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Efficacy of the oral supplement, Equine Omega Complete, for the prevention of gastric ulcers and alpha-tocopherol supplementation in horses

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Abstract

Background: Omega-3 fatty acid and alpha-tocopherol supplementation reduces gastric ulcer formation in humans and rodents; however, efficacy of prevention in horses is unknown. Equine Omega Complete (EOC) is an oral supplement containing omega-3 fatty acids and alpha-tocopherol.

Hypothesis/Objective: Determine if EOC supplementation prevents gastric ulcers and increases serum alpha-tocopherol concentrations in healthy horses.

Animals: Nine thoroughbred geldings; 5-13 years old.

Methods: Prospective randomized block design, repeated in crossover model. Horses were administered EOC, omeprazole, or water PO for 28 days. Horses underwent an established gastric ulcer induction protocol from days 21-28 via intermittent feed deprivation. Gastroscopies were performed on days 0, 21, and 28. Serum alpha-tocopherol concentrations were measured on days 0 and 28. The effects of treatment and time on ulcer grades were assessed with ordinal logistic regression, with significance at P-value <.05.

Results: Ulcer grades increased during ulcer induction in control and EOC but not omeprazole groups ($P = .02$). Grades increased in EOC-treated horses after ulcer induction from a median of 1 [95% confidence interval 0-2.5] (day 0) to 2.5 [1.5-3.5] (day 28) and were similar to the control group ($P = .54$). Serum alpha-tocopherol increased in EOC-treated horses from day 0 to day 28 (mean 2.2 ± 0.43 μg/mL to 2.96 ± 0.89 μg/mL; $P < .001$) with high individual variation; this increase was not different from omeprazole or control groups.

Conclusion and Clinical Importance: Supplementation with EOC for 28 days did not prevent gastric ulcer formation nor increase alpha-tocopherol concentrations relative to the control group.

KEYWORDS
colic, EGUS, squamous, stomach, vitamin E

Abbreviations: EGGD, equine glandular gastric disease; EOC, Equine Omega Complete; ESGD, equine squamous gastric disease.

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1 | INTRODUCTION

Gastric ulcers are frequently reported in horses and negatively affect performance.[1] Gastric ulcers can be classified as equine squamous gastric disease (ESGD) or equine glandular gastric disease (EGGD). Squamous disease likely occurs because of splashing of gastric acid onto the squamous portion of the stomach. Glandular disease is thought to be more associated with stress, use of anti-inflammatory drugs, and exercise level, but remains poorly understood.[2] Buffered oral omeprazole is the current gold standard therapy for treatment and prevention of ESGD; however, clinical signs might return if the underlying cause of ESGD is not addressed.[3] The major limitation of this treatment is cost. In addition, long term use of proton pump inhibitors are associated with progression of chronic renal disease, gastrointestinal microbiota changes, and micronutrient deficiencies in people and laboratory animals.[4,5]

Various alternative medications and supplements are commercially available as gastric ulcer preventatives for use after, or in conjunction with, omeprazole; however, few products have supporting peer-reviewed data showing efficacy. Equine Omega Complete (EOC; O3 Animal Health, LLC, South Boyle, MS) is an oral supplement comprised of soybean oil, wild caught fish oil, and *d*-alpha tocopherol. Omega-3 fatty acids, found in fish oil, are used to treat gastric ulcers associated with *Helicobacter pylori*, as well as gastric neoplasias in humans with some success.[6,7] Omega-6 fatty acids, present in soybean oil, decrease gastric acid output in ponies.[8] In rats, alpha-tocopherol supplementation decreases the frequency and increases the rate of healing of gastric ulcers.[9] Additionally, alpha-tocopherol concentration is frequently low in horses that lack pasture access and are not receiving dietary supplementation.[10,11] Alpha-tocopherol is needed for appropriate neuromuscular development and function and deficiency is associated with weakness and muscle atrophy.[12] If efficacious, a supplement such as EOC could provide gastric support for horses, as well as needed alpha-tocopherol supplementation to horses in deficient areas. Because of limited treatment and prevention options for gastric ulcers and the cost associated with the current therapies, there is benefit in identifying alternative options.

The goal of this study was to objectively compare EOC with the gold standard treatment (omeprazole) as a preventative for squamous gastric ulcers. A secondary aim of the study was to investigate the change in serum alpha-tocopherol with EOC supplementation. It was hypothesized that supplementation with EOC would not be superior to the gold standard in the prevention of experimentally induced gastric ulcers but would increase serum alpha-tocopherol concentrations.

2 | MATERIALS AND METHODS

2.1 | Animals

All animals were housed and cared for in accordance with an approved Institutional Animal Care and Use Committee protocol from the University of California, Davis (Protocol #21497). Twelve horses were screened for systemic illness via physical examination. Horses had no history of gastrointestinal disease within 1 year. Horses were withheld from feed for approximately 16 hours and were sedated with detomidine hydrochloride (0.006-0.02 mg/kg IV) to facilitate gastroscopy. A 3.25-m gastroscope (Olympus Corporation of the Americas, Center Valley, PA) was passed up the nostril and into the stomach. The scope was passed to the level of the pylorus, and at least 3 attempts were made to visualize the pylorus in all horses. The entire squamous portion of the stomach was visualized, and deionized water was used to rinse any portion of the stomach obscured by food or saliva. Squamous and glandular lesions were recorded and described. All squamous ulceration was graded by 3 reviewers based on the European College of Veterinary Internal Medicine consensus statement on equine gastric ulcers.[2] One reviewer graded the ulcers in real time, and 2 additional reviewers graded them at a later date using representative photos taken during each examination. All reviewers were blinded to horse treatment group. Nine systemically healthy horses were enrolled in the study, all with baseline squamous gastric ulcer grades <2, as defined in the consensus statement.[2] Glandular lesions at enrollment included a small polyp near the pylorus and mild glandular hyperemia (N = 1 each), and the pylorus could not be visualized in 1 horse. Glandular mucosa was within normal limits for the remaining horses. All horses were Thoroughbred geldings, with a median and range age of 10 (5-13) years. Weights at intake ranged from 480 to 610 kg (median 550 kg).

2.2 | Study design

This was a randomized, blinded, placebo-controlled study. After enrollment, the horses were randomly divided into 3 groups. Oral treatment was initiated on day 0 with each group receiving either 118 mL water (negative control), approximately 2 mg/kg buffered omeprazole paste (1.8-2.2 mg/kg by weight as gold standard; Gastrogard, Boehringer Ingelheim Animal Health USA Inc., Duluth, GA) or 118 mL EOC supplement (treatment) once daily. Dosing of EOC was based on the label for the product, in which a 4 oz (118 mL) serving was described to contain 8.8 g omega-3 fatty acids, including 1.0 g docosahexaenoic acid (DHA) and 1.5 g eicosapentaenoic acid (EPA); 47.5 g omega-6 fatty acids; 20.5 g omega-9 fatty acids; and 1250 IU *d*-alpha tocopherol. Blood was obtained for baseline serum alpha-tocopherol concentrations at the time of enrollment, before first treatment. Therapy was initiated once daily for 21 days via individual feed bags, left in place until the treatment was consumed within 20 minutes. To standardize treatment, EOC and water were administered as a top dressing in 0.5 lb sweet cob (Farmers Best Sweet Cob for Horses and Livestock, Keyes, CA) to mimic supplementation by an owner. Omeprazole was administered directly PO, followed by providing the same volume of sweet cob. Sweet cob was selected as the vehicle because of its negligible alpha-tocopherol concentration (0 IU per product label). All treatments were administered before morning feedings, except for day 1 when they were administered after gastroscopy and recovery from sedation. Throughout the treatment period, horses were housed in group dry lots and fed a diet of grass hay (1.5%-2% body weight daily).

Following the 21-day treatment period, horses were moved to individual paddocks and withheld from feed for 16 hours. Free access to water was provided throughout this time. Horses underwent routine gastroscopy as described above, with representative images saved and shared with 2 blinded reviewers and real time gastric ulceration grades recorded by the third reviewer. Horses then underwent an established squamous gastric ulceration induction protocol via intermittent feed deprivation.[13] Briefly, horses were alternatively fasted for periods of 12 hours (day 21) or 24 hours (day 22, 24, 27) over 7 days, with a total of 96 hours of feed restriction. All horses continued the respective treatment, with daily sweet cob administration, throughout ulcer induction. Following completion of squamous ulcer induction, horses underwent standard gastroscopy and grade of squamous gastric ulceration was recorded. Observations of the pylorus were recorded for completeness but were not a primary focus as the gastric induction protocol is intended to induce changes in squamous mucosa. Blood was obtained at the time of gastroscopy on day 28 only for measurement of serum alpha-tocopherol concentrations. The study was repeated 2 additional times in a crossover model until each horse had received each treatment. All horses underwent a 4-week washout period between treatment periods. This period was selected to provide sufficient time for systemic and tissue elimination of omeprazole and alpha-tocopherol.[14,15]

2.3 | Monitoring

Horses were monitored throughout the treatment periods for changes in appetite, attitude, manure production and urination. During gastric ulcer induction and on days gastroscopies were performed, horses were monitored with daily physical exams as well as monitoring manure production, urination, and attitude.

2.4 | Alpha-tocopherol

Blood was obtained for serum alpha-tocopherol testing in plain vacutainers (BD Vacutainer, Becton Dickinson and Company, Franklin Lakes, NJ) and was protected from light and allowed to sit for greater than 30 minutes to clot at room temperature. Blood was then centrifuged (2000$\times g$ for 15 minutes at -20°C) and serum separated and frozen at -80°C until the time of analysis. After completion of all 3 treatment periods, all samples were shipped on ice to Michigan State University for analysis of alpha-tocopherol concentrations in 1 batch via high performance liquid chromatography as described.[10]

2.5 | Supplement analysis

Aliquots of EOC were shipped in light protected, insulated containers for evaluation of alpha-tocopherol concentration at Michigan State University and fatty acid analysis at an independent commercial nutritional laboratory (Dairy One Forage Laboratory, Ithaca, NY).

2.6 | Statistical analysis

A power calculation was performed for sample size, with alpha set at .05 and power set at 80% using commercially available software (KaneSP Sample Size Calculator, https://clincalc.com/stats/samplesize/asp). To achieve 80% power to detect an ulcer grade change of at least 2, 7 horses were required. Nine horses were selected for even distribution into the 3 treatment groups.

Cohen's kappa statistics were used to assess interobserver reliability for the 3 reviewers grading gastric ulcers. Weighted kappa was reported to account for order of categories (ie, ulcer grades 1 and 2 being more similar than grades 1 and 4). Two reviewers (A and B; 1 real time and 1 using recorded images) had good agreement of ulcer grades, and 1 outlier (Reviewer C) was identified. The outlier's grades were excluded based on the poor reliability.

Data normality was assessed via Shapiro-Wilk testing. Normally distributed data were reported as mean and SD, and nonnormally distributed data were reported as median and 95% confidence intervals (CIs). The effect of block was analyzed using the nonparametric Kruskal-Wallis test, and no significant effect of block was identified. Because ulcer grade is an ordinal variable, ordinal logistic regression was performed using the model $y = \text{ulcer grade} \sim \text{time} + \text{treatment}$. All assumptions for the use of ordinal regression were met, including no multicollinearity and proportional odds. Changes in serum alpha-tocopherol concentrations as related to time, treatment group, and treatment block were evaluated using a mixed-effects analysis. All analysis was performed with open-source software (R packages polr and brant) and graphs created using GraphPad Prism (San Diego, CA). Significance was set at $P < .05$.

3 | RESULTS

3.1 | Interobserver reliability

Weighted kappa between observers were 0.133 (Reviewers A and C), 0.135 (Reviewers B and C), and 0.744 (Reviewers A and B). Gastric ulcer grades provided by the 2 reviewers with kappa 0.744 were included in statistical analysis.

3.2 | Animals

Six horses completed 2 of 3 treatment periods, with 1 horse removed from the control group during each treatment cycle. One horse was removed because of colic, unrelated to gastric ulcer formation as the horse had gastroscopy performed that day and was found to have grade 0 ESGD; 1 for a fever of unknown origin, and 1 horse for grade 4 gastric ulceration before ulcer induction. All horses were treated and recovered without additional complications. In total, 9 horses completed the EOC treatment, 9 completed the omeprazole treatment, and 6 horses completed the control protocol.

One horse consistently did not eat the supplement well and was hand fed the supplement and sweet cob at approximately 50% of the feedings, and at 5 administrations, the estimated remaining volume of the supplement was provided PO via a dosing syringe because of unwillingness to eat. Three additional horses received oral dosing of the supplement less than 3 times throughout the treatment period, but otherwise consistently finished the supplement in feeding bags. There were no concerns for finishing feed in any other treatment group. All horses lost weight over time with a median and range body weight of 550 (480-610) kg at the time of enrollment compared to 516 (442-570) kg at the conclusion of the study. The median weight loss throughout the study was 30 (2-110) kg. There was no effect of treatment or block on weight change (ie, gain or loss) during this study ($P = .67$ and $P = .08$, respectively) nor was there any interaction of block and treatment on weight change ($P = .61$).

3.3 | Supplement analysis

Analysis of an aliquot of EOC yielded a variety of fatty acids, predominantly linoleic (40.3% dry matter basis), oleic (19.7%), and palmitic (10.2%). In total, the supplement was determined to contain approximately 8 g omega-3 fatty acids per serving, comprised of alpha-linolenic (5.66 g), EPA (1.42 g), and DHA (0.93 g); approximately 40 g per serving omega-6 fatty acids; and 20 g omega-9 fatty acids. Analysis of an aliquot of EOC for alpha-tocopherol concentration revealed approximately 14.5 IU natural alpha-tocopherol per serving.

3.4 | Gastric ulcers

There was no significant difference in gastric ulcer grades in any group between gastroscopies on day 0 (baseline) and day 21 (before ulcer induction). Using ordinal logistic regression, the coefficients of time, day 28 ($P < .01$, 95% CI 0.96-3.19), and omeprazole treatment ($P < .01$, 95% CI −3.38 to −0.93) were significant when compared to controls. The EOC group had median (95% CI) scores of 1 (0-2.5) on day 0, 0 (0-2) on day 21, and 2.5 (1.5-3.5) on day 28. The control group had a significant increase in gastric ulcer grade after ulcer induction, with a median (95% CI) score of 2.5 (1-4) on day 28 compared to 1.5 (0-2) on day 0 ($P < .01$; Figure 1). The omeprazole group had no significant increase in gastric ulcer formation on day 28 (1 [0-2]) compared to day 0 (1 [0-2]). There was no significant difference between gastric ulcer grades of controls and EOC treated horses on day 28 after ulcer induction (95% CI −0.75 to 1.43; $P = .54$).

The glandular mucosa was evaluated as convenient. One horse in the omeprazole treatment group developed a polypoid structure between day 21 and 28 during the first block that persisted throughout blocks 2 and 3 but did not change in appearance. In all other horses, lesions appreciated at enrollment remained present and unchanged, with the exception of occasional mild hyperemia, throughout the study.

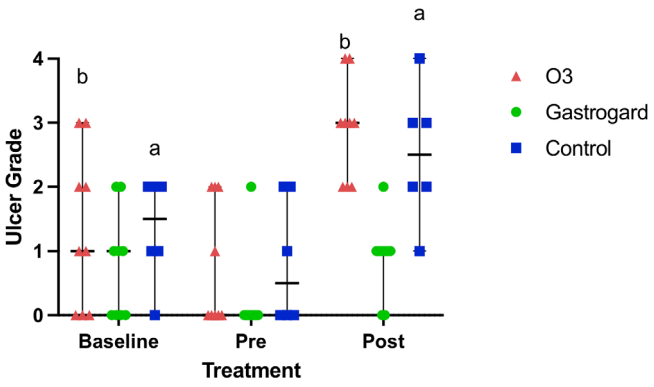

FIGURE 1 Gastroscopy results and squamous ulcer grades at baseline (day 0), before induction of ulcers (day 21) and after induction of ulcers (day 28) in 9 adult horses. Values represent median and 95% confidence intervals. a and b represent a significant difference between the baseline and post gastroscopy grades in the control and Equine Omega Complete ($P = .02$) groups. Significance is set at $P < .05$.

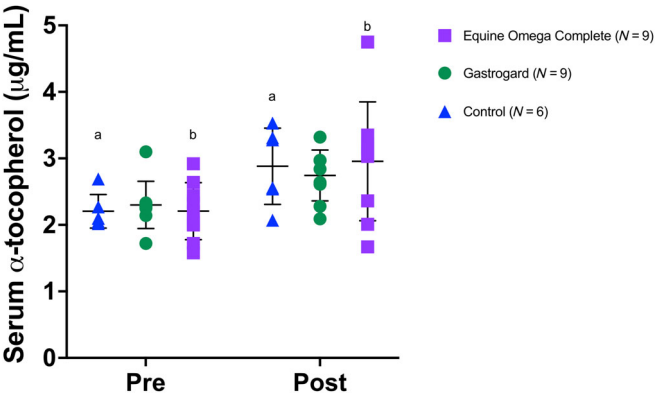

FIGURE 2 Pre (day 0) and post (day 28) treatment serum alpha-tocopherol concentrations in 9 adult horses after administration of an omega fatty acid and alpha-tocopherol supplement (Equine Omega Complete). Horizontal black line represents the mean, and error bars represent the SD. a and b represent a significant difference between the pre and post treatment concentrations in the control ($P = .01$) and Equine Omega Compete ($P < .001$) groups, respectively. Significance is set at $P < .05$.

3.5 | Alpha-tocopherol concentrations

There was a significant increase in alpha-tocopherol concentrations between day 0 and day 28 in both the control and EOC treated horses ($P = .01$ and .001, respectively; Figure 2). There was high intraindividual variation in alpha-tocopherol concentrations achieved in horses after receiving EOC, with differences between day 0 and day 28 concentrations ranging from a minimum of −0.29 μg/mL to a maximum of 1.83 μg/mL. In the multivariate analysis evaluating for the effects of time (day 0 compared to day 28), treatment block (blocks 1, 2, and 3), and treatment (EOC, omeprazole, and control), time and treatment block had significant effects on alpha-tocopherol concentrations, with an increase in concentrations between days

0 and 28 ($P < .001$) and an increase in concentrations in blocks 1 and 2 when compared to block 3 ($P < .001$). However, when controlled for time and block, there was no significant difference in serum alpha-tocopherol concentrations between the 3 treatment groups ($P = .97$).

4 | DISCUSSION

In this study, we did not detect an effect of EOC supplementation to prevent gastric ulcer formation. Control horses developed significantly higher grade gastric ulcers and buffered omeprazole treated horses had significantly lower grade gastric ulcer formation. These findings support that the model of gastric ulcer induction was effective and that EOC does not prevent experimental gastric ulcer formation in adult horses when used at the labeled dose for 28 days. Additionally, although supplementation with EOC resulted in an increase in serum alpha-tocopherol concentrations, it was highly variable among horses and did not demonstrate a significant increase when compared to the control and omeprazole treated groups. Independent analysis of a representative sample of the supplement showed alpha-tocopherol concentrations to be lower than that reported on the label, whereas fatty acid concentrations and proportions were similar to the label claims.

Omeprazole inhibits the Na-K ATPase pump and thus decreases the amount of HCl in the stomach and raises the gastric pH.[3] This increase in pH leads to less squamous mucosal injury and thus less gastric ulcer formation. Equine Omega Complete is labeled to contain omega-3 fatty acids and alpha-tocopherol. Although there is anecdotal evidence of success with omega-3 fatty acids and alpha-tocopherol in preventing and treating gastric ulcers in humans and other species, the mechanism of action for these effects is unknown but suggested to be associated with antioxidant effects.[6,7] Equine Omega Complete also contains soybean oil, a source of linoleic acid (omega-6 fatty acid) that aids in reducing gastric ulcer formation.[8] Supplementing both omega-3 and omega-6 fatty acid through EOC administration did not have a demonstrable protective effect in this study, and approved omeprazole formulations remain the gold standard treatment for ESGD. This is similar to a study that evaluated the ability of corn oil, refined rice bran oil, and crude rice bran oil, to prevent gastric ulcers after a 6 week treatment period and found no effect on ulcer prevention.[16] However, the 3 oils evaluated in the former study were primarily sources of omega-6 fatty acids, with less omega-3s. Additionally, this study identified a significant increase in gastric ulcer grade of all groups over time but no effect of block or treatment group order. The increase in gastric ulcer grade over time could be because of persistent stress associated with the study or repeated gastric ulcer induction.

Serum alpha-tocopherol concentrations did not significantly increase in the EOC treated group compared to the control group. The lack of increase could be because of the relatively short treatment window, poor absorption, or lack of active alpha-tocopherol in the product. Alpha-tocopherol concentrations in the supplement tested at an independent laboratory revealed markedly low concentrations compared to the product label. Although this should be interpreted with caution as it was a different batch of EOC than that used in the study, reduced alpha-tocopherol in the product could provide a reasonable explanation for the lack of increase in serum alpha-tocopherol in the treated group. It is possible that the alpha-tocopherol added to the supplement at time of production protected the fatty acids in the product from oxidation, leading to a decrease in the remaining available effective alpha-tocopherol. The low amount of alpha-tocopherol in the tested product limits any conclusions regarding efficacy of alpha-tocopherol in prevention of gastric ulcers.

Despite the relatively low alpha-tocopherol concentration measured in a presumptively representative sample of the supplement, an unexpected finding in this study was the increase in alpha-tocopherol concentrations in all horses over time, which was significant in the EOC and control groups. Grass hay analysis was not performed for alpha-tocopherol before study initiation and, although grass hay is typically deficient in alpha-tocopherol, this hay could have contained higher than expected concentrations. Additionally, because all horses lost weight throughout the study, and as alpha-tocopherol is a fat-soluble vitamin primarily stored in adipose tissue, it is also possible that this change in body fat composition could have affected serum alpha-tocopherol concentrations or that alpha-tocopherol continued to be released over time, even once supplementation was discontinued.[15] The sweet cob grain label stated that it contained negligible levels of alpha-tocopherol and is unlikely to have been a contributing factor.

There are several limitations to this study, the first being that gastric ulcer formation was assessed utilizing a specific model over a short period of time. Induced and naturally occurring gastric ulcers could behave differently, with additional variables implicated in natural ulcer formation.[2] Although a study investigating the prevention of naturally occurring gastric ulcers offers challenges of its own, additional studies using this supplement with naturally occurring gastric ulcers could yield different results. Additionally, the small number of horses in this study and the relatively short treatment window before gastric ulcer induction could have affected the results, especially as 3 control horses were removed from the study, reducing the sample size. Treatment for longer than 21 days before gastric ulcer induction could yield different results for EOC treated horses, and further research is indicated utilizing a longer treatment period or use as an adjunct with omeprazole. The authors also had difficulty encouraging certain horses to eat the supplement consistently and infrequently had to administer the supplement directly PO, which could have affected the results. The high level of interobserver variability between gastric ulcer grades is unusual but was likely associated with some grades assigned based on photos rather than in real time.[17] Differences in brightness/quality of viewing monitors likely contributed to the variation in images reviewed remotely. Videorecording of gastroscopy or all observers assigning ulcer grades in real time may have reduced variability. Finally, the measured low concentration of alpha-tocopherol in the supplement prevents conclusions from being established regarding utility of alpha-tocopherol in prevention of gastric ulcers.

In conclusion, we did not detect that EOC prevented gastric ulcer formation when compared with a negative control and the gold standard treatment (omeprazole). Additionally, although alpha-tocopherol concentrations increased in EOC treated horses over time, the effect

was highly variable by individual, and independent testing of the supplement showed lower alpha-tocopherol concentrations than expected.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the University of California Davis IACUC, protocol #21497.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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