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1 **Treatment with etamsylate reduces haemolactia in lactating dairy cows.**

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12 Short Title: **Treatment of haemolactia with etamsylate**

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26 **Summary**

27 This Technical Research Communication describes the efficacy of etamsylate to reduce haemolactia
28 in dairy cows. A dairy cow with haemolactia produces milk that is reddish or pinkish due to the
29 presence of blood. Haemolactia causes economic loss because bloody milk is rejected by the
30 industry and the consumers. A total of 58 dairy cows with haemolactia were included in the study
31 and randomly divided into 2 groups: a treated group (TG, n=31) and a control group (CG, n=27).
32 Treatment (TG) consisted of three consecutive daily doses of etamsylate at 15 mg/kg (equivalent to
33 2 mL of Hemo 125 mg/mL injectable solution/15 kg body weight), delivered intramuscularly. Milk
34 production (L) was recorded daily for 7 days, whether or not blood was detected in milk. The mean
35 number of days with the presence of blood in milk in the treatment group was significantly lower
36 (3.4 d) than in the control group (4.9 d). Treatment with etamsylate did not significantly affect milk
37 yield. In conclusion, treatment with etamsylate reduces the number of days blood is observed in
38 milk and it does not have any negative effect on milk production.

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40 Key words: Haemolactia; blood; milk; treatment; dairy cow.

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42 Haemolactia (the presence of blood in milk) is a clinical sign often observed in dairy cows, but also
43 in other mammal species (Ayaz, 1999; George *et al.* 2008; Purohit *et al.* 2014). The main causes of
44 haemolactia are diapedesis due to hyperaemia during the post-calving period, trauma or mastitis.
45 Milk can be slightly tinged with blood, clots can be observed or it can be pure blood. Milk with
46 blood is not sellable; therefore, in cases of haemolactia, farmers are concerned about economic loss,
47 a waste of labour time and a risk of mixture with suitable milk. Etamsylate (2.5-dihydroxy-benzene-
48 sulfonate diethyl ammonium salt) is a synthetic haemostatic, anti-hemorrhagic and non-
49 thrombogenic drug indicated in cases of capillary bleeding (Garay *et al.* 2006). Etamsylate has been
50 used in human and veterinary medicine for over 40 years in Europe. The first studies demonstrated
51 an effect on primary haemostasis in several species (Laporte, 1961; Deacock & Birley,
52 1969; Vinazzer, 1980). In cows, the haemostatic action of etamsylate could be useful in reducing
53 bleeding in cases of haemolactia. This study was designed to evaluate the efficacy of etamsylate
54 (Hemo 125 mg/mL injectable solution, Ecuphar, Barcelona, Spain) in reducing the presence of
55 blood in milk in dairy cows with the aim of reducing the number of days milk has to be discarded.

56

57 **Materials & Methods**

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59 All procedures involving animals were approved by the Ethics Committee of the University of
60 Lleida (DAMM 0700) under EU legislation and in the spirit of good clinical practice for dairy
61 cows.

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63 Cows with haemolactia from 9 dairy cow commercial dairy farms in Spain were included in the
64 study. Farms milked between 135 to 1250 cows and milk yield ranged between 9100 and 11500 kg
65 of milk per cow (3.6% Fat and 3.3% Protein) in 305 days. Cows were housed in straw-bedded, free-
66 stall barns and were fed a total mixed ration consisting of corn silage, grass silage and concentrates.
67 All lactating cows were under regular milk quality and mastitis control carried out by specialised
68 veterinarians. Visual examination of milk and mammary gland palpation during the milking routine
69 was mandatory. A case of haemolactia was clinically scored as detailed in Figure 1. Milk production
70 was recorded daily for a period of 7 days starting at the time blood was detected in milk in each of
71 the included cows. Causes of haemolactia were established as follows: Parturition (presence of
72 blood in milk during the first 14 days in milk (DIM); this is considered physiological but with a
73 negative impact on the amount of milk sold), mastitis (clinical, subclinical or chronic), trauma and
74 defects (trauma with machinery, tools, buildings on the farm; over milking; stepping on the
75 mammary gland and udder defects), or unknown (unknown cause of presence of blood in milk).
76 When mastitis was diagnosed, the same treatment based on antibiotics and NSAID was applied for

77 both groups (treatment and control negative group) in all farms.

78

79 The study was designed as a randomised, blind and multicentre study. All cases fulfilling the
80 inclusion criteria were randomised in two groups (the treatment group TG and the negative control
81 group CG) following the randomisation list performed *ad hoc* for this study with the program nQuery
82 Advisor. Cows in the TG received three consecutive daily doses of etamsylate at 15 mg/kg
83 (equivalent to 2mL of Haemo 125 mg/ mL injectable solution/15 kg body weight), delivered
84 intramuscularly (withdrawal period for milk: 0 days/ meat: 1 day). Cows included in the CG group
85 received no treatment. Treatment was initiated as soon as blood in milk was detected. The primary
86 variable for treatment efficacy evaluation was the number of days with the presence of blood in
87 milk. As secondary variable, daily milk production was recorded for 7 days starting on the first day
88 that blood was observed.

89 All statistical analyses were carried out using the Statgraphics Centurion XVII (Version 17.0.16).
90 For all analyses, the individual cow was used as the experimental unit. The significance level (P)
91 was set at 0.05. The variables included in the statistical analyses were classified as nominal (first
92 parturition versus multiparous cows), ordinal (parity), and quantitative non-continuous (number of
93 days with the presence of blood in milk) or continuous (milk production). To show the homogeneity
94 between experimental groups (TG and CG), a contingency table (Chi-square test) was used to
95 compare the nominal variables: primiparous *versus* multiparous, initial blood scores and causes of
96 haemolactia. With the aim of comparing the groups for parity, DIM and milk production at the
97 beginning of the trial, the Mann-Whitney U test was performed. Statistical analyses were performed
98 to compare the outcome variables between the two experimental groups (TG or CG). Thus, the
99 number of days with the presence of blood in milk and the average milk production throughout the
100 study (7 days) were compared between groups by means of a non-parametric Mann-Whitney U test.
101 Finally, a survival analysis was carried out to decipher if the treatment with etamsylate shortened
102 the duration of haemolactia versus the control group.

103

104 **Results**

105 A total of 58 cases were included in the study, 31 in the TG and 27 in the CG. In total, 36.2% of the
106 cases (n=21) suffered from haemolactia during post-parturition period, 36.2% cows (n=21) had a
107 trauma in the mammary gland and/or teats, 12.1% suffered from mastitis (n=7) and in 15.5% of the
108 cows (n=9) the cause of haemolactia was unknown. No significant association between the parity
109 (primiparous/multiparous) and the experimental group (TG/CG) was detected. Further, no
110 significant differences were detected between groups for DIM, the cause of haemolactia, initial
111 blood score and milk production between experimental groups (TG/CG) at the beginning of the

112 trial. These results showed the basal homogeneity between groups and allowed a comparison of the
113 effect of treatment on the main response variables without the presence of confounding factors.
114 Significant differences between experimental groups (TG versus CG) were observed for the days
115 with a presence of blood in milk after treatment began including all the causes of haemolactia (TG=
116 3.4 ± 1.5 days and CG= 4.9 ± 2.7 days). This result was confirmed with the survival analysis (Figure
117 2). Treatment with etamsylate significantly shortened ($P<0.05$) the duration of haemolactia versus
118 the control group. Moreover, it should be noted that the length of haemolactia was significantly
119 higher in both groups when the cause was parturition or trauma (parturition= 3.9 ± 0.5 days and
120 trauma= 5.0 ± 0.5 days) compared to other causes (mastitis= 3.1 ± 0.9 days and unknown= 3.6 ± 0.7) but
121 a significant reduction ($P<0.05$) was consistently observed in TG versus CG for all possible causes
122 of haemolactia. Average milk production for the TG group (27.04 ± 8.53 L) was higher than for the
123 CG group (24.30 ± 10.87 L) but the observed differences were not statistically significant ($P=0.056$)
124 (Table 1).

125

126 **Discussion**

127 Different treatments and techniques have been studied to control or prevent haemolactia in cows:
128 calcium solutions (Rhadostits *et al.*, 2007), vitamin K, phytotherapy (Umadevy & Umakhanthan,
129 2010), coagulants (Radostits *et al.*, 2007; George *et al.*, 2008; Zuhair, 2016), vasoconstrictors
130 (Venkatesan *et al.*, 2017), vitamin C, antioxidants, camphor (Raval *et al.*, 1998), antibiotics and
131 blood transfusion (George *et al.*, 2008). Despite the large number of options for the treatment of
132 haemolactia, many of these strategies lack conclusive data on cure rates, cure times and production
133 differences between treated and untreated cows. Some of the proposed products are expensive,
134 difficult to apply and/or cannot be applied to animals whose products are intended for human
135 consumption. To the best of our knowledge, no previous studies have explored the use of etamsylate
136 to treat cows diagnosed with haemolactia. According to our results, there should be registered
137 products containing etamsylate to treat cows for haemolactia. Fortunately, there is available a
138 registered medicinal product in Spain, Portugal, Cyprus and Malta.

139 In conclusion, the results clearly demonstrate that treatment with etamsylate is efficacious to reduce
140 haemolactia. Our study paves the way for additional studies on the use of etamsylate in the
141 treatment of haemolactia in dairy cows for their productive and economic benefits.

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147 **Table 1.** Effect of etamsylate treatment in cows with haemolactia (duration of the presence of blood
 148 in milk and average daily milk production for 7 days after blood detection).
 149

	TG [†] (n=31)	CG [‡] (n=27)	<i>P</i> -value
Presence blood in milk (d)	3.4±1.5	4.9±2.7	0.0099 (*)
Average milk production (L)	27.±8.5	24.3±10.9	0.056 (ns)
DIM [□] (d)	99.8±114.8	71.7±102.7	0.1953 (ns)
Parity	2.3±1.3	2.1±1.0	0.9461(ns)
First parturition (%)	29.03	29.63	0.9757 (ns)
Multiparous (%)	70.97	70.37	

150 (*) *P*-value < 0.05 show significant differences.

151 (ns) Non-significant.

152 [†]TG, treated group.

153 [‡]CG, control group.

154 [□]DIM, days in milk.

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186 **Figure legends:**

187

188 **Figure 1:**

189 Milking routine and clinical scoring for blood in milk. When haemolactia was observed, the case
190 was clinically scored as follows: no blood (0), milk slightly tinged with blood (1), milk
191 moderately tinged with blood (2), milk severely tinged with blood (3).

192

193 **Figure 2:**

194 Survival analysis of the proportion (from 0 to 1) of cows with haemolactia in cows treated with
195 etamsylate versus controls after seven days of blood detection. Dotted lines represent the
196 95% confidence interval.

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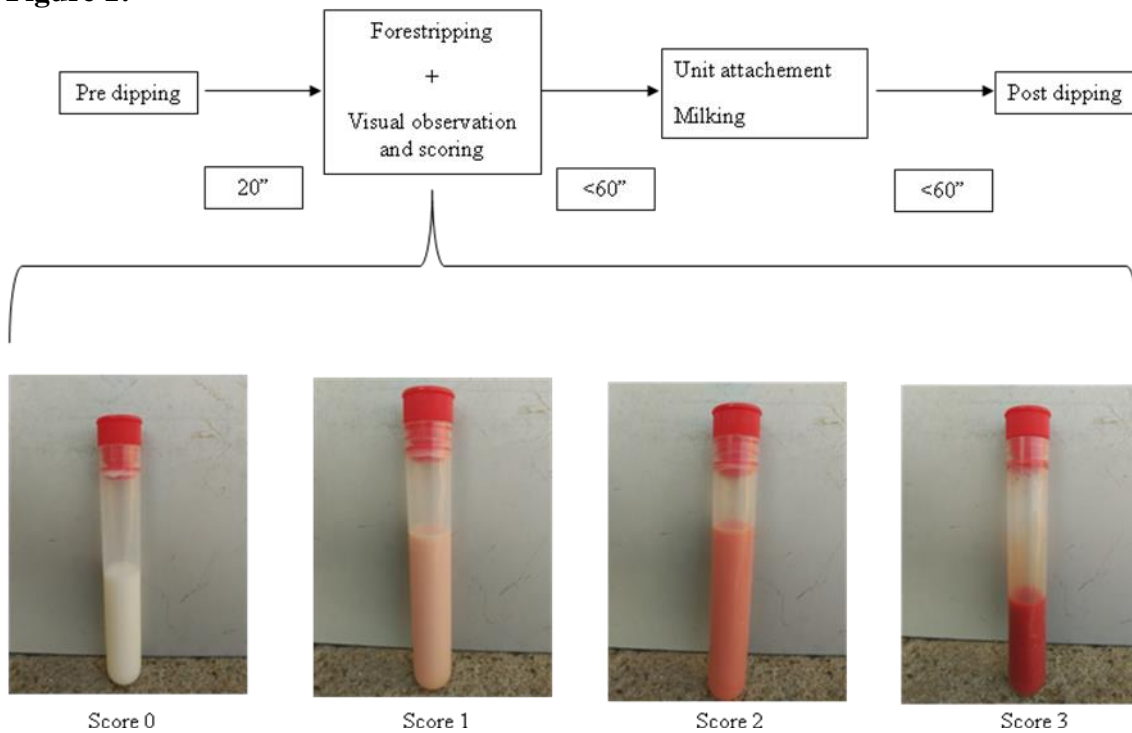
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221 **Figure 1:**



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223 Score 0, no blood.

224 Score 1, milk slightly tinged with blood.

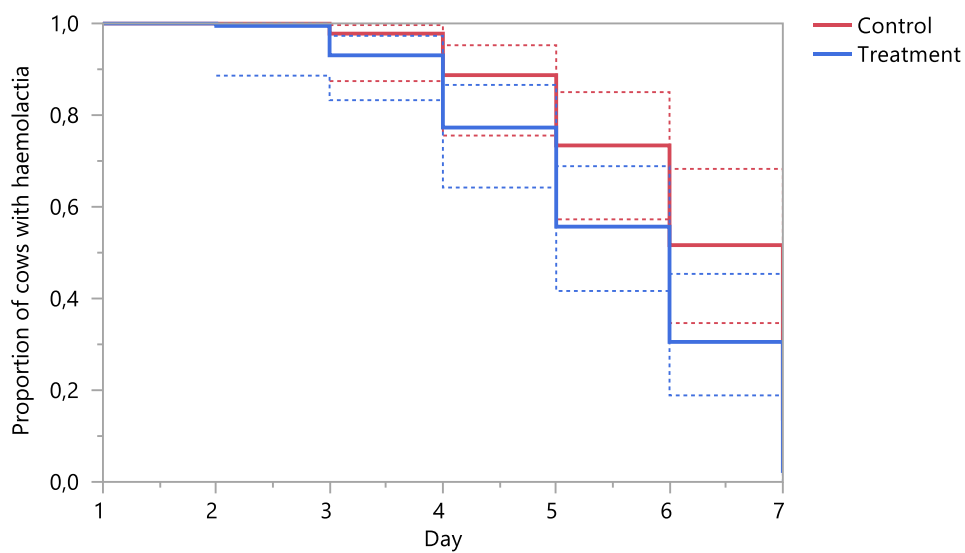
225 Score 2, milk moderately tinged with blood.

226 Score 3, milk severely tinged with blood.

227

228 **Figure 2:**

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