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Article

Effect of an intraruminal monensin bolus on blood β-hydroxybutyrate, peripartum diseases, milk yield and solids in Holstein cows

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Abstract:

Administration of monensin to dairy cows during the transition period may improve cow health, although this is debated. An evaluation of the effects of an intraruminal controlled-released bolus of monensin on health and milk production in transition Holstein cows was done in a Chilean dairy farm. Seventy-seven (77) cows at 21 d before expected parturition were randomly assigned to either a treatment (n= 37) or a control (n= 40) group. The treatment group received a controlled-release oral bolus that delivered sodium monensin at a rate of 335 mg/d for about 95 d. For the first 10 d postpartum cows were clinically examined daily. From 21 d prepartum to 21 d postpartum, data were collected, considering the presence of fever (t°≥ 39.5 °C), postpartum diseases, weekly blood β-hydroxybutyrate (BHB) concentrations, and body condition score. Comparisons of milk production, milk solids (protein and fat percentage) and somatic cell counts (SCC) during the first 100 d of lactation were conducted. Blood BHB concentrations (mmol/L) were similar between groups (P>0.05). No differences were observed on the incidences of ketosis, fever, puerperal

metritis, or retained fetal membranes. Endometritis tended to be less frequent in the treatment group than the control group (P=0.08). Monensin did not significantly improve milk yield, fat content, or SCC content. However, cows treated with monensin produced milk with higher protein content during the first week postpartum than the control group (P<0.05). Treated cows also exhibited better improvement on body condition score (P<0.05) between dry-off and parturition and minor losses on body condition score (P<0.05) between parturition and 21 d postpartum than control group.

Key words: Monensin, Intraruminal bolus, Diseases, Postpartum, Dairy cow.

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Introduction

Transition period for dairy cattle is defined as the final 21 d of gestation to 21 d postpartum. During this period, stress and metabolic changes make cows more susceptible to disease[1-3]. Most (75 %) diseases in dairy cattle occur within the first month of lactation and 50 % of metabolic and infectious diseases arise during the transition period[4]. There is also a decrease in dry matter intake (DMI) and an increase in energy demands due to fetal growth and increased postpartum milk yield[1]. Consequently, dairy cows experience a typical negative energy balance (NEB), which is mostly characterized by mobilization of fat from the adipose tissue. Mobilized fat is transported through the plasma as non-esterified fatty acids (NEFA) to the liver following several metabolic pathways. When glucose levels are normal, NEFA are re-esterified to triglycerides and transported to the blood in the form of very low density lipoproteins[5]. If glucose levels are low, NEFA enter the mitochondria and oxidize to acetyl-CoA to continue in the Krebs cycle or form ketone bodies. Oxaloacetate is required to enter the Krebs cycle, which originates mainly from glucose. Since the adaptive response to NEB is poor and glucose is directed to the mammary gland for lactose synthesis, formation of ketone bodies increases, resulting in clinical or subclinical ketosis[5]. Subclinical ketosis is characterized by circulating β-hydroxybutyrate (BHB) levels ≥ 1.2 mmol/L in the absence of clinical signs[6-8]. Ketosis can be diagnosed by quantifying ketone bodies in urine (acetoacetate), milk (BHB), serum (BHB), plasma (BHB), and blood (BHB)[9]. Cows that

develop ketosis produce less milk and are at higher risk of experiencing other postpartum diseases, which can lead to reduced fertility[10,11], and subsequent significant losses for the dairy industry[7,12].

Disease predisposition is higher during the transition period in dairy cows, highlighting the importance of prevention strategies, including adequate nutritional management. The use of additives such as monensin, an ionophore which alters ruminal fermentation in favor of propionic acid production (the principal gluconeogenic precursor in ruminants) might contribute to lowering the incidence of ketosis and related disorders[13,14]. As a result, milk production, and fertility may improve[2,15].

The present study was designed to address the hypothesis that cows treated with an intraruminal monensin bolus will have lower blood BHB concentrations, lower postpartum disease incidence and higher milk production than cows without monensin. The objective was to evaluate the effect of an intraruminal controlled-release sodium monensin capsule (300 mg monensin per day for 95 d) on postpartum BHB concentrations, peripartum disease incidence, milk production and solids in Holstein cows from a Chilean commercial dairy farm. Variables included in the study were the environment and climate (Mediterranean), type of forage and quality (hay, alfalfa silage and corn silage) and concentrate quality (based on corn grain, soybean meal, canola meal, wheat middlings, cotton seed, and byproducts), etc.

Material and Methods

Dairy and animals

The study was conducted in a commercial dairy farm from central Chile (33.8° S, 71.3° W). Average annual rain fall is 235 mm, annual mean minimum temperature is 2 °C and maximum is 30 °C[16]. The experimental animals were 400 Holstein lactating cows housed in a free-stall system bedded with sand. Milking was done three times a day, and average mature equivalent milk production was 12,800 kg (305 d, 2X). Between 45 and 60 d before expected parturition (BEP), cows were dried, housed in a dry-lot and fed typical diets for dry cows. Four weeks BEP, cows were moved to a prepartum lot and fed an anionic diet

supplemented with a glucose precursor (propylene glycol; 200 g/cow/d). The supplement was not fed during the postpartum period. Cows delivered in a maternity pen. After parturition cows were moved to a postpartum group until 21 d in lactation. Diets were formulated to meet or exceed nutritional requirements according to the Cornell Net Carbohydrate and Protein System[17], using a commercial software (NDS, RUM & N Sas, Reggio Emilia, Italy).

Experimental design

Considering a difference in blood BHB concentration of 0.2 mmol/L between a treatment group (1.0 mmol/L) and a control group (1.2 mmol/L; cutoff value for subclinical ketosis), with a SD= 0.22, 95% confidence interval and 80% power[6], a sample size of 30 cows per group was calculated. The experiment was initiated with 40 animals per group to compensate for any involuntary elimination and ensure the minimum number of animals based on the sample size calculation. Animals were randomly assigned to each group 28 d BEP. In the treatment group each animal was orally administered a controlled-release sodium monensin bolus that releases a daily dose of ~ 335 mg sodium monensin over a 95-d period (Rumensin® capsule, Elanco, Greenfield, IN, USA). Each bolus displayed a tracking number which was matched with the cow's identification number to allow identification if the bolus were regurgitated. Prepartum treatment and control cows were housed and handled indistinguishable in the same corral, receiving the same diet (Table 1 and 2). Therefore, they were exposed to the same environmental and management conditions. Both prepartum and postpartum lots were inspected daily to identify any regurgitated bolus. If one was found, its condition was assessed and, if not damaged, it was re-administered. Damaged boluses were replaced with a new bolus.

Table 1: Composition (kg/day, dry matter base) of pre- and postpartum diets fed to cows in the monensin treatment and control groups

Ingredients	Prepartum	Postpartum
Alfalfa hay	0.90	2.65
Corn silage	5.04	6.24
Wheat straw	1.8	-
Corn grain	0.44	3.98
Soybean meal	0.45	2.5
Canola meal	0.25	0.29
Wheat middlings	0.88	2.03
Bypass fat	-	0.09
Wet Brewers	2.45	1.6
Calcium carbonate	0.049	0.09
Anionic salt	0.87	-
Minerals	0.12	0.1
Vitamins	0.032	0.015
Mycotoxin binding agent	0.05	0.05
Gluconeogenic precursor[1]	0.02	-
Yeasts	0.01	0.01
Total dry matter	13.22	19.64

[1] Precursor based on 50% propylene glycol.

Table 2: Nutritional composition of pre- and postpartum diets fed to cows in the monensin treatment and control groups

Nutrients	Prepartum	Postpartum
Dry matter, %[1]	48.5	49.5
Crude protein, % DM[1]	15.2	15.9
Soluble protein, % CP[1]	26.6	27.3
Degradable protein, % DM[2]	9.49	9.08
ADF, % DM[1, a]	27.4	18.3
aNDFom, % DM[1, b]	47.1	35.0
peNDF, % MS [2, c]	32.3	21.6
NFC, % DM[1, d]	25.1	37.2
Starch, % DM[1]	16.6	23.5
EE, % DM[1]	4.59	5.01
Ash, % DM[1]	7.99	6.96

Ca, % DM[1]	0.89	0.85
P, % DM[1]	0.41	0.41
Mg, % DM[1]	0.40	0.31
Na, % DM[1]	0.23	0.32
K, % DM[1]	1.02	1.13
S, % DM[1]	0.21	0.21
Cl, % DM[1]	1.23	0.30
$NE_{Lac,}$ Mcal/kg DM[2]	1.19	1.60
DACD, mEq/kg DM[3]	-90	+210

[1] Laboratory analysis.
[2] Calculated from formulas after laboratory analysis.
[3] Dietary anionic-cationic difference formula: $(Na^+ + K^+) – (Cl^- + S^-)$.
[a] Acid detergent fiber.
[b] Ash-free, amylase-treated neutral detergent fiber.
[c] Physically effective neutral detergent fiber.
[d] Non-fibrous carbohydrates.

Blood samples

Blood samples were collected at 7, 14, 21 and 28 d postpartum to assess plasma BHB concentrations with a portable hands held meter (FreeStyle Optium®, Abbott Diabetes Care Inc., Alameda, CA). Test sensitivity was 94.8% (CI95%: 92.6-97.0) and specificity was 97.5% (CI95%: 96.9-98.1)[(9)]. Subclinical ketosis was defined as a BHB concentration ≥ 1.2 mmol/L[(6-8)].

Body condition, postpartum diseases and milk production

Body condition score (BCS) was assessed by the same person at assignment, at parturition and 28 d postpartum. A five-point scale with 0.25 unit increments based on a standard methodology was used[(18)].

The initial step in identifying postpartum diseases was rectal temperature using a digital thermometer at 3, 5 and 7 d postpartum. Within 24 h postpartum, retained fetal membranes (RMF) was diagnosed, which were defined as membranes present in the vulva, vagina or in utero detected by vaginal examination 24 h postpartum[19]. Within the first two weeks of lactation, daily rectal palpation was done to identify any foul-smelling puerperal discharge or metritis, defined as uterine inflammation with abnormal genital discharges, with or without systemic signs, occurring within the first 14 d in lactation[20]. Possible mastitis was evaluated in the milking parlor by visual milk inspection; clinical mastitis was defined as visually abnormal milk (e.g. coagulated, aqueous, fibrin residues and/or pus) in one or more quarters. Mammary secretions may or may not be accompanied by signs of udder inflammation (heat, swelling or redness)[19]. Examinations for endometritis were done 25 to 38 d postpartum using a vaginoscope. Any purulent or mucopurulent discharge during this period of time was defined as endometritis[20].

Milk production was measured weekly through a Chilean Dairy Herd Official test up to 90 d of lactation, using proportional meters (Waikato Milking Systems LP, Verona, WI 53593, USA). Milk fat and protein percentages, and somatic cell count (SCC) were measured weekly during the first 3 wk of lactation, using a commercial laboratory (COOPRINSEM, Osorno, Chile).

Statistical analysis

Statistical data analysis was conducted using the SAS 9.4 software[21]. Postpartum disease incidence was compared by logistic regression considering treatment effect as the main variable, and adjusting for lactation number and BCS at parturition. Adjusted odd ratio (AOR) and 95% confidence intervals (CI 95%) were calculated. The concentrations of BHB, fat and protein percentages and SCC were analyzed by ANOVA repeated measures considering as explanatory variables the effect of treatment, day of sample, lactation number (2, $\geq$ 3), BCS at parturition and their interactions. Fat and protein percentages were transformed to the arc sine of the square root, with the formula of Blis[22]. The SCC was transformed to a linear score with the formula $\log_2(SCC/100)+3$, following Dabdoub and Shook[23]. Mixed models were built considering the best covariance structure based on the goodness-of-fit test[24]. Body condition score was assessed based on changes in body condition score from prepartum to delivery to 21 days postpartum. This variable was

analyzed using a multivariate ANOVA ($P \leq 0.05$). Tendency was considered when P values were between 0.1 and 0.05.

Results

The final analysis included 40 cows in the control group and 37 in the treatment group. Three cows were excluded from the treatment group: one died of enterotoxemia shortly after parturition, and two aborted a few days after monensin bolus administration.

Average BHB blood concentrations (± standard mean error) (mmol/L) did not differ between the two groups over time ($P>0.05$) (Table 3); in other words, the time-group interaction had no significant effect and both curves were parallel. The largest difference (though not significant; $P>0.05$) in BHB occurred at day 7 postpartum when concentrations in the control group averaged 0.7 mmol/L and those in the treatment group 0.57 mmol/L.

Table 3: Results of analysis of variance for repeated measurements and least means squares for BHB (mmol/L) in the control and treatment groups during the first four weeks postpartum

Effect	DF num[1]	DF den[2]	F	*P*
Treatment	1	74	0.14	0.70
Week	3	225	1.30	0.27
Treatment by week	3	225	1.20	0.31
Lactation	1	74	1.74	0.19

Blood BHB Concentrations (mmol/L)

Week	Control	Monensin	SEM[3]	*P*
1	0.695	0.573	0.062	> 0.05
2	0.605	0.597	0.062	> 0.05
3	0.595	0.608	0.062	> 0.05
4	0.658	0.716	0.062	> 0.05

[1] Numerator degrees of freedom.
[2] Denominator degrees of freedom.
[3] Standard error of mean.

Table 4: Changes in body condition score between prepartum and parturition, and parturition and postpartum in treatment and control groups

Group	Difference in BCS Calving -prepartum	SEM[1]	*P*
Monensin	0.17	0.04	0.015
Control	0.01	0.04	

Group	Difference in BCS Postpartum - calving	SEM	*P*
Monensin	-0.13	0.04	0.008
Control	-0.31	0.04	

BC = body condition; SEM= standard error of mean.

At assignment, BCS did not differ between groups (3.28 for control group, 3.21 for treatment group; *P*>0.05) (Table 4). Body condition score was different at parturition, with treatment group exhibiting a higher BCS (3.21) than the control group (3.12). The difference was more noticeable at 28 d postpartum (3.14 for treatment *vs* 2.78 for control).

Only a tendency (*P*=0.08) was observed for disease incidence. A lower rate of endometritis in treated cows (14 %) than control cows (30 %) was reported. Ketosis incidence was 15 *vs* 27%, RFM was 23 *vs* 16 %, metritis was 45 *vs* 30 %, and fever was 25 *vs* 16 %, for treated and control group, respectively. All these differences were not significant (*P*>0.05).

Milk production over time did not differ between the two groups (*P*>0.05) (Figure 1). At 7 days postpartum (wk 1) production was 37.4 kg in the control group and 36.0 kg in the treatment group (*P*>0.05), a difference that remained unchanged throughout the 10-wk study period. Interaction group by week was clearly not significant, implying that both curves were parallel. For milk solids, only the percentage of protein in wk 1 differed between the groups, being higher in the treatment group (3.47 %) than in the control group (3.16 %) (Table 5, Figure 2). However, total kilograms of protein per week did not differ between the groups at any time. The same was true for milk fat percentage and total kilograms (*P*>0.05) (Table 5, Figure 3); although in Week 1 postpartum milk fat content was 4.10 % in the treatment group and 3.71 % in the control group. Finally, the linear SCC scores did not differ between groups in Weeks 1, 2, and 3 (*P*>0.05); linear scores were 2 to 2.5 for both groups (200 to 300,000 cells per ml, approximately), except in wk 2 (1.57 for treatment group and 2.05 for the control group; *P*>0.05) (Figure 4).

Figure 1: Average weekly milk production in treatment and control groups

The interaction group by time was not significant (*P*>0.05).

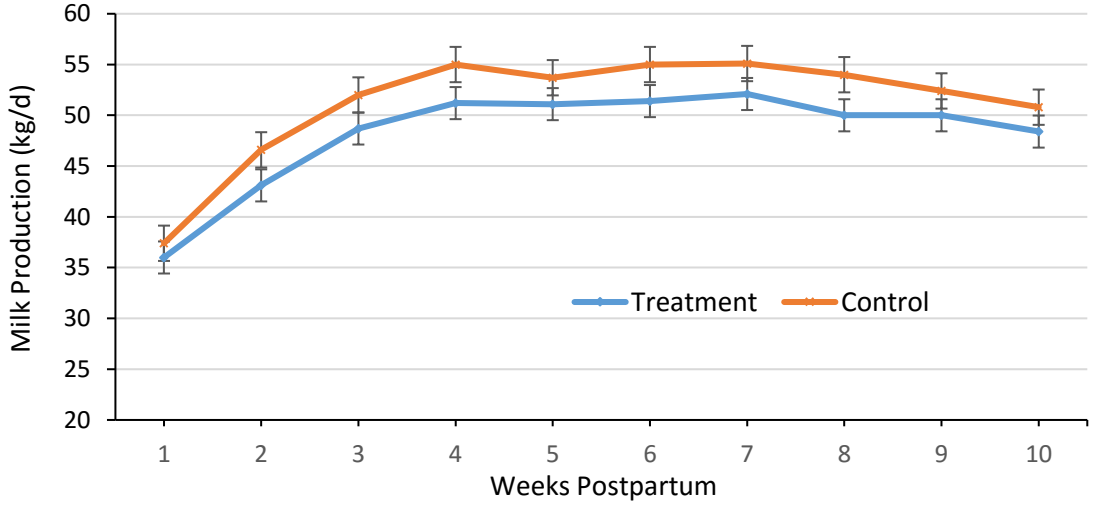
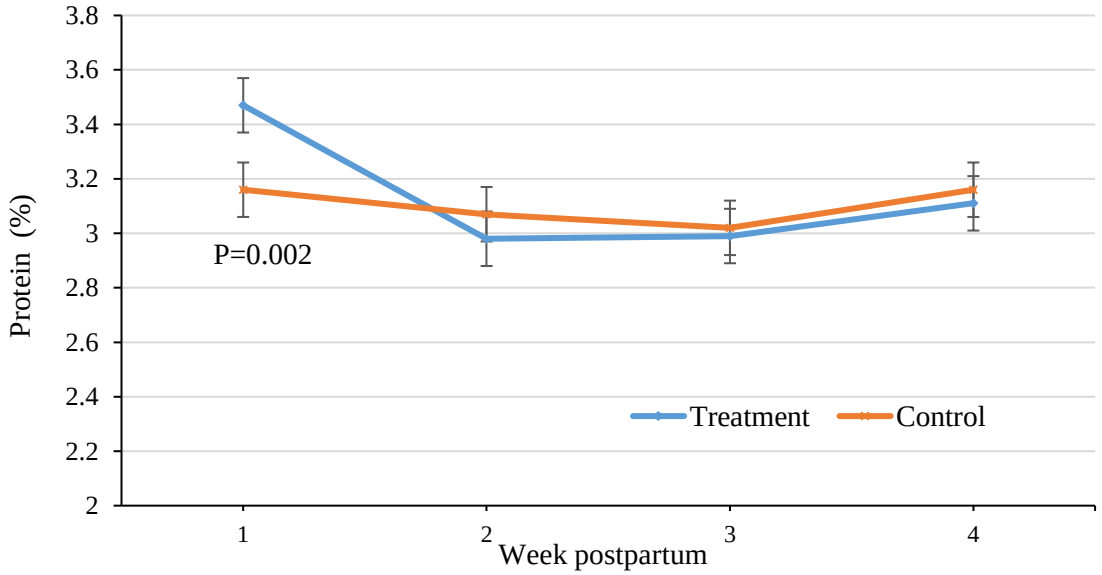


Table 5: Milk fat and protein percentages in the treatment and control groups during the first four weeks postpartum

% Fat				
Week	**Control**	**Monensin**	**SEM**	***P***
1	3.88	4.26	0.61	> 0.05
2	3.36	3.19	0.59	> 0.05
3	4.43	4.26	0.60	> 0.05
4	3.40	3.45	0.61	> 0.05
% Protein				
Week	Control	Monensin	SEM	*P*
1	3.19	3.51	0.06	0.002
2	3.12	2.99	0.06	> 0.05
3	3.06	3.00	0.06	> 0.05
4	3.16	3.11	0.06	> 0.05

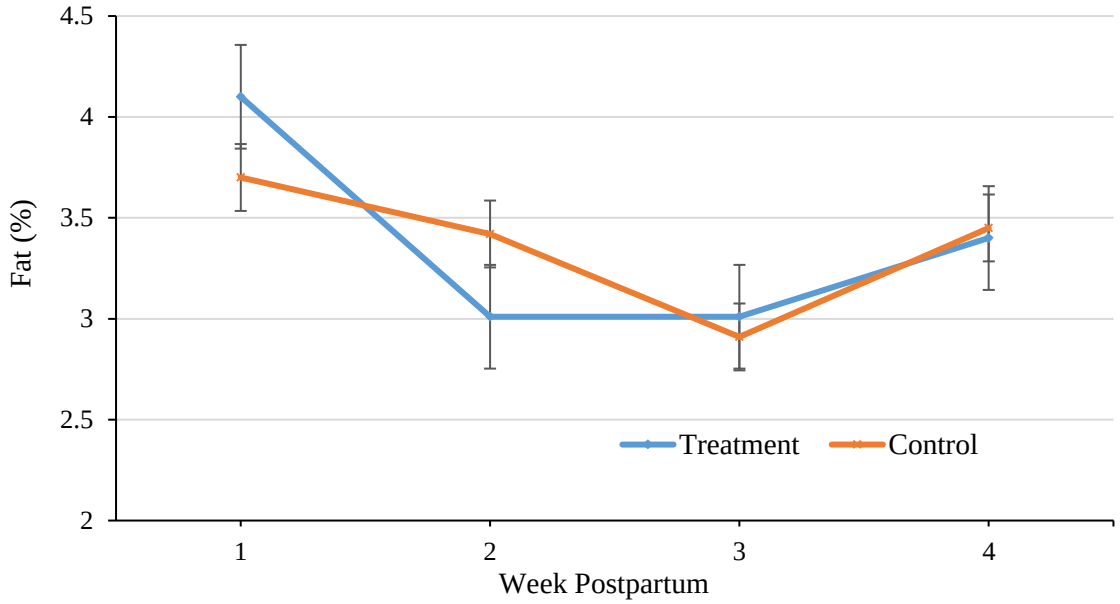
SEM= standard error of mean.

Figure 2: Milk protein percentage during first four weeks postpartum in treatment and control groups



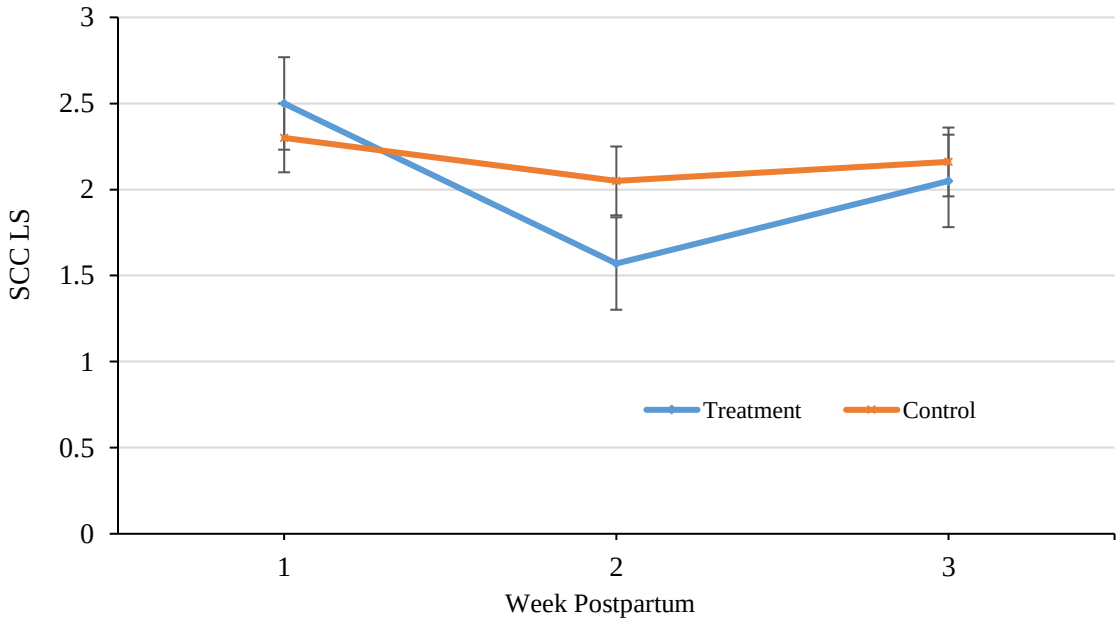
Significant differences ($P \leq 0.05$) in week 1.

Figure 3: Milk fat percentage during first four weeks postpartum in treatment and control groups



Interaction group by week not significant (P>0.05).

Figure 4: Somatic cell count linear score during first three weeks postpartum in treatment and control groups



Interaction group by week not significant (P>0.05).

SCC LS = Somatic cell count linear score

Discussion

Use of sodium monensin in dairy cows is illegal in many countries, but is permitted in the US, Chile and Argentina. One of the strengths of the present study is that the cows in the treatment and control groups were housed in the same lot, and were handled in the same way throughout the study period; consequently, the effect of corral and/or management practices on the study variables were identical, decreasing variability of statistical models. However, one of the shortcomings of this study was that some postpartum variables could only be assessed weekly and only during the first 30 days in lactation. Although most metabolic changes occur during early postpartum, there are undoubtedly longer term effects that can influence milk production, solids content, and fertility variables beyond the first month of lactation. The present study was conducted in a commercial dairy where animals are moved to different production groups after 30 d in lactation. This made study variables unfeasibly to evaluate for a longer period of time. Despite these minor limitations significant differences were identified in variables such as milk protein percentage, diseases such as endometritis, and changes in BCS.

The present results indicate some benefits for the application of a controlled-release monensin bolus in Holstein cows during the transition period under the farm management conditions. At fourth week of lactation, BCS was significantly lower in the control group cows than in the treatment group cows. This may indicate that treatment with monensin aided cows to experience a reduced amount of postpartum BCS losses. Similar results have been reported in other studies evaluating the effects of monensin use on BCS. Indeed, monensin supplementation in cows led to less loss of BCS during early lactation in comparison to a control group, and helped to maintain or increase BCS from the assignment of animals (prepartum) to parturition[25,26]. Lower BCS losses could be the result of increased energy and protein availability caused by the effect of monensin on ruminal fermentation. This mechanism could be partially explained by an increase in the molar proportion of propionic acid with a simultaneous decrease in the molar proportion of acetate and butyrate in the rumen[27]. The increase in ruminal propionate could be accompanied by a reduction in the amount of methane produced in the rumen and an increase in blood glucose concentrations[14,28], either for milk synthesis or fat deposition[2,5]. It is also known that monensin decreases L-lactate concentrations[28,29], and affects nitrogen metabolism by decreasing ruminal nitrogen ammonia ($N\text{-}NH_3$) production[28], consequently raising duodenal flow of amino acids. However, BHB blood concentrations in the present study did not differ between the control and treatment groups, contrasting with several worldwide studies

indicating that monensin exhibits a marked anti-ketogenic effect[26,30-32]. Among these studies is the classic meta-analysis, summarizing 59 studies from around the world encompassing a total of 4,000 dairy cows[14]. This meta-analysis showed that sodium monensin in dairy cows lowered BHB concentrations by 13 %, especially during the first month of lactation. This also occurred in grazing cows. Nonetheless, in the same meta-analysis two studies reported that monensin-treated cows had higher BHB concentrations than those in the control cows. A partial explanation for the lack of difference in BHB levels observed in the present results may be the prepartum diet supplementation with gluconeogenic precursors in the form of propylene glycol. A high proportion of propylene glycol escapes ruminal degradation and is absorbed in the small intestine, while the rest is metabolized to propionate[33,34]. In the liver propylene glycol is converted into glucose, mainly through the lactaldehyde pathway and subsequent oxidation to lactate[35]. Unfortunately, it was not possible to infer a positive or negative potential interaction between propylene glycol and monensin in the current experimental scenarios.

No differences were observed between groups in terms of peripartum disease incidence. This differs from previous studies[13,36], which stated that monensin indirectly improves immune function by improving the energy status. Indeed, the use of a controlled slow-release bolus containing monensin was also reported to improve BCS from dry-off to calving, compared to a control group. In addition, losses of BCS between parturition and postpartum were lower in the treated than the control group, resulting in fewer diseases[36]. However, most of the diseases in the present trial are within normal limits reported by previous studies [19]. The exceptions were metritis and endometritis; the control group had a higher incidence (> 30 %) than the treatment group, which tended to develop fewer uterine infections.

The ANOVA mixed models for repeated measurements is a very powerful statistical tool to compare the parallelism of curves of continuous variables over time because it analyzes a correlation matrix between each measurement over time. In this analysis each mean in a given time covaries by the mean of the previous measurement, generating a covariance structure of high statistical power[24]. No differences in milk production were observed between the two groups. This is consistent with other studies indicating that monensin does not affect milk production[13,37]. Moreover, most studies have shown no effect of pre- or postpartum propylene glycol administration on milk production levels in dairy cows[38,39]. It is quite possible that the effects of prepartum propylene glycol administration on milk production and blood BHB concentration masked any positive effect of monensin that could have on these variables. When monensin and propylene glycol are administered in conjunction they can have a positive or negative interaction on the glucose and energy metabolic pathways in dairy cows. This suggests that some metabolic pathways can be saturated when a large amount of propionate is available to the liver, which marginally affects glucose synthesis. Both the control and treatment groups may therefore have produced sufficient glucose to

meet the requirements for milk production and maintain low ketone body concentrations. The excess of potential glucose synthesized by the treatment group (monensin and propylene glycol) might have helped to decrease the negative energy balance and reduce the postpartum losses of BCS. Unfortunately, no studies have yet proven the hypothesis of a possible interaction between monensin and propylene glycol in transition dairy cows. One study did compare dairy cows fed propylene glycol and cows fed monensin to a control group. They found that propylene glycol group exhibited higher glucose and lower BHB concentrations than the monensin group, with not differences in milk production[40]. These findings constitute partial support for the present results. Future research needs to be addressed to test the implications of both compounds in dairy cows to identify any potential beneficial or antagonistic interaction effect between monensin and propylene glycol.

Milk protein exhibited a higher percentage at day 7 postpartum in the treatment group, although overall there were no differences in the total kilograms of milk protein between the treatment and control groups. This contrasts with a previous report stating that monensin increased total protein production (kg) but decreased its percentage in milk[14]. Treatment with monensin did not, however, affect milk fat percentage, again contrasting with a previous study indicating that monensin lowers milk fat percentage, and acetate and butyrate production in the rumen, leading to an overall reduction in lipogenic precursors for fatty acids synthesis in the mammary gland[14].

The metabolic dynamics of the dairy cow in the transition period, especially during early postpartum, is complex and multifactorial. It is known that insulin plays a fundamental role during these periods, and that cows experience a state of insulin-resistance towards the end of gestation and in early lactation as a metabolic strategy to spare glucose for the fetus and mammary gland in early postpartum[41]. Future studies are encouraged to investigate glucose and insulin concentrations to attempt to elucidate the impact of insulin on cow metabolic status during early postpartum period when glucose precursor are administered.

No differences in SCC were observed between the control (57,000 cells/ml) and treatment (51,000 cells/ml) groups. These values are well below the recommended SCC (200,000 cells/ml) for an acceptable milk quality. These SCC are also in agreement with the low incidence of clinical mastitis observed in the present study.

The reduction in BCS losses observed in early lactation might be the consequences of feeding good quality diets and adequate nutritional management, as well as proper handling and better cow-comfort in the pre- and postpartum period. These conditions could have lowered energy requirements, resulting in less mobilization of body reserves. This in turn would maintain low BHB concentrations, leading the animals to a better health and milk production in both groups. The present results suggest that the administration of monensin provides benefits in well-managed dairy cattle receiving properly feed management and handled under

adequate cow-comfort conditions. Low incidence of diseases on the studied dairy farm is most likely the result of good management practices such as early disease diagnosis and opportune treatment, especially in early postpartum cows.

Conclusions and implications

Use of a controlled-release monensin bolus in dairy cows improved postpartum BCS dynamics, with a tendency of lower uterine infections and a slight improvement in milk protein content. Under the studied conditions monensin caused no differences in milk production and blood BHB concentration between both groups.

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