Meloxicam administration in the management of postoperative pain and inflammation associated with caesarean section in beef heifers: Evaluation of reproductive parameters

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Abstract

Post-operative pain and inflammation are normal physiological reactions to caesarean section. Their management in cattle have rarely been investigated. This surgical procedure negatively affects reproductive function with, for example, a reduction in fertility resulting in an increase in calving interval. In this multicenter clinical trial, the objective was to evaluate the impact on reproductive performance of meloxicam injected before caesarean section to manage post-operative pain and inflammation. Meloxicam is a non-steroidal anti-inflammatory drug. One hundred and twenty-seven Charolais heifers (*n* = 127) were recruited from 47 farms in six French veterinary practices in the Burgundy region. The heifers underwent a non-elective standardized caesarean section operation. Heifers were randomly assigned to one of two groups: meloxicam (*n* = 66), intravenous meloxicam injection before surgery, or control (*n* = 61). Reproductive performance and health information were recorded from the time of the caesarean section to the next calving or to culling. In our study, meloxicam administration before caesarean section had no effect on the incidence of retained placenta (18.2% of treated *vs* 25.0% of control cows, p=0.35). The pregnancy rate was higher in treated than in control cows (83.1% *vs* 67.8%, p=0.04 after multivariate analysis) and a survival analysis showed that the median calving interval was 35 days shorter in the meloxicam ($t_{50\%}$=417 days) compared to the control group ($t_{50\%}$=452 days, p=0.05). A trend was also observed for culling rate to be lower in treated (4.7%) compared to control cows (13.3%, p=0.09). In conclusion, this study suggests that there is a beneficial effect of meloxicam administration before caesarean section on reproductive performance in Charolais heifers.

Keywords

Meloxicam; C-section; Non-Steroidal Anti-Inflammatory drug; reproduction; beef heifers; pain management.

1. Introduction

The livestock industry needs to take it into consideration the increase in public concern regarding animal welfare and should evaluate the benefits of new farming practices [1]. Managing pain in farm animals is an integral part of animal welfare. However, a major difficulty lies in the perception and the evaluation of pain in animals [2,3]. Veterinarians and farmers generally agree on the nature and sources of pain in ruminants, but there is less consensus concerning the perception of its intensity and the need for its management [4]. A commission of the French National Research Institute for Agriculture, Food and Environment (INRAE) recommended to minimize animal pain in farms using a “3S” approach: “*suppress*, *substitute* or *soothe*” [5]. Although some painful procedures can be “*suppressed*” or “*substituted*”, there is currently no alternative to caesarean section (C-section) in many cases of dystocia (foetal-pelvic disproportion, uterine torsion, complicated breech presentation…). C-section is more painful than natural delivery [6]. Despite being performed often on farms, C-section leads to visceral and somatic pain which have consequences on post-surgical recovery [7]. The pain is responsible for a decrease in physical activity and is often associated with decreased in feed intake [6], exacerbating the early lactation energy deficit frequently observed in the postpartum period, which often results in a decrease in fertility [8-11].

The use of anti-inflammatory drugs, steroidal (AIS) or non-steroidal (NSAID), in the peripartum period has rarely been studied and the few results available are often inconclusive (for reviews [12,13]). Effectiveness would appear to depend on the molecules used and the interval between the onset of the painful act (calving or C-section) and treatment [14-16]. Flunixin meglumine (NSAID), administered within 24 hours of delivery [17] or during C-section [18], is associated with increased prevalence of retained placenta. Conversely, the administration of carprofen (NSAID) increased feed intake in the days following calving and increased long-term milk production [19]. In another study, the use of meloxicam (NSAID) during C-section decreased pain indicators [20]. In addition, calves born to dams treated with meloxicam prior to C-section spent more time sucking and had higher serum immunoglobulin G (IgG) levels, indicating better transfer of passive immunity (serum IgG content > 15 g/L) [21].

Finally, a recent clinical study showed an improvement in reproductive performance in animals when mastitis was treated with meloxicam [22]. Based on this study a simulation model showed that the management of inflammation as an integral part of mastitis treatment during the first 120 days postpartum could also have economic benefits [23].

Based on these observations, managing both pain and inflammation during C-section may be associated with an improvement in reproductive performance. Therefore, in this study we aimed to investigate reproductive performance (retained foetal membranes rate, pregnancy rate, calving interval, culling rate) in beef heifers receiving a non-steroidal anti-inflammatory treatment (meloxicam) prior to C-section.

2. Material and methods

This field study was performed in the Burgundy region (France) from December 2015 to September 2017. All procedures carried out in the present study were approved by the Ethical Committee in Clinical Research of the National Veterinary School of Alfort (France) under protocol # 2018-12-07.

2.1. Animals

This study was conducted on Charolais heifers (beef cattle) and focused on non-elective caesarean deliveries following dystocia. The animals included in the study were about three years old, nulliparous and from farms with a standard calving interval of less than 400 days and for which veterinary and animal husbandry records were available. In addition, the heifers had to be free from bovine viral diarrhea virus (BVDV) and infectious bovine rhinotracheitis (IBR) virus, no known infertility problems and with a body condition score (BCS) between 2 and 4 (scale 1-5). Exclusion criteria were: C-sections that resulted in post-operative complications (uterine prolapse, metritis, peritonitis) or peroperative anomalies (tearing of the uterus, failed surgical procedure), since these factors are known to have a negative impact on fertility. A total of 127 heifers from 47 farms were included in the study.

2.2. Study design

The objective of this multicenter field trial with randomized clinical cases was to monitor the fertility of beef heifers after treatment with meloxicam (a NSAID, n = 66) or control (without a NSAID, n = 61) in the management of pain and inflammation during C-section. The surgery under farm conditions was performed by seventeen veterinarian bovine obstetricians from six different veterinary clinics. For each investigator, the two experimental groups were randomly assigned. At the time of each C-section, the veterinarian opened an envelope indicating the group (meloxicam or control group) and the surgical protocol to be followed. A control visit was conducted the following day to check for placenta expulsion and to monitor the general condition of the cow. After the C-section, natural mating was used to initiate a new gestation. Cows were followed over a 520-day period at the end of which the different parameters of interest were recorded (cf. 2.4 data).

2.3. Surgery

In order to limit bias, the surgical protocol was standardized using a consensus on the technique to perform a bovine C-section published in 2007 by a French technical veterinary association [24].

In the control group, heifers only received local anesthesia. In the meloxicam group, in addition to local anesthesia, heifers received 0.5 mg meloxicam /kg liveweight(Metacam®, Boehringer Ingelheim Animal Health France, Lyon, France) intravenously (jugular vein) before beginning the surgery. For each procedure (meloxicam and control groups), premedication was performed using 10 ml of clenbuterol (Planipart®, Boehringer Ingelheim Animal Health France, Lyon, France) to induce tocolysis to facilitate manipulation and exteriorization of the gravid uterine horn. Procaine was used for local anesthesia (Procamidor®, Axience S.A.S., Pantin, France) and the surgical approach was carried out on the left flank of a standing animal. The flank had been previously sheared or shaved. The surgeon wore sterile gloves and used sterilized equipment. After its exteriorization, the uterus was opened on its large curve with a single-use scalpel. After calf removal, the uterus was sutured with two separate continuous suture patterns, at least one of which was inverted (Lembert or Cushing pattern), using a round needle and absorbable synthetic threads. Before closing the uterus, 1 g of amoxicillin (intra-uterine bolus, Clamoxyl®, Zoetis, Malakoff, France) was placed in the lumen of the uterus. Each veterinarian closed the laparotomy incision using the technique that he/she was familiar with. After surgery, a broad-spectrum antibiotic therapy (penicillin/dihydrostreptomycin) was initiated for at least four days.

2.4. Data

Several parameters were recorded to evaluate reproductive performance: the incidence of retained placenta (RP), pregnancy rate after surgery, calving interval (calving in the year n+1, extracted from BDIVET, a French national database) and culling rate. RP was defined as the presence of foetal membranes in the uterus by visual or vaginal examination more than 24 hours after calving [25]. Pregnancy diagnosis was performed by ultrasound (after 30 days post-mating) or by transrectal palpation (after 60 days post-mating).

Parameters known to influence reproductive performance were also recorded: season of heifer birth (autumn, winter, spring), age and body condition score (BCS) at C-section, season of calving and surgery records (size of the uterine incision, length of surgery defined as the time from the start of the preparation of the animal for surgery - including premedication - to the end of the cutaneous suture, first uterine suture pattern: puncturing or inverting).

2.5. Statistical analyses

RP and the first uterine suture pattern were defined as binary variables. Each remaining quantitative variable was transformed into a qualitative variable. Three classes of variable were created using arbitrarily thresholds in order to obtain a relatively balanced distribution of animals among the classes (Table 1). Data were entered in Microsoft Office Excel 2016 and imported into SAS® Studio 3.8 (SAS® University Edition) and GraphPad Prism® software (version 9.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

2.5.1. Univariate analysis

Meloxicam and control groups were compared using the Chi-square test for qualitative variables (RP rate and culling rate).

2.5.2. Multivariate analysis

A treatment effect on pregnancy rate and calving interval was investigated using multivariate models to take into account the variables known to influence the reproductive performance of primiparous cows (BCS at C-section, birth period, age at C-section, month of C-section, retained placenta, surgical technique). A treatment effect on the incidence of retained placenta and culling rate could not be tested by multivariate analysis because there were too few observations in the different classes for these two variables.

Univariate analysis was performed to assess the relationship between explicative variables, pregnancy rate and calving interval (CI) comparing the percentage of pregnant cows or mean CI for the different levels of the explicative variable (Chi square test for the first parameter, T test or ANOVA for the second). All the variables associated with pregnancy rate at the threshold of 20% were introduced in the multivariate logistic regression models together with the treatment effect (GLIMMIX procedure of SAS® Studio). A backward stepwise elimination of non-associated ($p>0.10$) variables was performed to develop the models. The model with the lowest Akaike's Information Criterion was retained.

The same approach was used to investigate the association between explicative variables and CI in linear multivariate models (MIXED procedure of SAS® Studio).

2.5.3. Survival analysis

A survival analysis was performed to investigate the interval between C-section and the next calving or culling. The advantage of this analysis was that it included all cows that were involved in the study, including those that did not calve after breeding.

The estimation of the survival functions was carried out using the Kaplan-Meier method. The log-rank test was used to compare the two survival curves.

3. Results

3.1. Descriptive analysis

In the present study, the predominant causes of dystocia were foetomaternal disproportion and incomplete dilation of the vulva or cervix. The other causes were irreducible uterine torsion (one case) and a bad foetal position that could not be corrected by obstetrical manipulation (two breech presentations and three uncomplicated posterior presentations).

The main characteristics of our sample are listed in Table 1. The variables recorded before surgery («heifer birth season», «age and body condition score C-section», «C-section period») and during surgery («size of the uterine incision», «length of surgery», «first uterine suture pattern») were not different between the meloxicam and control groups.

3.2. *Meloxicam effect on reproductive performance*

Of the 127 heifers included in the study, 126 were used to examine the variable «retained placenta» (one cow died after the intervention), 124 for «pregnancy rate» (two cows culled before breeding) and 124 for «culling rate» (three died during the study). The prevalence of RP after C-section was 21.4% (27/126), the pregnancy rate was 75.8% (94/124), the calving interval (CI) was 412±40 days (mean±sd) and the culling rate was 9.7% (12/124).

The main effects of meloxicam administration before C-section on reproductive performance are summarized in Table 2. The incidence of retained placenta was not significantly different between the meloxicam and the control group. The culling rate tended ($p=0.09$) to be lower in the meloxicam compared to the control group.

In the multivariate analysis, six variables were related to pregnancy rate at the threshold of 20% («treatment», «heifer birth season», «C-section period», «BCS», «size of the uterine incision», «length of surgery»). In the best multivariate model, pregnancy rate was higher ($p<0.05$) in the heifers that received meloxicam prior to C-section compared to controls. Three variables were related to CI at the threshold of 20% («treatment», « heifer birth season», «age at C-section»). After bias correction by multivariate analysis, treatment effect on CI was not significant (meloxicam, 406.6±6.7 *vs* control, 417.5±8.0, $p=0.20$).

Finally, figure 1 shows the Kaplan-Meier survival plot (days from C- section to next calving) for heifers receiving meloxicam or control before surgery. The median survival time (i.e. median calving interval) was 35 days shorter in the treatment group ($t_{50\%}$=417 days) compared to the control group ($t_{50\%}$=452 days, $p=0.05$).

4. Discussion

The objective of this field trial was to evaluate the impact of pre-C-section administration of a NSAID (meloxicam), in pain and inflammation management, on the fertility of Charolais beef heifers. The effects of meloxicam administration preceding C-section were evaluated by comparison with a group of control animals that only received the local anesthesia.

This study was conducted during the 2016 breeding season on Charolais heifers in the Burgundy region, one of the main breeding areas for this breed in

France [26]. Meloxicam and control groups showed similar results for parameters such as «heifer birth season», «age and body condition at C-section», and «C-section period» (Table 1). These results are consistent with the data collected across France for Charolais heifers during the same period. In our study, age at first calving (C-section) was between 31 and 39 months old and represented 84% of calvings for this breed [26]. Two calving periods are usually described in Charolais heifers: «autumn calving» and «winter calving» [26]. Since C-sections took place from December to May, this study focused on «winter calving». This calving period is known to be associated with lower reproductive performance due to a delay in the resumption of ovarian cyclicity 60 to 70 days after parturition (23-65% of cows with normal ovarian cyclicity) compared to «autumn calving» cows (70-80% of cows with normal ovarian cyclicity) [27-30]. At first calving, the recommended body condition score (BCS) for beef heifers is 2.75 to 3 (scale 1-5) [27,31]. Heifers with BCS of 2.5 or less at calving are more likely to experience a delay in the resumption of ovarian cyclicity, related to negative energy balance. This results in a prolonged calving interval [32]. In comparison, heifers with a high BCS (>3.5) at calving have an increased risk of dystocia [31]. In our study, dystocia was used as an inclusion criterion necessitating a C-section. With less than 15% of the heifers having a BCS of 2.5 or less (scale 1-5), it can therefore be assumed that the impact of negative energy balance on our data is limited.

In 2010, a survey of 710 bovine veterinary practitioners in Europe listed the differences in performing a C-section [33,34]. In order to avoid potential biases related to the use of different surgical techniques in our study, the surgical protocol was standardized according to the recommendations of the French technical veterinary association [24]. As a result of procedure standardization, the only variation factors related to surgery were: «the size of the uterine incision», «the nature of the first uterine suture pattern» and «the length of the procedure». The form of the first uterine suture pattern was not dictated in the surgical procedure, but the majority of veterinarians (>85%) chose a simple continuous suture pattern. The average length of surgery was 31±7 minutes, which is much shorter than the average time (54±12 minutes) reported in Europe in 2010 [34]. In the geographical area of our study, C-section is a very common practice for heifers: veterinarians routinely perform C-sections and farmers have become accustomed to preparing the heifer (restraint, hair removal, washing of the surgical area). This preparation time, which can represent 30% of the total time for the procedure [34], was not included in the present study, which may explain the shorter length for the procedure observed in the present experiment. Finally, no difference was observed for these variation factors between the two experimental groups.

Following C-section, the animals were monitored over a 520-day period during which reproductive performance (retained placenta rate, gestation rate, calving rate, calving interval and culling rate) was recorded. C-section is known to impair fertility, resulting in a lower conception and calving rates, and increased calving interval. Compared to a normal calving population, the decrease in pregnancy rates due to C-section ranged from 15% to 27% [35,36]: previous studies reported conception rates of 48-80% [10,36,37] and calving rates of 41-52% [35,38]. The higher pregnancy rate (75.8%) observed in this experiment may be explained by the fact that the animals in our study were heifers intended for replacement when the other studies involved animals with varying parities including multiparous cows, whose fertility is known to be lower compared to heifers.

A reduction in fertility results in a longer calving interval. In the present study, the mean calving interval for the Charolais primiparous cows after C-section was 412±40 days. These data are consistent with the results of a study which analyzed 111,871 calvings and reported a calving interval of 426 days for Charolais cows with C-section [38]. In contrast, in France, for the same breeding season (2016), the calving interval in the Charolais breed was reported to be 396±60 days [26]. C-section is associated with an increase in the incidence of retained placenta and culling rate for infertility. In the present experiment, the overall incidence of retained placenta was 21% which is higher than the incidence encountered in elective caesarean section in Belgian Blue cows (3.5%) [39] but consistent with the incidence reported (26-35%) in other studies [9,40-42]. The overall culling rate for infertility in the present study was 9.7%, similar to that previously reported in beef cattle (9%) [40].

The aim of anti-inflammatory treatment with meloxicam before C-section is to reduce inflammation in the reproductive tract following surgery and to decrease the pain associated with the surgery. The mechanisms of pain go well beyond nociception and include cortical integration of negative emotions associated with pain as well as complex interplay of excitatory and inhibitory pathways [43]. Due to the complexity of the pain network and its multiphase kinetics, pain management requires multimodal analgesia, i.e. the use of complementary molecules capable of combating different aspects of pain genesis [43,44]. Local anesthetics are powerful molecules for suppressing nociception and as such are commonly used in surgery [44,45]. However, after a single injection, their short-term action makes them unsuitable to alleviate post-operative pain and they are ineffective in preventing the development of post-incisional inflammation and the resulting peripheral hyperalgesia [43]. Opioids and NSAIDs are effective analgesics, particularly for post-operative pain. While opioids powerfully strengthen inhibitory pathways in the central nervous system, NSAIDs suppress inflammation-induced peripheral hyperalgesia due to nociceptor sensitization by inflammation mediators [44,45]. However, C-section analgesia still often only includes the use of local anesthetics [46], this does not achieve the goals of pain management. In human medicine, caesarean analgesia usually includes combinations of local anesthetics, NSAIDs and opioids [47,48]. Opioids are not approved for use in food-producing animals, but meloxicam is a long-acting NSAID approved in the European Union for use in livestock. Finally, the pre-emptive use of local anesthetics and meloxicam in combination has been shown to be effective in reducing the pain and distress in cattle associated with dehorning, castration [45,46,49] and C-section [20].

Despite these observations on pain management, the contrasting results of studies investigating the impact on fertility of the administration of anti-inflammatory drugs around calving have long hindered their use in obstetrics. For instance, ketoprofen administered just after or within 24 hours of calving had no effect on fertility [50]. Similar results were observed with carprofen administered within three weeks of parturition [16]. Studies on flunixin meglumine given after calving even reported an increase in postpartum disorders (retained placenta, metritis) that affected reproductive performance [17,18]. These studies differ from the present study because of the type of drug used and the timing of the NSAID administration in relation to the onset of the painful procedure. It would appear that the beneficial effects are more pronounced when analgesia is implemented prior to the surgery [51], which was the case in our study. Our data show that meloxicam prior to surgery increased pregnancy rate by 15% and shortened median survival time (i.e. median calving interval) by 35 days compared to control. The survival analysis, contrarily to the comparison of CI averages, takes into account the cows which did not calve after breeding and shows that more cows were likely to calve in a shorter time period after C-section in the meloxicam than the control group. These positive effects on reproduction may be related to peroperative pain management, which results in improved comfort in animals after C-section [20] and better food intake in the days following surgery [19], thus limiting the adverse effects on reproduction [8].

Furthermore, while some studies reported an increased incidence of RP when using flunixin meglumine during the peripartum period [17,18], previous experiments using meloxicam did not appear to have a similar effect on the incidence RP [52,53]. The present experiment confirmed the results of the latter studies.

Finally, among the long-term benefits, a decreased risk of culling for infertility was reported when using meloxicam at calving [54] and flunixin during C-section [9]. This helps to reduce cow replacement rate and thus improves the longevity of the animals. Although the difference is not significant, the culling rate in our study was lower in the meloxicam group.

5. Conclusions

Our study suggests that administering meloxicam before C-section in order to limit pain and inflammation does not compromise subsequent reproductive performance in beef heifers. On the contrary, the results of the present study indicate that the administration of meloxicam prior to C-section is associated with increased pregnancy rate and tends to shorten the calving interval, with no increase in the risk of retained placenta. These results are consistent with existing data. However, further studies are required to confirm these using a larger group of animals and other breeds, both beef and dairy cows.

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Authors' contributions

Vincent Mauffré: formal analysis, supervision, validation, writing – original draft,
Thomas Cardot: investigation, formal analysis, visualization
Guillaume Belbis: conceptualization, validation
Vincent Plassard: writing – review & editing
Fabienne Constant: writing – review & editing
Sandrine Bernard: resources
Nicolas Roch: conceptualization, funding acquisition
Arnaud Bohy: conceptualization, funding acquisition
Nicolas Nehlig: resources
Andrew Ponter: writing – review & editing
Bénédicte Grimard: formal analysis, writing – review & editing
Laurence Guilbert-Julien: conceptualization, funding acquisition, supervision, validation, writing – review & editing

Declaration of interest

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Table 1. Comparison of meloxicam and control groups.

Charolais heifers (n = 127) underwent a non-elective standardized caesarean section operation. Heifers were randomly assigned to one of two groups: meloxicam (n = 66), intravenous meloxicam injection before surgery, or control (n = 61).

Variable	**Meloxicam group**		**Control group**		**Total**		**p-value**
	n (/66)	**%**	**n (/61)**	**%**	**n (/127)**	**%**	
Heifer birth season							
Autumn (12/21/09 to 12/20/12)	12	18%	9	15%	21	17%	*0.74*
Winter (12/21/12 to 13/14/03)	42	64%	42	69%	84	66%	
Spring (13/15/03 to 13/21/06)	11	16%	8	13%	19	15%	
Missing data	1	2%	2	3%	3	2%	
C-section period							
December 2015	25	38%	22	36%	47	37%	*0.11*
January 2016	33	50%	23	38%	56	44%	
February-May 2016	8	12%	16	26%	24	19%	
Age at C-section							
31-33 months	8	16%	5	13%	13	10%	*0.78*
34-35 months	25	74%	24	74%	49	39%	
36-39 months	32	8%	30	10%	62	49%	
Missing data	1	2%	2	3%	3	2%	
Body Condition Score at C-section[a]							
< 3	8	12%	9	15%	17	13%	*0.30*
3	23	35%	28	46%	51	40%	
> 3	35	53%	24	39%	59	46%	

Size of the uterine incision							
20-29 cm	8	12%	12	20%	20	16%	*0.29*
30-39 cm	51	77%	46	75%	97	76%	
40-49 cm	7	11%	3	5%	10	8%	
1st uterine suture pattern type							
Simple continuous	59	89%	52	85%	111	87%	*0.48*
Inverting (Cushing or Lembert)	7	11%	9	15%	16	13%	
Length of surgery							
< 30 minutes	18	27%	14	23%	32	25%	*0.25*
30-35 minutes	36	55%	22	36%	58	46%	
> 35 minutes	10	15%	2	3%	12	9%	
Missing data	2	3%	23	38%	25	20%	
Average length (minutes)±SD	32±8		29±6		31±7		

[a] scale 1-5
[b] defined as the time from the start of the preparation of the animal for surgery - including premedication - to the end of the cutaneous suture

Table 2. Comparison of reproductive performance for meloxicam and control groups.

Charolais heifers (n = 127) underwent a non-elective standardized caesarean section operation. Heifers were randomly assigned to one of two groups: meloxicam (n = 66), intravenous meloxicam injection before surgery, or control (n = 61).

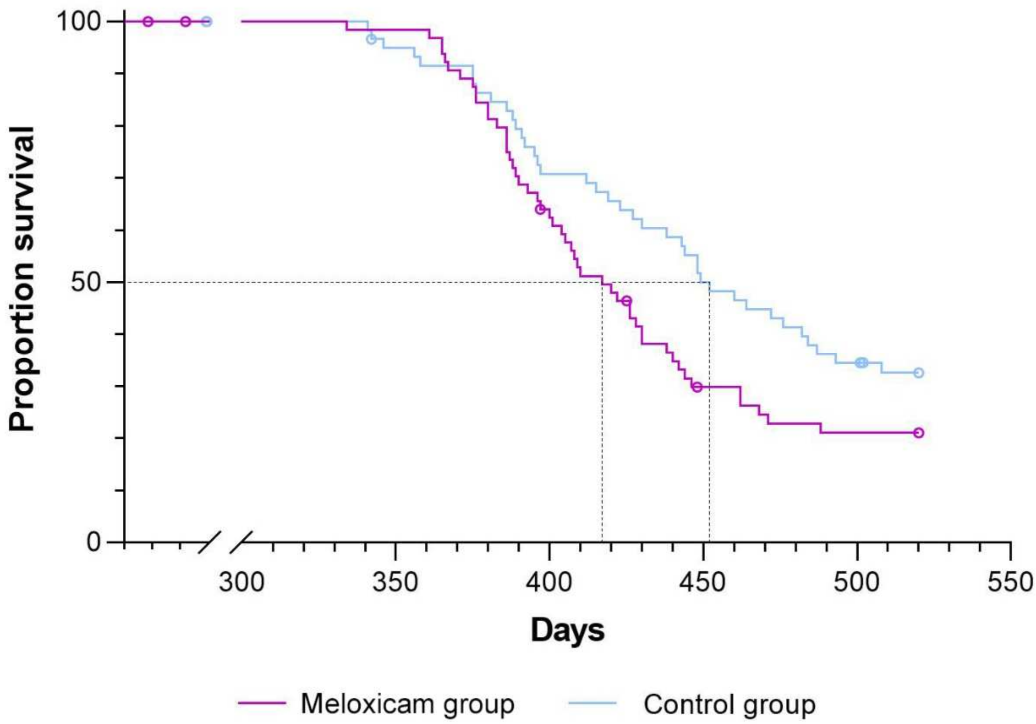
Reproductive parameters	Meloxicam group	Control group	p-value
Retained placenta (%)[a]	18.2 *(12/66)*	25.0 *(15/60)*	0.35
Pregnancy rate (%)[b]	83.1 *(54/65)*	67.8 *(40/59)*	0.04
Calving Interval (days) *(mean ± standard error)*	406.6 ±6.7	417.5 ±8.0	0.20
Culling rate (%)	4.7 *(3/64)*	13.3 *(8/60)*	0.09

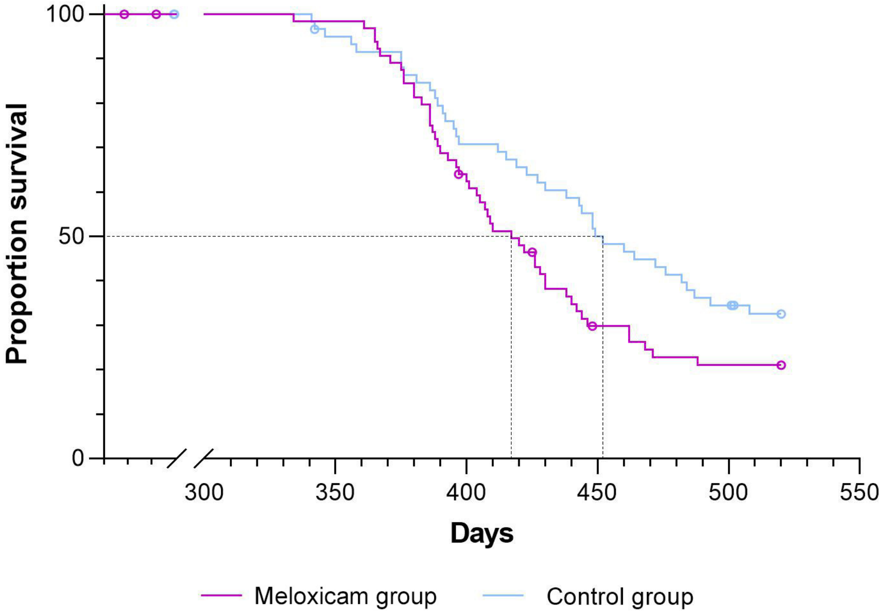
[a] retained placenta was defined as the presence of foetal membranes in the uterus by visual or vaginal examination more than 24 hours after calving

[b] pregnancy diagnosis was performed by ultrasound (after 30 days post-mating) or by transrectal palpation (after 60 days post-mating)

Figure 1. Kaplan-Meier survival plot (days from caesarean section to next calving) for Charolais heifers (n = 127) receiving meloxicam before the caesarean section (meloxicam group, n = 66) or only local anesthesia (control group, n = 61).

The dashed line indicates the median survival time, i.e the calving interval (meloxicam group, t=417 days; control group, t=452 days, p=0.050 - log-rank test) and the dots the censored animals (subjects who left the study, or the study ended before calving occurred). Each animal was followed for a 520-days period.





Proportion survival
100
50
0
300
350
400
450
500
550
Days
Meloxicam group
Control group