



A double-blind block randomized clinical trial on the effect of zinc as a treatment for diarrhea in neonatal Holstein calves under natural challenge conditions^{☆,☆☆}



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ABSTRACT

Diarrhea is the leading cause of death in neonatal calves and contributes to major economic losses. The objective of this double-blind randomized clinical trial was to evaluate the effect of oral inorganic or organic zinc supplementation as a treatment for neonatal diarrhea in calves. Seventy nine 1 to 8 day old male Holstein calves on a California calf ranch were block randomized to one of 3 treatments within 24 h from their first onset of diarrhea. Calves received a daily dose of either a placebo composed of 80 mg of zinc-free powder, 381.54 mg of zinc methionine (Met) (equivalent to 80 mg of zinc), or 99.69 mg of zinc oxide (ZO) (equivalent to 80 mg of zinc) in 2 L of a zinc-free oral rehydration solution (ORS). Calves were treated once daily until normal fecal consistency or for a maximum of 14 days. Upon enrollment and exit, calves were weighed, and blood, feces, and liver biopsies were collected for trace mineral analysis. Fecal samples at enrollment and exit were tested for *E. coli* K99, *Cryptosporidium* spp., rotavirus and coronavirus. Pre-treatment liver zinc concentrations for the 71 calves in the placebo, zinc Met, and ZO treatment groups were 710.6 (SEM = 147.7), 852.3 (SEM = 129.6), and 750.7 (SEM = 202.9) mg/kg dry weight (DW), respectively. Exit liver zinc concentrations for the calves in the placebo, zinc Met, and ZO treatment groups were 728.9 (SEM = 182.9), 1141.0 (SEM = 423.8), and 636.8 (SEM = 81.5) mg/kg dry weight, respectively. Although statistically non-significant, there were clinically important findings identified for each of zinc Met and ZO treatments. Calves treated with zinc Met gained on average 40 g/day during a diarrhea episode compared to a weight loss of 67 g/day on average in the placebo-treated calves (Power 19.9%). Calves treated with ZO had 1.4 times higher hazard of clinical cure compared to calves in the placebo group

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(Power 5.3%). Calves that were fecal positive to *cryptosporidium* spp. at enrollment and treated with zinc Met had higher odds of testing negative at exit compared to placebo calves (Odds Ratio (OR) = 16.0). In contrast, calves treated with ZO tended to recover (fecal score = 1) one day earlier compared to calves treated with a placebo (8.5 d vs. 9.7 d). The current trial identified clinically important findings that warrant further research to investigate zinc's therapeutic effect for calf diarrhea.

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1. Introduction

Considerable economic losses may be incurred from neonatal diseases during calf rearing. In 2006, 8% of pre-weaned heifers and 2% of weaned heifers died primarily due to diarrhea and other gastrointestinal illnesses (NAHMS, 2010). Similarly in pediatrics, diarrhea is the leading cause of death in children under the age of 5 years in developing countries and is estimated to cause 3 million deaths annually (Bhutta et al., 2000; Hoque et al., 2009). In 2004, based on numerous randomized clinical trials, the World Health Organization recommended zinc supplementation of oral rehydration solutions to decrease the duration and severity of infant diarrhea (Bhutta et al., 1999; Faruque et al., 1999; Penny et al., 1999). Infants with diarrhea for more than 10 days had significantly lower serum zinc levels compared to healthy infants or infants with other non-gastrointestinal illnesses (Naveh et al., 1982), suggesting gastrointestinal loss of zinc (Hoque et al., 2009). Zinc-supplemented ORS also resulted in increased recovery rates, reduced mortality and a reduction in use of antibiotics (Bhandari et al., 2008; Bhutta et al., 2000, 1999). Although the exact underlying mode of action of zinc is still not known, (Hoque et al., 2009) a mucosal-protective role, enhanced cell-mediated immunity, and modification of intra-luminal electrolyte secretion and absorption mechanisms have been proposed (Atia and Buchman, 2009; Fischer Walker et al., 2009; Hoque et al., 2009). Similar benefits of zinc-supplemented ORS on diarrhea in calves could significantly impact the economics and sustainability of the production system by reducing antibiotic use for treatment of calf diarrhea. Zinc studies have demonstrated its beneficial effects in piglets and rats, and on calf growth and fetal development (Graham et al., 2010, 1984; Owusu-Asiedu et al., 2003). However, the therapeutic use of zinc in calves with diarrhea has not been studied. A comparison of inorganic and organic formulations of zinc such as zinc oxide (ZO) and zinc methionine (Met), respectively, is warranted because of differences in zinc bioavailability (Wedekind et al., 1992). A greater effectiveness of an inorganic zinc formulation in treating calf diarrhea compared to an organic formulation may be evidence of zinc's local intra-luminal mode of action given its poor absorption in the intestines (absorption coefficient of ZO = 0.12 compared to 0.40 for zinc Met) (Cousins, 1985). On the other hand, if zinc Met is found to be more effective than ZO in treating diarrhea this may be evidence for a systemic mode of action given the greater bioavailability of zinc Met compared to ZO. In addition, because zinc is an antagonist of copper (NRC, 2001), a comprehensive assessment of trace minerals is necessary when administering zinc to calves.

The hypothesis of this block-randomized double-blind clinical trial is that neonatal Holstein calves with diarrhea supplemented with either zinc Met or ZO will experience reduced days to recovery from diarrhea, reduced mortality, and reduced weight lost during the diarrhea episode compared to the placebo treated calves. The objective of this clinical trial was to compare the effect of a daily dose of ZO or zinc Met equivalent to 80 mg of zinc, or a placebo for a maximum of 14 days on fecal output and recovery in otherwise untreated 1 to 8 day-old Holstein bull calves with neonatal diarrhea on a California calf ranch. A secondary objective was to assess the effect of zinc Met or ZO on serum and liver zinc, copper, and iron concentrations.

2. Materials and methods

2.1. Study population

All procedures were approved by the University of California Davis Institutional Animal Care and Use Committee (protocol number 16232). The clinical trial was conducted between June and September 2011 on a large California calf ranch in the San Joaquin Valley housing approximately 70,000 Holstein calves, 40,000 of which were of preweaning age. Calves enrolled included all male Holsteins that developed diarrhea for the first time between 1 and 8 days of age. Calves were excluded from the study if they had a previous incident of diarrhea since birth or signs of disease other than diarrhea, such as an umbilical abscess, pneumonia, or meningitis, or if they were previously treated with antimicrobial drugs. Calves with diarrhea were identified by a veterinarian (AG) prior to enrollment.

2.2. Sample size estimation

Due to lack of estimates in neonatal calves, the sample size estimation was based on the difference between serum zinc levels of infants with and without diarrhea. The increase in serum zinc levels post treatment in calves was assumed to be similar to that in infants (Naveh et al., 1982). Hence the sample size was calculated to detect a statistically significant difference in serum zinc concentrations in treated calves (mean $\pm$ SD, 87 ± 20 μ g/dl) and placebo calves (100 ± 14 μ g/dl) with a power of 80% and level of significance of 5%. A total of 22 calves per group were required. Allowing for a 15% loss to follow-up, a total of 26 calves per group ($n = 78$ total) were required in the study.

2.3. Study design and zinc administration

Prior to initiation of the study, zinc concentrations of water, calf starter grain, milk replacer, and electrolyte

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