IV.

TABLE IV
Findings on APGAR Sub-Dimensions of Calves

	Life Hazard	Depression	High Vital Activity	Total
Experiment	1 3,3%	4 13,3%	25 83,3%	30 100,0%
Control	2 6,7%	12 40,0%	16 53,3%	30 100,0%
Total	3 5,0%	16 26,7%	41 68,3%	60 100,0%

Calves in both groups were given points and determined as 7 – 8 points (high vital activity), 4 – 6 points (depression), and 0 – 3 points (life-threatening). The chi-Square test was applied to TABLE IV and a significant difference was found ($P < 0.05$). When the table was examined, it was observed that the calves with high vital activity were mostly in the experimental group.

This experimental study, it was aimed to determine the effect of Meloxicam application on the quality of life and developmental status of calves. When the findings obtained from the study were examined, the vital activities of the calves treated with Meloxicam were higher than the calves without Meloxicam. This result may mean that Meloxicam administration is effective in the quality of life of calves. Depression symptoms are a condition that can be observed in the first months of calves from birth. It can be said that Meloxicam's application reduces depression. The depressive state of the calves in the experimental group decreased at a high rate. Body posture, eye gaze, sucking reflex, movement, the position of the ears, and palpebral reflex score parameters were determined as depression symptoms of the calves. Depression decreased or absent sucking reflex, fever or hypothermia, mucous discoloration, diarrhea, meningitis, and acute death are common in calves. Many studies have proven that depression causes death in newborn calves [38, 39, 40, 41, 42, 43].

This is very pleasing. The danger can be reduced by increasing the quality of life of calves. Postnatal viability is very important in determining the adaptation of the offspring to environmental conditions. The most important factor in the health and vitality of calves is that they are fed with sufficient quantity and quality of colostrum in the first stages of birth. The results obtained from this finding are supported by other studies [9, 18, 44].

CONCLUSION

As conclusions of this study found these; Meloxicam can reduce diarrhea-related deaths. The total protein value is not affected by Meloxicam. It has been proven that depression causes newborn calves to die; Meloxicam application reduces depression in newborn calves. Also, as a result of the application of Meloxicam, Albumin levels can be influenced.

Conflict of interest

The authors of this study declare that there is no conflict of interest with the publication of this manuscript.

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