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Vincent Mauffré, Thomas Cardot, Guillaume Belbis, Vincent Plassard, Fabienne F. Constant, Sandrine Bernard, Nicolas Roch, Arnaud Bohy, Nicolas Nehlig, Andrew A. A. Ponter, et al.

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

Alexander Bolotin, Anne Aucouturier, Alexei Sorokin, Elena Bidnenko

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REVISED

1

2 **Meloxicam administration in the management of**  
3 **postoperative pain and inflammation associated with**  
4 **caesarean section in beef heifers: evaluation of**  
5 **reproductive parameters**

6

7 Vincent Mauffré <sup>a,b</sup>, Thomas Cardot <sup>b</sup>, Guillaume Belbis <sup>b</sup>, Vincent Plassard <sup>b</sup>,  
8 Fabienne Constant <sup>a,b</sup>, Sandrine Bernard <sup>c</sup>, Nicolas Roch <sup>c</sup>, Arnaud Bohy <sup>c</sup>, Nicolas  
9 Nehlig <sup>d</sup>, Andrew Ponter <sup>a,b</sup>, Bénédicte Grimard <sup>a,b</sup>, Laurence Guilbert-Julien <sup>e</sup>

10

11 <sup>a</sup> Université Paris-Saclay, UVSQ, INRAE, BREED, 78350, Jouy-en-Josas, France

12 <sup>b</sup> Ecole Nationale Vétérinaire d'Alfort, 94700, Maisons-Alfort, France

13 <sup>c</sup> Groupement Technique Vétérinaire Bourgogne-Franche-Comté, GTV BFC, 10 la  
14 Platière, 71150 Fontaines, France

15 <sup>d</sup> Boehringer Ingelheim Animal Health, 29 avenue Tony Garnier, 69007 Lyon, France

16 <sup>e</sup> Laboratoire National de Contrôle des Reproducteurs, 13 rue Jouet, 94700 Maisons-  
17 Alfort, France

18

19 Corresponding author: Vincent Mauffré, e-mail address: [vincent.mauffre@vet-alfort.fr](mailto:vincent.mauffre@vet-alfort.fr)

20

21 **Abstract**

22 Post-operative pain and inflammation are normal physiological reactions to  
23 caesarean section. Their management in cattle have rarely been investigated. This  
24 surgical procedure negatively affects reproductive function with, for example, a  
25 reduction in fertility resulting in an increase in calving interval. In this multicenter  
26 clinical trial, the objective was to evaluate the impact on reproductive performance of  
27 meloxicam injected before caesarean section to manage post-operative pain and  
28 inflammation. Meloxicam is a non-steroidal anti-inflammatory drug. One hundred and  
29 twenty-seven Charolais heifers ( $n = 127$ ) were recruited from 47 farms in six French

30 veterinary practices in the Burgundy region. The heifers underwent a non-elective  
31 standardized caesarean section operation. Heifers were randomly assigned to one of  
32 two groups: meloxicam ( $n = 66$ ), intravenous meloxicam injection before surgery, or  
33 control ( $n = 61$ ). Reproductive performance and health information were recorded  
34 from the time of the caesarean section to the next calving or to culling. In our study,  
35 meloxicam administration before caesarean section had no effect on the incidence of  
36 retained placenta (18.2% of treated vs 25.0% of control cows,  $p=0.35$ ). The  
37 pregnancy rate was higher in treated than in control cows (83.1% vs 67.8%,  $p=0.04$   
38 after multivariate analysis) and a survival analysis showed that the median calving  
39 interval was 35 days shorter in the meloxicam ( $t_{50\%}=417$  days) compared to the  
40 control group ( $t_{50\%}=452$  days,  $p=0.05$ ). A trend was also observed for culling rate to  
41 be lower in treated (4.7%) compared to control cows (13.3%,  $p=0.09$ ). In conclusion,  
42 this study suggests that there is a beneficial effect of meloxicam administration  
43 before caesarean section on reproductive performance in Charolais heifers.  
44

## 45 **Keywords**

46 Meloxicam; C-section; Non-Steroidal Anti-Inflammatory drug; reproduction; beef  
47 heifers; pain management.  
48

## 49 **1. Introduction**

50 The livestock industry needs to take it into consideration the increase in public  
51 concern regarding animal welfare and should evaluate the benefits of new farming  
52 practices [1]. Managing pain in farm animals is an integral part of animal welfare.  
53 However, a major difficulty lies in the perception and the evaluation of pain in animals  
54 [2,3]. Veterinarians and farmers generally agree on the nature and sources of pain in  
55 ruminants, but there is less consensus concerning the perception of its intensity and  
56 the need for its management [4]. A commission of the French National Research  
57 Institute for Agriculture, Food and Environment (INRAE) recommended to minimize  
58 animal pain in farms using a “3S” approach: “*suppress, substitute or soothe*” [5].  
59 Although some painful procedures can be “*suppressed*” or “*substituted*”, there is  
60 currently no alternative to caesarean section (C-section) in many cases of dystocia

61 (foetal-pelvic disproportion, uterine torsion, complicated breech presentation...). C-  
62 section is more painful than natural delivery [6]. Despite being performed often on  
63 farms, C-section leads to visceral and somatic pain which have consequences on  
64 post-surgical recovery [7]. The pain is responsible for a decrease in physical activity  
65 and is often associated with decreased in feed intake [6], exacerbating the early  
66 lactation energy deficit frequently observed in the postpartum period, which often  
67 results in a decrease in fertility [8-11].

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

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

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

## 91 **2. Material and methods**

92 This field study was performed in the Burgundy region (France) from December  
93 2015 to September 2017. All procedures carried out in the present study were  
94 approved by the Ethical Committee in Clinical Research of the National Veterinary  
95 School of Alfort (France) under protocol # 2018-12-07.

96

### 97 **2.1. Animals**

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

### 109 **2.2. Study design**

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

### 122        **2.3.     Surgery**

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

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

### 145        **2.4.     Data**

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

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

159

## 160 **2.5. Statistical analyses**

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

168

### 169 **2.5.1. Univariate analysis**

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

172

### 173 **2.5.2. Multivariate analysis**

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

181 Univariate analysis was performed to assess the relationship between  
182 explicative variables, pregnancy rate and calving interval (CI) comparing the  
183 percentage of pregnant cows or mean CI for the different levels of the explicative



184 variable (Chi square test for the first parameter, T test or ANOVA for the second). All  
185 the variables associated with pregnancy rate at the threshold of 20% were introduced  
186 in the multivariate logistic regression models together with the treatment effect  
187 (GLIMMIX procedure of SAS® Studio). A backward stepwise elimination of non-  
188 associated ( $p>0.10$ ) variables was performed to develop the models. The model with  
189 the lowest Akaike's Information Criterion was retained.

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

193

### 194 **2.5.3. Survival analysis**

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

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

201

## 202 **3. Results**

### 203 **3.1. Descriptive analysis**

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

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

214

### 215 **3.2. Meloxicam effect on reproductive performance**

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

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

226 In the multivariate analysis, six variables were related to pregnancy rate at the  
227 threshold of 20% («treatment», «heifer birth season», «C-section period», «BCS»,  
228 «size of the uterine incision», «length of surgery»). In the best multivariate model,  
229 pregnancy rate was higher ( $p<0.05$ ) in the heifers that received meloxicam prior to C-  
230 section compared to controls. Three variables were related to CI at the threshold of  
231 20% («treatment», « heifer birth season», «age at C-section»). After bias correction  
232 by multivariate analysis, treatment effect on CI was not significant (meloxicam,  
233 406.6±6.7 vs control, 417.5±8.0,  $p=0.20$ ).

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

## 239 **4. Discussion**

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

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

247 France [26]. Meloxicam and control groups showed similar results for parameters  
248 such as «heifer birth season», «age and body condition at C-section», and «C-  
249 section period» (Table 1). These results are consistent with the data collected across  
250 France for Charolais heifers during the same period. In our study, age at first calving  
251 (C-section) was between 31 and 39 months old and represented 84% of calvings for  
252 this breed [26]. Two calving periods are usually described in Charolais heifers:  
253 «autumn calving» and «winter calving» [26]. Since C-sections took place from  
254 December to May, this study focused on «winter calving». This calving period is  
255 known to be associated with lower reproductive performance due to a delay in the  
256 resumption of ovarian cyclicity 60 to 70 days after parturition (23-65% of cows with  
257 normal ovarian cyclicity) compared to «autumn calving» cows (70-80% of cows with  
258 normal ovarian cyclicity) [27-30]. At first calving, the recommended body condition  
259 score (BCS) for beef heifers is 2.75 to 3 (scale 1-5) [27,31]. Heifers with BCS of 2.5  
260 or less at calving are more likely to experience a delay in the resumption of ovarian  
261 cyclicity, related to negative energy balance. This results in a prolonged calving  
262 interval [32]. In comparison, heifers with a high BCS (>3.5) at calving have an  
263 increased risk of dystocia [31]. In our study, dystocia was used as an inclusion  
264 criterion necessitating a C-section. With less than 15% of the heifers having a BCS of  
265 2.5 or less (scale 1-5), it can therefore be assumed that the impact of negative  
266 energy balance on our data is limited.

267 In 2010, a survey of 710 bovine veterinary practitioners in Europe listed the  
268 differences in performing a C-section [33,34]. In order to avoid potential biases  
269 related to the use of different surgical techniques in our study, the surgical protocol  
270 was standardized according to the recommendations of the French technical  
271 veterinary association [24]. As a result of procedure standardization, the only  
272 variation factors related to surgery were: «the size of the uterine incision», «the  
273 nature of the first uterine suture pattern» and «the length of the procedure». The form  
274 of the first uterine suture pattern was not dictated in the surgical procedure, but the  
275 majority of veterinarians (>85%) chose a simple continuous suture pattern. The  
276 average length of surgery was  $31 \pm 7$  minutes, which is much shorter than the average  
277 time ( $54 \pm 12$  minutes) reported in Europe in 2010 [34]. In the geographical area of our  
278 study, C-section is a very common practice for heifers: veterinarians routinely  
279 perform C-sections and farmers have become accustomed to preparing the heifer

280 (restraint, hair removal, washing of the surgical area). This preparation time, which  
281 can represent 30% of the total time for the procedure [34], was not included in the  
282 present study, which may explain the shorter length for the procedure observed in the  
283 present experiment. Finally, no difference was observed for these variation factors  
284 between the two experimental groups.

285 Following C-section, the animals were monitored over a 520-day period during  
286 which reproductive performance (retained placenta rate, gestation rate, calving rate,  
287 calving interval and culling rate) was recorded. C-section is known to impair fertility,  
288 resulting in a lower conception and calving rates, and increased calving interval.  
289 Compared to a normal calving population, the decrease in pregnancy rates due to C-  
290 section ranged from 15% to 27% [35,36]: previous studies reported conception rates  
291 of 48-80% [10,36,37] and calving rates of 41-52% [35,38]. The higher pregnancy rate  
292 (75.8%) observed in this experiment may be explained by the fact that the animals in  
293 our study were heifers intended for replacement when the other studies involved  
294 animals with varying parities including multiparous cows, whose fertility is known to  
295 be lower compared to heifers.

296 A reduction in fertility results in a longer calving interval. In the present study,  
297 the mean calving interval for the Charolais primiparous cows after C-section was  
298  $412\pm 40$  days. These data are consistent with the results of a study which analyzed  
299 111,871 calvings and reported a calving interval of 426 days for Charolais cows with  
300 C-section [38]. In contrast, in France, for the same breeding season (2016), the  
301 calving interval in the Charolais breed was reported to be  $396\pm 60$  days [26]. C-  
302 section is associated with an increase in the incidence of retained placenta and  
303 culling rate for infertility. In the present experiment, the overall incidence of retained  
304 placenta was 21% which is higher than the incidence encountered in elective  
305 caesarean section in Belgian Blue cows (3.5%) [39] but consistent with the incidence  
306 reported (26-35%) in other studies [9,40-42]. The overall culling rate for infertility in  
307 the present study was 9.7%, similar to that previously reported in beef cattle (9%)  
308 [40].

309 The aim of anti-inflammatory treatment with meloxicam before C-section is to  
310 reduce inflammation in the reproductive tract following surgery and to decrease the  
311 pain associated with the surgery. The mechanisms of pain go well beyond  
312 nociception and include cortical integration of negative emotions associated with pain

313 as well as complex interplay of excitatory and inhibitory pathways [43]. Due to the  
314 complexity of the pain network and its multiphase kinetics, pain management  
315 requires multimodal analgesia, i.e. the use of complementary molecules capable of  
316 combating different aspects of pain genesis [43,44]. Local anesthetics are powerful  
317 molecules for suppressing nociception and as such are commonly used in surgery  
318 [44,45]. However, after a single injection, their short-term action makes them  
319 unsuitable to alleviate post-operative pain and they are ineffective in preventing the  
320 development of post-incisional inflammation and the resulting peripheral hyperalgesia  
321 [43]. Opioids and NSAIDs are effective analgesics, particularly for post-operative  
322 pain. While opioids powerfully strengthen inhibitory pathways in the central nervous  
323 system, NSAIDs suppress inflammation-induced peripheral hyperalgesia due to  
324 nociceptor sensitization by inflammation mediators [44,45]. However, C-section  
325 analgesia still often only includes the use of local anesthetics [46], this does not  
326 achieve the goals of pain management. In human medicine, caesarean analgesia  
327 usually includes combinations of local anesthetics, NSAIDs and opioids [47,48].  
328 Opioids are not approved for use in food-producing animals, but meloxicam is a long-  
329 acting NSAID approved in the European Union for use in livestock. Finally, the pre-  
330 emptive use of local anesthetics and meloxicam in combination has been shown to  
331 be effective in reducing the pain and distress in cattle associated with dehorning,  
332 castration [45,46,49] and C-section [20].

333 Despite these observations on pain management, the contrasting results of  
334 studies investigating the impact on fertility of the administration of anti-inflammatory  
335 drugs around calving have long hindered their use in obstetrics. For instance,  
336 ketoprofen administered just after or within 24 hours of calving had no effect on  
337 fertility [50]. Similar results were observed with carprofen administered within three  
338 weeks of parturition [16]. Studies on flunixin meglumine given after calving even  
339 reported an increase in postpartum disorders (retained placenta, metritis) that  
340 affected reproductive performance [17,18]. These studies differ from the present  
341 study because of the type of drug used and the timing of the NSAID administration in  
342 relation to the onset of the painful procedure. It would appear that the beneficial  
343 effects are more pronounced when analgesia is implemented prior to the surgery  
344 [51], which was the case in our study. Our data show that meloxicam prior to surgery  
345 increased pregnancy rate by 15% and shortened median survival time (i.e. median

346 calving interval) by 35 days compared to control. The survival analysis, contrarily to  
347 the comparison of CI averages, takes into account the cows which did not calve after  
348 breeding and shows that more cows were likely to calve in a shorter time period after  
349 C-section in the meloxicam than the control group. These positive effects on  
350 reproduction may be related to peroperative pain management, which results in  
351 improved comfort in animals after C-section [20] and better food intake in the days  
352 following surgery [19], thus limiting the adverse effects on reproduction [8].

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

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

362

## 363 **5. Conclusions**

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

372

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## 378 **Authors' contributions**

379 **Vincent Mauffré:** formal analysis, supervision, validation, writing – original draft,

380 **Thomas Cardot:** investigation, formal analysis, visualization

381 **Guillaume Belbis:** conceptualization, validation

382 **Vincent Plassard:** writing – review & editing

383 **Fabienne Constant:** writing – review & editing

384 **Sandrine Bernard:** resources

385 **Nicolas Roch:** conceptualization, funding acquisition

386 **Arnaud Bohy:** conceptualization, funding acquisition

387 **Nicolas Nehlig:** resources

388 **Andrew Ponter:** writing – review & editing

389 **Bénédicte Grimard:** formal analysis, writing – review & editing

390 **Laurence Guilbert-Julien:** conceptualization, funding acquisition, supervision,  
391 validation, writing – review & editing

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580

581 **Table 1. Comparison of meloxicam and control groups.**

582 Charolais heifers (n = 127) underwent a non-elective standardized caesarean section operation. Heifers were randomly assigned to  
 583 one of two groups: meloxicam (n = 66), intravenous meloxicam injection before surgery, or control (n = 61).  
 584

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

585

<sup>a</sup> scale 1-5

586

<sup>b</sup> defined as the time from the start of the preparation of the animal for surgery - including premedication - to the end of the cutaneous suture

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

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

592

<b>Reproductive parameters</b>	<b>Meloxicam group</b>	<b>Control group</b>	<b>p-value</b>
Retained placenta (%) <sup>a</sup>	18.2 (12/66)	25.0 (15/60)	0.35
Pregnancy rate (%) <sup>b</sup>	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

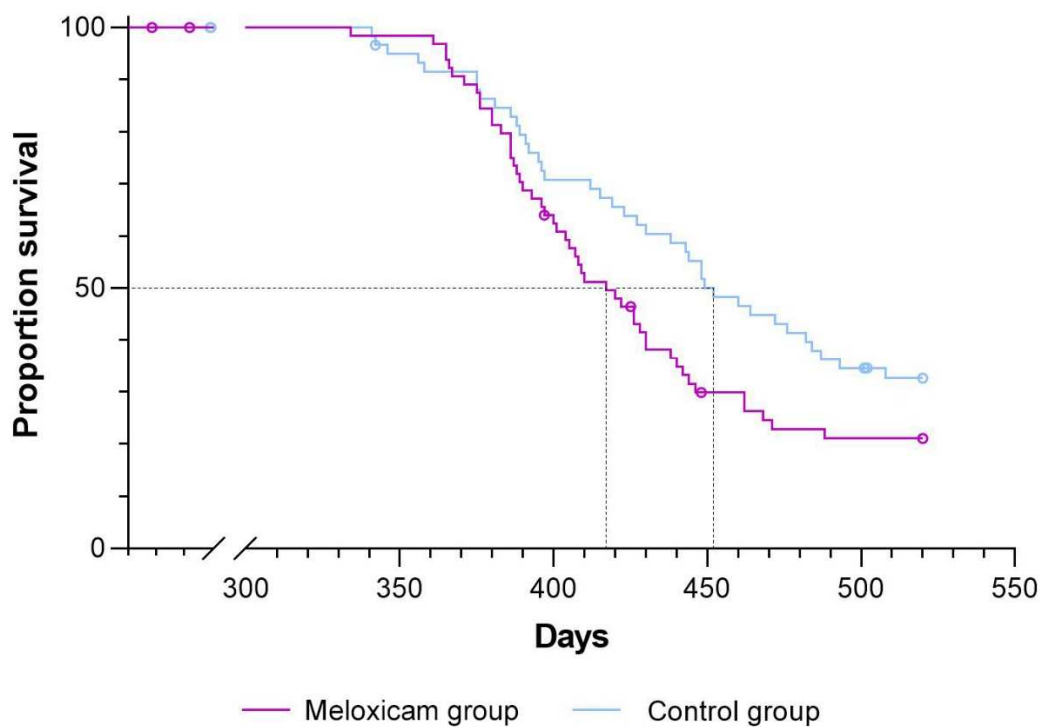
593 <sup>a</sup> retained placenta was defined as the presence of foetal membranes in the uterus by visual or vaginal  
 594 examination more than 24 hours after calving

595 <sup>b</sup> pregnancy diagnosis was performed by ultrasound (after 30 days post-mating) or by transrectal  
 596 palpation (after 60 days post-mating)

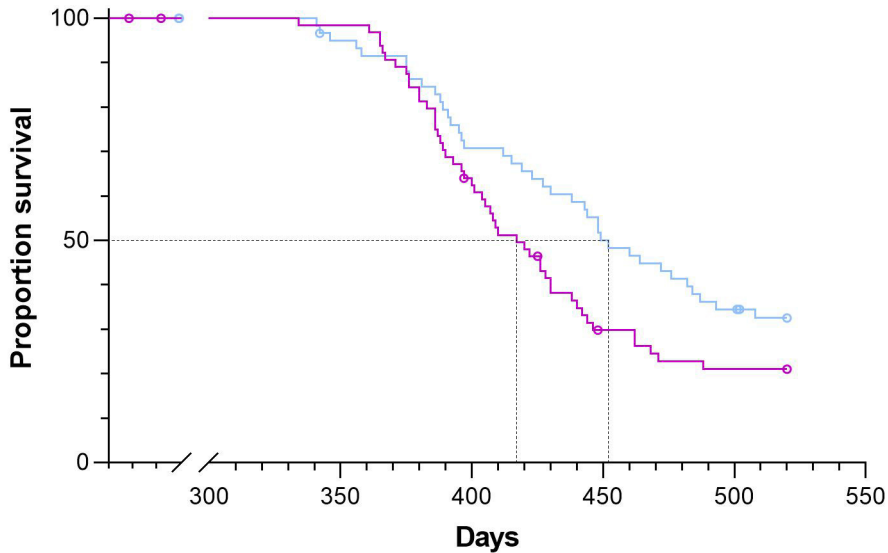


597 **Figure 1. Kaplan-Meier survival plot (days from caesarean**  
598 **section to next calving) for Charolais heifers (n = 127)**  
599 **receiving meloxicam before the caesarean section**  
600 **(meloxicam group, n = 66) or only local anesthesia (control**  
601 **group, n = 61).**

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



606  
607



— Meloxicam group      — Control group