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Original Research

Polysaccharide Treatment Reduces Gastric Ulceration in Active Horses

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ABSTRACT

Equine gastric ulceration effects condition, performance, and behavior. Prevalence of ulcers in horses can reach 80% to 100%. After reviewing the literature, we propose an oral polysaccharide preparation will be effective in treating equine gastric ulceration. Ten adult horses with gastric ulceration were used to evaluate the clinical efficacy of a polysaccharide gel containing a blend of hyaluronan and schizophyllan for 30 days. Posttreatment gastroscopies were conducted to determine treatment findings, and images were scored. Percent healing was assessed comparing initial images to posttreatment findings. Of the horses treated with the combinational therapy, 90% showed complete resolution and/or improvement in ulcerative areas, increased appetite, weight gain, and positive behavioral changes. This study provides evidence that gastric ulceration in active horses can be successfully treated with a naturally safe and effective polysaccharide blend of hyaluronan and schizophyllan.

1. Introduction

1.1. Gastric Ulceration in Horses

Prevalence of gastric ulcers (or equine gastric ulcer syndrome [EGUS]) is high in performance horses. Prevalence of ulcers in various equine disciplines can reach 80% to 100% [1–5]. Exercise increases gastric acid production, exposes gastric mucosa to acidic pH more readily, and decreases gastrointestinal blood flow [6]. Equine gastric ulceration is attributed to small stomach anatomy, constant acid secretion, high-grain diets, transport stress, stall confinement, and chronic nonsteroidal anti-inflammatory drug use [6]. The only definitive diagnosis for EGUS is gastroscopy and postmortem evaluation.

Equine gastric complications ultimately arise from an imbalance between mucosal irritants (hydrochloric acid, pepsin, bile acids, and organic acids) and mucosal protective factors (mucus, bicarbonate) [1]. Glandular gastric ulcers are most likely due to decreased blood flow, mucus production, and bicarbonate secretion. Decreased prostaglandin synthesis has also been implicated in the cause of glandular gastric ulcers. Decreased prostaglandin synthesis correlates with decreased mucosal blood flow, stimulation of gastric acid secretion, and inhibition of bicarbonate secretion by the glandular mucosa [6]. Current treatment options for gastric ulceration in horses include proton pump inhibitors (PPIs) (omeprazole), H2 blockers (ranitidine), and physical mucosal protectants (sucralfate).

We hypothesize that an oral polysaccharide blend will be effective for treating gastric ulceration.

1.2. Polysaccharides and Gastric Healing

Research has shown the promise of polysaccharides' ability to confer protection from gastric ulceration. A plant-derived antiulcer polysaccharide fraction was shown to be effective in healing experimentally induced chronic ulcers in rodents [7]. In the same experimental model, bacterial

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cell wall polysaccharides were effective in healing gastric ulcers. Levels of epidermal growth factor and basic fibroblast growth factor increase in the polysaccharide-treated gastric tissues indicating healing at the cellular level [8].

Additional studies provide further evidence that polysaccharide fractions also exhibit ulcer healing capacity [9,10].

1.3. Hyaluronan

Hyaluronan is a glycosaminoglycan found ubiquitously in the body, and its role in the gastrointestinal tract is multifaceted. In the intestine, hyaluronan is vital for fluid exchange to and from the blood [11,12]. In addition to functioning in normal gastric and intestinal tissue homeostasis, hyaluronan plays a role in the intestinal innate immune response. Dysregulation of the production and/or catalysis of hyaluronan may promote intestinal inflammation and disease [13].

Hyaluronan has established itself as a protectant through its ability to confer defense to intestinal mucosa. A recent study evaluated the effects of hyaluronan on ulcerative gastric mucosa in Sprague-Dawley rats [14]. The high-molecular-weight hyaluronan-containing gel significantly protects the gastric mucosa against injury with reduction of ulcerative areas in the gastric wall and reduction/inhibition of edema. In addition, the high-molecular-weight hyaluronan gel induces greater healing compared to the PPI omeprazole [14]. An additional study demonstrated that administration of hyaluronan in young horses stimulates PGE2 expression by measurable quantification [15].

1.4. Schizophyllan

Schizophyllan is a neutral polysaccharide characterized molecularly as a β-1,3 beta-glucan with β-1,6 branching found as an integral cell wall constituent of Schizophyllan commune—a common fungus utilizing wood as a growth substrate [16]. Schizophyllan is known for its ability to activate the immune response by targeting the maturation, differentiation, and proliferation of immune cells in the host: dendritic cells, macrophages, natural killer cells, B-lymphocytes, and T-lymphocytes via plasma membrane-bound receptor Dectin1 [17]. Beta-glucans, including schizophyllan, are scientifically proven biological defense modulators that have the ability to nutritionally potentiate the immune response.

Research supports the safety of beta-glucan polysaccharides for use in horses. One study demonstrated that administration of a 1,3-beta-glucan to pregnant mares increased the cellular immune response in foals. Clinical examinations during the neonatal and postnatal period did not reveal any abnormalities in these foals [18]. From this study, it is evident that oral administration of a beta-glucan polysaccharide improves immunity quantitatively.

2. Materials and Methods

2.1. Animals

All protocols were carried out in adherence to ethical guidelines on animal welfare. The study was reviewed and approved by the Hagyard Equine Medical Institutes Clinical Studies Review Committee prior to the start of the study. Written informed consent for study participation was obtained from horse owners, see complete description of participants in Table 1.

2.2. Gastroscopy

Subjects fasted 12 hours prior to gastroscopic examination. Horses were sedated with 100 mg/mL xylazine (AnaSed LA MWI, Boise, ID) at a dosing range of 0.25 to 0.5 mg/kg IV. An Olympus CV-100, CLV U20 (Olympus, Lake Success, NY) three-meter video colonoscope, and Stryker digital capture device software (Styker Endoscopy, San Jose, CA) were used for gastroscopies.

Table 1
Signalment, clinical signs, and posttreatment findings of study participants.

Case	Signalment	Clinical Signs Upon Initial Evaluation	% Weight	Posttreatment Notes
1	5-y Wmbl mare; show horse	Aggressive behavioral patterns under saddle	+3.09	Positive response; monumental improvement in attitude
2	7-y TB gelding; 3-d eventing horse	Acute colic without previous presentation	−0.97	Positive response
3	24-y QH gelding; trail horse	Weight loss, girthy, poor appetite, teeth recently floated	+4.22	Positive response; improved attitude and appetite; brighter; no longer girthy
4	3-y TB race filly	Difficulty maintaining weight; poor appetite; loose manure	+5.78	Positive response; improvement in weight, appetite, and manure
5	2-y TB race colt	Mild persistent colic; poor weight gain	NA	Positive response; brighter disposition
6	3-y TB race filly	Poor performance in training and in maiden race	+5.65	Positive response
7	3-y TB race filly	Poor performance; history of difficulty gaining weight	+6.75	Positive response; improved appetite
8	5-y SB race gelding	Poor performance; weight loss; decreased appetite	+0.89	Positive response
9	6-y TB gelding; show horse	Irritable attitude and aggressive behavioral patterns	−2.00	Positive response; increase in training and not feed may account for weight loss
10	11-y TB broodmare	History of mild, intermittent colic	NA	Nonresponder

Abbreviations: NA, not available; QH, Quarter Horse; SB, Standardbred; TB, Thoroughbred; wmbl, Warmblood.
Patient signalment reveals a broad range of age, breed, sex, and activity/background of the study participants. Subjects presented with symptoms of possible gastric ulceration after failure of traditional therapies. After 30-day treatment with the polysaccharide blend, % weight gain/loss and clinical response are noted.

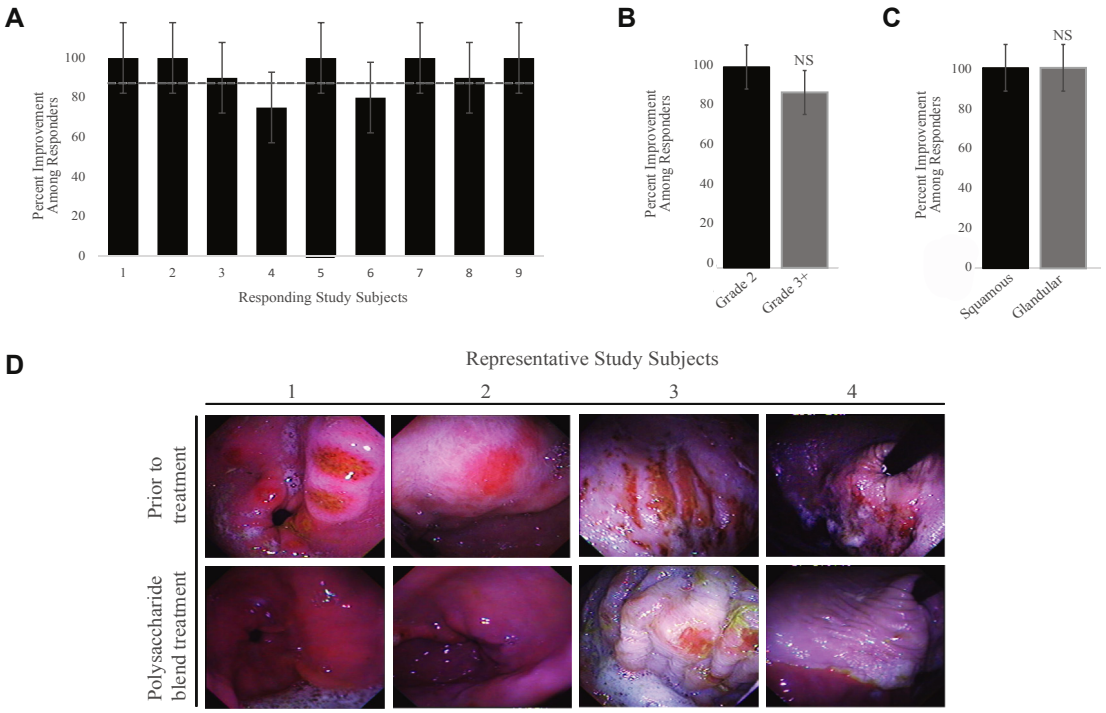

Fig. 1. Effects of 30-day polysaccharide treatment on gastric ulceration in active horses. A 30-day treatment with a polysaccharide blend containing high-molecular-weight hyaluronan and the beta-glucan schizophyalln resulted in a clinically significant positive response in 90% (9/10) of the treated horses. Response to treatment is shown (A) and compared to the average positive response of 87.3% (dashed line). The polysaccharide treatment was effective for ulcer grades 2 and 3+ (B) and on both squamous and glandular ulcers (C) without significant difference among compared groups. Representative gastroscopic images show significant ulcerative healing with polysaccharide treatment (D). Data are reported as mean improvement (±SD), where $P \leq .05$. NS, not significant; SD, standard deviation.

2.3. Experimental Protocol

Ten horses underwent pretreatment gastroscopy for diagnosis and scoring of existing ulcers. Participants were administered 1 to 2 ounces of a polysaccharide blend (MHB3 Hyaluronan [240–480 mg]; Betacan Schizophyllan [60–120 mg], Cogent Solutions Group, LLC, Lexington, KY) daily for 30 days. Dosing was determined at the time of diagnosis and based upon patient history and severity of condition. Subjects underwent posttreatment gastroscopy to determine treatment effects. Administration of the polysaccharide blend was controlled by the owners and given at the same time(s) daily. Horses prescribed 1 ounce (240 mg hyaluronan, 60 mg schizophyllan) were treated once daily, whereas horses prescribed 2 ounces (480 mg hyaluronan; 120 mg schizophyllan) were administered 1 ounce twice daily (8–10 hours apart). Compliance was verified during the posttreatment assessment. Throughout the study's duration, the animals' lifestyle and dietary programs were not altered. Nutraceuticals and/or prescribed gastroprotectants were discontinued.

2.4. Ulcer Grade

During the initial gastroscopy, the governing veterinarian diagnosed squamous and glandular stomach ulcers based on severity from grades 0 to 4. Grading was based upon the following criteria: grade 0 = healthy, nonulcerated stomach with no appearance of hyperkeratosis; grade 1 = areas of hyperkeratosis; grade 2 = small, single, or multifocal lesions; grade 3 = large single or extensive superficial lesions; and grade 4 = extensive lesions with areas of apparent deep ulceration [1]. Pretreatment and follow-up images were scored without patient identifiers, in random order, and by one veterinarian to eliminate observational bias. Percent healing was clinically assessed by comparing the initial gastroscopic images to posttreatment findings and considering number, severity, and size of glandular and nonglandular ulcers in pretreatment and posttreatment images; that is, a reduction in ulcer number from 10 to 2 during the course of treatment would equate to an 80% improvement.

2.5. Statistical Analysis

Statistical comparisons were evaluated by a one-way analysis of variance with Tukey's correction unless otherwise stated. Differences were considered statistically significant if the P value was $< .05$.

3. Results

3.1. Effects Polysaccharide Blend Treatment

Of the horses treated with the combinational therapy, 90% showed complete resolution and/or improvement in

ulceration. Improvement included gross morphological assessment and blind, randomized scoring of pretreatment and posttreatment gastroscopic images. Scoring took into account improvement in number, severity, and size of glandular and nonglandular ulcers. Posttreatment scores were calculated based upon an improvement in ulcer score and the reduction of total numbers present. In those horses that responded positively, an 87.3% improvement was noted (Fig. 1A). In the horses that responded to the treatment, response was independent of ulcer grade and type (Figs. 1B and 1C). One horse did not respond by showing no change in ulcerative load after polysaccharide treatment.

In addition to gross morphological changes (Fig. 1D) in gastroscopy images, trainers noticed improvement in behavior, appetite, weight gain, and symptoms of colic in the responders (Table 1). Behavioral changes were noted by animal owners via personal communication at the posttreatment evaluation and may be prone to speculation and bias.

This study demonstrates the efficacy of a polysaccharide blend of hyaluronan and schizophyllan for healing EGUS in horses.

4. Discussion

Our findings are clinically significant as more horse owners and veterinarians seek alternative treatment options for EGUS based upon failures and side effects of current approved therapies [19].

Oxidative stress contributes to disease pathologies including gastric ulcer formation. While the mechanism of gastric healing promoted by polysaccharides has yet to be fully elucidated, those proposed include mucosal protective coating, antisecretory activity of gastric acid and pepsin, and radical scavenging activity [7]. Along with other polysaccharides, hyaluronan is an established antioxidant. It is thought to create a mechanical barrier limiting access to reactive oxygen species and thereby reducing the DNA damage response activation [20–22]. It is also speculated that the gastroprotective effects of hyaluronan could be attributed to its anti-inflammatory activity [14].

Our study reveals the benefits of treating gastric ulceration with a hyaluronan/schizophyllan conjugate. While long-term use of PPIs is traditionally well tolerated, it alters equine stomach pH which has been shown to alter digestion at both the organismal and cellular levels [19]. Additionally, the use of PPIs has been associated with renal failure in other species [23,24]. The polysaccharide blend provides a safe, nonpharmaceutical alternative to the use of PPIs.

We realize that our lack of controls is a weakness and limitation of this study. Our study was not conducted with a research cohort; instead, our subjects were adult horses in active training and participated at considerable expense to their owners. We understand that the scoring system utilized in this study may not be directly relevant for glandular ulcers. However, in order to ensure glandular and nonglandular data could be compared in a straight forward manner, we utilized a modified version of ulcer grading system from the European College of Equine Internal Medicine Consensus Statement on Gastric Ulcer Syndrome in Adult Horses [1].

The presence and severity of ulcers change over time with or without intervention. However, this study is unique in that participants were active adult horses that remained in daily training, and stress and/or activity levels were not altered.

Thus, we view these data as proof of concept to show the potential benefit of oral supplementation with a polysaccharide blend against gastric ulceration in the active adult horse.

5. Conclusions

Our study reveals that a polysaccharide blend of 240 to 480 mg high-molecular-weight hyaluronan and 60 to 120 mg of schizophyllan administered daily for 30 days demonstrates ulcerative healing. Of the horses treated, 90% showed complete resolution and/or improvement in ulcerative areas, increased appetite, weight gain, and positive behavioral changes.

Our study suggests that a polysaccharide blend represents a novel means to enhance gastric healing in the active horse. Additional investigations to further elucidate these findings and determine optimal protocols are warranted.

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