Treatment with etamsylate reduces haemolactia in lactating dairy cows.

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

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Summary

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

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

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

Materials & Methods

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

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

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

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

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

Results

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

trial. These results showed the basal homogeneity between groups and allowed a comparison of the effect of treatment on the main response variables without the presence of confounding factors.

Significant differences between experimental groups (TG versus CG) were observed for the days with a presence of blood in milk after treatment began including all the causes of haemolactia (TG= 3.4±1.5 days and CG= 4.9±2.7 days). This result was confirmed with the survival analysis (Figure 2). Treatment with etamsylate significantly shortened ($P<0.05$) the duration of haemolactia versus the control group. Moreover, it should be noted that the length of haemolactia was significantly higher in both groups when the cause was parturition or trauma (parturition=3.9±0.5 days and trauma= 5.0±0.5 days) compared to other causes (mastitis=3.1±0.9 days and unknown=3.6±0.7) but a significant reduction ($P<0.05$) was consistently observed in TG versus CG for all possible causes of haemolactia. Average milk production for the TG group (27.04±8.53 L) was higher than for the CG group (24.30±10.87 L) but the observed differences were not statistically significant ($P=0.056$) (Table 1).

Discussion

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

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

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

	TG† (n=31)	CG‡ (n=27)	*P*-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	

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

(ns) Non-significant.

†TG, treated group.

‡CG, control group.

□DIM, days in milk.

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Figure legends:

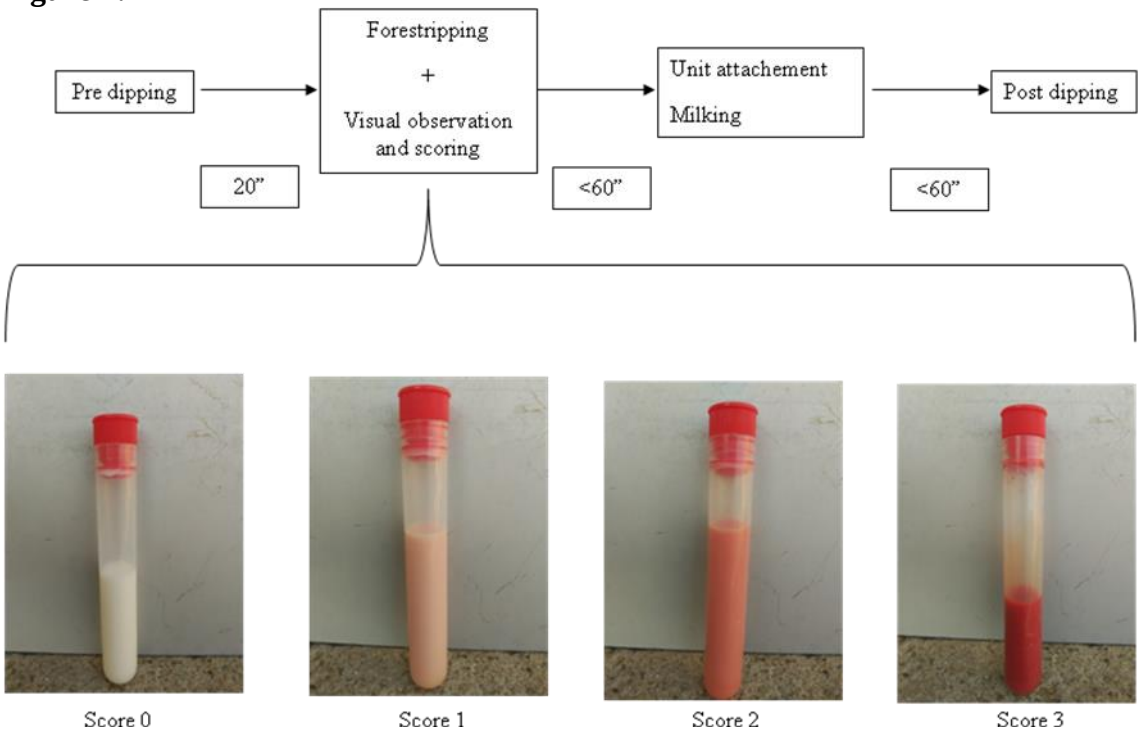
Figure 1:

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

Figure 2:

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

Figure 1:



Score 0, no blood.

Score 1, milk slightly tinged with blood.

Score 2, milk moderately tinged with blood.

Score 3, milk severely tinged with blood.

Figure 2: