A randomized clinical trial to evaluate the effect of oral zinc supplementation as a treatment for diarrhea in neonatal Holstein calves

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Introduction

Raising calves to maturity is vital for both the dairy and beef industry. Diarrhea is the leading cause of poor weight gain and death in neonatal calves and contributes to major economic losses in the dairy and beef industries. Antimicrobials are often ineffective against the common pathogens associated with calf diarrhea. Zinc-supplemented oral rehydration salt (ORS) therapy has been effective in reducing morbidity and mortality in children with diarrhea. The objective of this study was to evaluate the effect of oral inorganic and organic zinc supplementation as a treatment for diarrhea in neonatal calves.

Materials and Methods

This randomized clinical trial was conducted on a calf ranch in the San Joaquin Valley. Male Holstein calves (n = 78), 1 to 8 days old were identified by a veterinarian (AG) for study enrollment once every two weeks between June and September 2011. Calves were enrolled within 24 hours of diarrhea being diagnosed. Exclusion criteria included previous treatment with antimicrobials, concurrent disease such as pneumonia or naval ill, or the calf being in a moribund condition. Eligible calves were randomized into one of three groups. Calves received either a placebo composed of 80 mg of zinc-free powder, 381.54 mg of zinc methionine (equivalent to 80 mg of zinc), or 99.69 mg of zinc oxide (equivalent to 80 mg) dissolved in 2 L of a zinc-free ORS solution. Calves were treated once daily for up to 14 days or until normal fecal consistency was restored. For each calf, fecal consistency was classified on a scale from 1 to 3 (1 = normal; 2 = loose; 3 = watery) daily, and normal fecal consistency was considered restored when a calf had received a fecal score of 1 on two consecutive days (24 hours apart). The trial veterinarian (AG) and a calf ranch employee who assisted with the study were blinded to group allocation during study activities, which included sample collection, recording of observations, and treatment administration. Upon enrollment and exit, each calf was weighed, blood and fecal samples were collected, and a liver biopsy specimen was obtained for heavy metal screening. Additionally, a commercial ELISA kit was used to test fecal samples at enrollment and exit for *Escherichia coli* K99, *Cryptosporidium parvum*, rotavirus, and coronavirus. Calves that died during the study were necropsied and the cause of death was identified whenever possible. Data were analyzed with a Log-Rank (Mantel-Cox) test.

Results

At enrollment, calves in the three treatment groups were comparable as evidenced by similar pre-treatment weight ($P = 0.56$), rectal temperature ($P = 0.09$), and zinc concentrations in fecal ($P = 0.53$), liver ($P = 0.46$), and serum ($P = 0.63$) samples. Calves treated with zinc oxide had the fewest days to clinical cure from all pathogens (mean ± SEM, 8.5 ± 0.6 days) compared with results for calves treated with zinc methionine (9.9 ± 0.69 days) or the placebo (9.9 d ± 0.8 days); however, days to clinical cure from all pathogens did not differ significantly ($P = 0.19$) among the treatment groups. Conversely, calves that had *C. parvum*–positive fecal samples at enrollment and were treated with zinc oxide had significantly ($P < 0.01$) fewer days to clinical cure (7.0 ± 0.3 days), compared with calves that had *C. parvum*–positive fecal samples at enrollment and were treated with zinc methionine (11.0 ± 1.3 days) or placebo (10.4 ± 1.6 days). The difference in days to clinical cure for *C. parvum*–positive calves among treatment groups may be a reflection of the larger number of *C. parvum*–positive calves assigned to the zinc oxide group (n = 10) compared with that assigned to the zinc methionine (4) or placebo (5) groups. However, calves with fecal samples at enrollment that had positive results for *E. coli*, rotavirus, or corona virus were 86% less likely to acquire a *C. parvum* infection during the trial if treated with zinc oxide, compared with the risk for similar calves at enrollment treated with zinc methionine or the placebo ($P = 0.01$). Among treatment groups, the mean time to microbiological cure (ie, fecal sample at study exit tested negative for a specific pathogen) did not differ for calves that tested positive for *C. parvum* ($P = 0.20$), rotavirus ($P = 0.87$), or corona virus ($P = 0.56$) at study enrollment.

Significance

Faced with a substantial failure rate of labeled antimicrobials for the treatment of diarrhea in neonatal calves and the lack of effective antidiarrheal vaccines, oral zinc oxide may be an effective treatment to reduce morbidity and mortality associated with a parasitic diarrheal pathogen such as *C. parvum*. Since 2004, zinc therapy has been used in human medicine to decrease the duration and severity of infant diarrhea, and effective zinc formulations include sulfate, gluconate, and acetate. Results of randomized clinical trials in which zinc sulfate was used in humans provided evidence that zinc is an effective treatment for acute and persistent diarrhea; this trial is the first to report a similar effect in calves. The mechanism by which zinc may exert an antidiarrheal effect is not known; hence, further studies are warranted.