Oral Treatment with a Nutraceutical (Cosequin®) for Ameliorating Signs of Navicular Syndrome in Horses*

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ABSTRACT

Fourteen horses with a progressive forelimb lameness of 3 to 12 months' duration, diagnosed as navicular syndrome, were selected from clinical cases admitted to Auburn University Equine Hospital for evaluation of the efficacy of an orally administered nutraceutical (Cosequin®, Nutramax Laboratories, Inc., Edgewood, MD) for ameliorating clinical signs associated with naturally occurring navicular syndrome. Horses were randomly allocated to treatment with the nutraceutical or a placebo. Treatment was five scoops (16.5 g) of powder twice daily in the feed. The test group (n = 8) received a patented nutraceutical consisting of 9 g of FCHG49™ (a highly purified glucosamine HCl), 3 g of TRH122™ (a specific purified low-molecular-weight sodium chondroitin sulfate), and 600 mg of manganese ascorbate. The placebo group (n = 6) received an indistinguishable oral powder containing only excipients. Owners and the investigator were unaware of group assignments. The same investigator assessed lameness and overall clinical condition at enrollment and after 4 and 8 weeks of treatment. Lameness was assessed by an algofunctional lameness index, comprising a combined sum score of standing posture, hoof tester examination, and lameness scores at various levels of work. Overall clinical efficacy was rated on a visual analogue scale. Owners assessed lameness via a preassigned questionnaire, incorporating an algofunctional lameness index and overall clinical condition at weekly intervals. Radiographic examinations of the navicular bones were performed at enroll-

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ment and after 8 weeks of treatment. The median algofunctional lameness index and overall clinical condition scores assigned the investigator were significantly improved (P = .05) for horses treated with the nutraceutical compared with placebo-treated horses. The degree of improvement in algofunctional lameness index assigned by owners after 8 weeks was also significant (P = .045) between the treatment groups. Radiographic scores after treatment were not significantly different between the groups (P > .05).

INTRODUCTION

Navicular syndrome is an important disease of horses that is difficult to diagnose with certainty and equally difficult to treat. The etiology of navicular syndrome is not clearly understood and is the subject of debate.[1] Various events have been proposed as primary causes, including microthrombi with resulting ischemia in the navicular bone,[2] trauma due to excessive biomechanical loading of navicular tissues,[3] and metabolic abnormalities leading to primary remodeling of the navicular bone that secondarily involves the flexor surface fibrocartilage.[4] The fact that no one treatment is effective in all cases of navicular syndrome supports the idea that the disease may be multifactorial.[1]

Regardless of whether the primary insult in navicular syndrome is vascular, biomechanical, metabolic, or a combination of several factors, disease progression and the lesions that develop in symptomatic horses are similar to those encountered in degenerative joint disease (DJD).[5] Navicular syndrome has many pathologic characteristics that are similar to those of high ring bone and bone spavin, including changes in vascular channels within bony tissues, remodeling of subchondral bone, and destruction of the fibrocartilage flexor surface of the navicular bone.[1,6]

Degenerative joint disease and navicular syndrome may not, in fact, represent a specific disease entity, but rather may be the clinically recognizable end result of any of several pathologic joint changes.[1] Although not contributing definitively to the question of etiology, the classification of navicular syndrome as a form of DJD is important because it directs those interested in studying the pathogenesis and treatment of navicular syndrome to the large volume of ongoing research involving DJD in other joints and other species. Direct correlation between species, or between joints with differing biomechanics, cannot be made without careful consideration. However, many of the recent discoveries in osteoarthritic syndesmology and the improvement in clinical signs associated with the use of hyaluronic acid, polysulfated glycosaminoglycans, and intraarticular steroids for navicular syndrome can be regarded as contributing to a knowledge base for researchers of navicular syndrome.[7]

A significant development in the knowledge of DJD is the understanding that a loss of integrity in the articular cartilage is one of the fundamental lesions leading to changes in other joint tissues such as synovial lining and subchondral bone.[8] Treatments that attempt to support normal cartilage structure and function are termed *structure-modifying* and are currently receiving attention in veterinary medicine.[9–11]

The nutraceutical studied in the present trial has been found to improve symptoms of DJD in humans,[12,13] horses,[14] and dogs[15] and has also exhibited structure-modifying effects verified histologically in experimental models using rabbits,[16] rats,[17] and dogs.[18] Since one of the multifactoral pathogeneses of navicular syndrome is the development of degenerative disease in the fibrocartilage of the flexor surface of the navicular bone, causing changes in the underlying subchondral bone and its marrow,

it becomes logical to evaluate whether treatments that have proven effective for DJD would also be effective in navicular syndrome in horses. The purpose of the present study was to evaluate the effectiveness of one such treatment for ameliorating symptoms of navicular syndrome in a randomized double-blind, placebo-controlled clinical trial.

MATERIALS AND METHODS

Subjects

Fourteen horses (1 paint horse, 12 quarter horses, and 1 thoroughbred) were selected from clinical cases presented to the Auburn University Equine Hospital. There were 9 geldings, 4 mares, and 1 stallion, with a mean age of 10.8 ± 0.8 years and a mean weight of 521.8 ± 14.9 kg. Criteria for inclusion in the clinical trial included an age between 5 and 15 years and a progressive forelimb lameness of 3 to 12 months' duration diagnosed as navicular syndrome. The horses could have no other clinical findings in the distal limb and could not have been given any antiinflammatory treatment for at least 21 days before the start of the study. At enrollment, the horses underwent medical and lameness examinations to confirm the clinical and historical data. A signed, informed consent was obtained from all owners prior to initiation of treatment.

Clinical Evaluations

Clinical criteria used to diagnose navicular syndrome included a history of unilateral or bilateral forelimb lameness of insidious onset; a shortening of the cranial phase of the stride, with the toe of the foot contacting the ground before the heel; a lameness that was often accentuated when the horse was turned in the direction of the affected limb; and a resolution of lameness after anesthesia of the palmer digital nerve at the level of the collateral cartilages. Other clinical signs used to support the diagnosis of navicular syndrome were pointing of the affected limb when at rest; a pain response when pressure with hoof testers was applied across the middle third of the frog; a pain response to flexion of the distal interphalangeal joint; and an increase in lameness for a few strides following flexion of the distal interphalangeal joint for 1 minute.[4]

Allocation and Treatment

Horses were randomly allocated to either the nutraceutical (Cosequin®, Nutramax Laboratories, Edgewood, MD) or placebo group, using group assignments created before the start of horse recruitment, by means of a computer-based pseudorandom number generator. Both the nutraceutical and placebo treatment regimens were five scoops (16.5 g) of powder by mouth twice daily. This dose of the nutraceutical comprised 9 g of FCHG49™ (a highly purified glucosamine HCl), 3 g of TRH122™ (a purified low-molecular-weight sodium chondroitin sulfate), and 600 mg of manganese ascorbate (containing 80 mg of manganese). Placebo consisted of indistinguishable powder containing only excipients. Each batch of test substance was given a sequential number with the code concealed from the investigator. The sequential numbers were matched with the order of inclusion of eligible horses into the study. Neither the primary investigator nor the owner was aware of the group assignment.

Evaluations

Lameness was assessed for each horse by the investigator at enrollment and 4 and 8 weeks later. Lameness was rated by an algofunctional lameness index, which was a combined score of standing posture; hoof tester examination; phalangeal flexion test; lameness grades while trotting and longeing (AAEP scale 0–5; Table 1); and lameness after warm-up longeing for 5 minutes. The investigator also gave an overall

TABLE 1. Criteria for Evaluation of Algofunctional Lameness Index Mean by a Combined Sum Score of the Left and Right Forelimb of Horses

Test	*Criterion*	*Score*	
		Left	*Right*
Standing posture	Normal weight bearing	0	0
	Intermittent pointing foot	1	1
	Constant pointing foot	2	2
	Shifting weight	3	3
	Non–weight-bearing heel	4	4
Hoof tester examination	No response	0	0
	Slight	1	1
	Moderate	2	2
	Strong	3	3
	Very strong	4	4
Lameness while trotting (lameness classification)*		0	0
		1	1
		2	2
		3	3
		4	4
		5	5
Phalangeal flexion test	Sound	0	0
	No response to flexion but lame for 10 m on trot	1	1
	No response to flexion but lame for 20 m on trot	2	2
	Positive response to flexion and lame for >20 m	3	3
	Positive response to flexion still lame for >40 m	4	4
Lameness while longeing (lameness classification)*		0	0
		1	1
		2	2
		3	3
		4	4
		5	5
Lameness after 5 min of longeing	0 min	1	1
	1 min	2	2
	2 min	3	3
	3 min	4	4
	4 min	5	5
	5 min	6	6
	Remains lame	7	7
		TOTAL SCORE: _____	

**Lameness grade classification:* Grade 0: sound; Grade 1: difficult to observe, not consistently apparent regardless of circumstances; Grade 2: difficult to observe at a walk or trotting in a straight line, consistently apparent under certain circumstances (e.g., weight-carrying, circling, inclines, hard surfaces); Grade 3: consistently observable at a trot under all circumstances; Grade 4: obvious lameness; marked bobbing, hitching or shortened stride; Grade 5: minimal weight-bearing in motion and/or at rest, inability to move.

TABLE 2. Subjective Scoring System Based on Radiographically Detectable Degenerative Changes within the Navicular Bone of Each Forefoot of Horses

		Radiographic Findings		
Score	*Condition*	*Texture of Bone*	*Synovial Invagination*	*Shape/Borders*
0	Normal	Fine trabeculae; sharp interface between medullary cavity & flexor cortex	Not visible; several narrow, cone-shaped invaginations	Symmetric
1	Mild	Fine trabeculae; sharp interface	Some widened, pointed, or cone-shaped invaginations	Rough distal border; irregular medial and/or lateral borders
2	Moderate	Medullary sclerosis; loss of sharp interface between medullary & flexor cortex	Many widened & rounded invaginations	Enthesiophytes ("spurs") on medial & lateral borders; irregular distal border
3	Severe	Cystic lucencies	Many rounded, enlarged invaginations	Extensive new bone production; erosion of flexor cortex; fracture

clinical judgment of efficacy based on a visual analogue scale. The low numerical end of this scale represented the most favorable response (equivalent to normal condition), and the high numerical end represented the worst response (equivalent to very severe condition). The difference between scores before and after treatment expressed the degree of response.[20] To avoid being biased by the owner's perception of the horse's overall condition, the investigator had no contact with the owner except after examination of the horse.

Each owner assessed his or her horse's progress at weekly intervals on a questionnaire that incorporated an algofunctional lameness index of the following variables: degree of difficulty rising from a down position; lameness while standing; lameness while walking; lameness while trotting; and lameness while longeing. At the end of each examination, the owners also gave an overall clinical judgment of efficacy based on a visual analogue scale. Owners were instructed to record any adverse events observed throughout the study period and classify their severity.

Radiographs

The following weight-bearing radiographs were obtained at enrollment and at the completion of the study: dorsoproximal-palmarodistal oblique (65° and 45°), dorsoproximal-palmarodistal oblique 65° (1/3 technique), dorso 45° proximo 45° lateral-palmarodistomedial oblique, dorso 45° proximo 45° medial-palmarodistolateral oblique, lateromedial, dorsopalmar, palmaro 45° proximal-palmarodistal oblique.

The navicular bone was evaluated by two methods: Method one used a subjective score (0–3) based on the presence or absence of radiographically detectable degenerative changes within the navicular bone of each forefoot (Table 2). The second method of radiographic

staging was performed according to a standardized classification system.[19] Horses with severe radiographic changes of the navicular bone involving medullary sclerosis, enthesiophyte formation, large cystic lesions, or erosions of the flexor cortex were not included in the study.

Statistics

The algofunctional lameness index scores represent the sum of clinical assessment variables by the investigator and the owner. For analytic purposes, the investigator's assessments for the left and right forelimbs of each horse were summed. Data are presented as medians and ranges. Differences between groups for the change from baseline to the end of the study were evaluated by the Wilcoxon rank-sum test. Results were considered significant at $P \leq .05$.

RESULTS

Investigator Assessments

The median lameness score while trotting for the nutraceutical group improved from 3.5 at the beginning of the study to 1.0 after 8 weeks of treatment, in contrast with only a slight improvement for the placebo group ($P = .003$; Table 3). The pretreatment algofunctional lameness index median value for the nutraceutical group was 25.5 compared with 7.5 after 8 weeks of treatment. The algofunctional lameness index median value for the placebo group remained virtually unchanged over the treatment period, with a score of 19.5 before treatment and 21.0 at the completion of the study. The difference between group scores at 8 weeks was statistically significant ($P = .002$).

The median overall clinical condition scores at enrollment were 61.5 for the nutraceutical group and 44 for the placebo groups (Table 3). At the end of 8 weeks, the median score for the nutraceutical group was 22.0 versus 43.5 for the placebo group ($P = .002$).

Owner Assessments

The median algofunctional lameness index at enrollment was 202.5 for the nutraceutical group and 211.5 for the placebo group (Table 4). After treatment, the median lameness index was 120.6 for the nutraceutical group and 215.8 for the placebo group ($P = .045$).

The median initial clinical condition score was 59.0 for the nutraceutical group and 50.5 for the placebo group (Table 4). The median clinical score at the end of 8 weeks was 33.0 for the nutraceutical group and 51.0 for the placebo group. The difference between the groups at the end of the study approached significance ($P = .08$). No adverse events were reported by any horse owner during the study.

Radiographs

No significant clinical differences were observed ($P > .05$) for either group according to the two methods used to evaluate radiographs of the navicular bones for each horse before and after treatment (Table 5).

DISCUSSION

Significant improvement in the algofunctional lameness index was observed in the current study by both the investigator and the owners. The algofunctional indices used in this study are used frequently in human osteoarthritis research and are well-accepted research tools.[13,20]

The lack of significant improvement in the overall clinical condition scores assessed by the owners may be due to a placebo effect and a loss of statistical power. Even though owners were unaware of treatment assignments, it is possible that "wishful thinking" following administration of the placebo powder influenced their perception of lameness. Additionally, owner inexperience was evident in the greater variation observed among their assessments of lameness in relation to the same assessment by

TABLE 3. Lameness Evaluations and Clinical Signs of Navicular Syndrome in Horses, Scored by Investigator

Variable	*Time*	*Neutraceutical (n = 8) Median (Range)*	*Placebo (n = 6) Median (Range)*	P *value (Neutraceutical vs Placebo)**
Overall clinical condition efficacy	Baseline			
	4 wk	61.5 (29–87)	44.0 (39–61)	
	8 wk	24.0 (11–69)	42.5 (39–59)	
		22.0 (7–44)	43.5 (39–58)	.002
Algofunctional lameness index				
a. Standing posture	Baseline	1.0 (0–2)	1.0 (0–1)	
	4 wk	0.0 (0–1)	1.0 (0–1)	
	8 wk	0.0 (0–0)	1.0 (0–1)	.003
b. Hoof tester examination	Baseline	5.0 (0–7)	4.0 (0–5)	
	4 wk	2.0 (0–6)	3.0 (0–5)	
	8 wk	1.5 (0–2)	4.0 (0–4)	.009
c. Lameness while trotting†	Baseline	3.5 (2–5)	2.5 (2–3)	
	4 wk	1.5 (0–5)	2.5 (2–3)	
	8 wk	1.0 (0–2)	2.0 (2–4)	.003
d. Phalangeal flexion test	Baseline	3.5 (2–5)	2.5 (0–5)	
	4 wk	1.0 (0–4)	2.5 (1–5)	
	8 wk	0.0 (0–0)	3.0 (2–5)	.003
e. Lameness while longeing	Baseline	5.0 (3–7)	4.0 (3–7)	
	4 wk	2.5 (0–5)	4.5 (4–6)	
	8 wk	2.5 (0–4)	5.0 (3–6)	.002
f. Soundness after 5-min warm-up	Baseline	8.0 (4–8)	8.0 (4–8)	
	4 wk	4.0 (0–8)	8.0 (4–8)	
	8 wk	4.0 (0–8)	7.0 (4–8)	.03
Lameness index	Baseline	25.5 (14–36)	19.5 (16–27)	
Total score, a–f	4 wk	9.5 (2–29)	20.5 (16–25)	
	8 wk	7.5 (1–15)	21.0 (16–24)	.002

*Difference in clinical signs (from baseline to 8 wk) between the placebo and nutraceutical.
†Sum score representing the lameness grade scores of both the left and right forelimbs.

the investigator. Since each of the 14 horses had a different owner, interobserver variability could diminish actual differences between the treatments.

An important goal in the treatment of horses with joint disease is to reduce pain and swelling and arrest the cascade of pathologic events that lead to the disruption of the dynamic balance essential for the preservation of a functional joint. Although there was significant improvement in clinical signs, conclusions cannot be drawn regarding the mecha-

TABLE 4. Lameness Evaluations and Clinical Sign Scores of Navicular Syndrome in Horses, Scored by Owner

Variable	*Time*	*Nutraceutical (n = 8) Median (Range)*	*Placebo (n = 6) Median (Range)*	P *value (Nutraceutical vs Placebo)**
Overall clinical condition of efficacy	Baseline	59.0 (45–73)	50.5 (22–71)	
	4 wk	53.5 (2–69)	46.0 (19–65)	
	8 wk	33.0 (1–67)	51.0 (20–66)	.08
Algofunctional lameness index				
a. Difficulty rising from a down position	Baseline	21.0 (0–92)	29.0 (4–47)	
	4 wk	11.0 (1–57)	28.0 (4–41)	
	8 wk	3.5 (1–54)	23.0 (4–53)	.3
b. Lameness while standing	Baseline	23.0 (1–50)	30.0 (4–55)	
	4 wk	19.0 (1–48)	33.5 (4–52)	
	8 wk	17.0 (1–49)	28.5 (4–51)	.3
c. Lameness while walking	Baseline	45.0 (1–71)	28.5 (17–76)	
	4 wk	32.5 (1–74)	26.0 (12–76)	
	8 wk	23.0 (1–79)	28.0 (10–76)	.4
d. Lameness while trotting	Baseline	61.0 (2–76)	51.0 (22–86)	
	4 wk	52.0 (4–78)	51.0 (13–86)	
	8 wk	21.0 (1–71)	54.0 (16–86)	.03
e. Lameness while longeing	Baseline	64.0 (46–73)	63.0 (22–84)	
	4 wk	59.0 (28–77)	57.0 (14–74)	
	8 wk	29.0 (24–71)	57.5 (16–83)	.2
Lameness index	Baseline	202.5 (6.3–349)	211.5 (112.5–269)	
Total score, a–e	4 wk	156.0 (8.8–316)	209.5 (75–254)	
	8 wk	120.6 (5–265)	215.8 (71–265)	.045

*Difference in clinical signs (from baseline to 8 wk) between the placebo and Nutraceutical.

TABLE 5. Subjective and MacGregor Scores for Radiographicic Evaluations for Horses Diagnosed with Navicular Syndrome

Variable	*Time*	*Nutraceutical (n = 8) Mean (SEM)*	*Placebo (n = 6) Mean (SEM)*	P-*value (Nutraceutical vs Placebo)*
Subjective assessment*	Baseline	0.63 (0.30)	0.67 (0.33)	
	8 wk	0.69 (0.28)	0.75 (0.40)	
	Change	0.06 (0.06)	0.08 (0.08)	.9
MacGregor score	Baseline	7.25 (2.04)	8.83 (2.04)	
	8 wk	7.25 (2.07)	8.92 (2.04)	
	Change	0.00 (0.57)	0.08 (0.66)	.7

*According to the scoring system (0–3) described in Table 2.

nism(s) of action of the nutraceutical used in this study (Cosequin®). However, some theoretical possibilities can be offered based on previous research.

Although much is still unknown about the etiology and pathogenesis of the various forms of DJD, it is well known that a decrease in glycosaminoglycan content is associated with loss of integrity of cartilage and other connective tissues in many joint disorders, including DJD.[21] Glycosaminoglycans are essential in cartilage and other connective tissues for compressive qualities and transfer of forces. These factors in turn influence the metabolism of connective tissue cells. One of the primary causes of pathologic decreases in glycosaminoglycan content within connective tissues is the action of metalloproteinases. Compounds that decrease metalloproteinase activity are expected to have protective effects in connective tissues and numerous metalloproteinase inhibitors, including chondroitin sulfate, are currently under scrutiny.[22]

Chondroitin sulfate, an endogenous glycosaminoglycan, has been shown in cell culture to inhibit metalloproteinases, interleukin-2, and complement activation.[23,24] Cosequin® contains a specific grade of chondroitin sulfate with documented oral absorption.[25,26] Recent studies demonstrate beneficial effects from oral and intramuscular administration of chondroitin sulfate in horses and rabbits with experimentally induced arthritis.[16,27,28] Chondroitin sulfate is the main proteoglycan on the platelet surface and is a part of the normal control of coagulation.[29] Previous researchers have theorized that pathologic decreases in endogenous chondroitin sulfate production could predispose animals to formation of microthrombi and associated peripheral ischemia.[30] Either as an etiology or a secondary event, ischemia is evidently a common event in DJD, including navicular syndrome.[1] An antiischemic effect of the chondroitin sulfate component is potentially a mechanism of action by which Cosequin® might exert a beneficial effect in navicular disease.

Cosequin® contains pharmaceutical grade glucosamine, which has been shown in cell culture to increase the synthesis of glycosaminoglycans by chondrocytes and other connective tissue cells.[16,31,32] Glucosamine also has been shown to inhibit the effects of several inflammatory agents in vivo and to be an effective oral treatment in experimental models of generalized subacute inflammation, or arthritis.[33,34] Glucosamine, however, does not have direct analgesic properties.[33]

The combination of FCHG49™ glucosamine HCl and TRH122™ low-molecular-weight sodium chondroitin sulfate has been shown to be synergistic.[16,35] Cosequin® has been extensively studied and widely used in veterinary medicine for several years in the United States to treat osteoarthritis in companion animals with no therapy-limiting side effects.[14,15,36,37] In one prospective equine study, significant improvements in lameness scores, flexion test results, and stride length were seen in horses with naturally occurring DJD after treatment.[14] In another study, the severity of experimentally induced DJD in dogs (via cranial cruciate ligament transection) was reduced after treatment with the compound.[18] A significant decrease in lesions was observed in one study using a rabbit menisectomy model of osteoarthritis, [16] and pretreatment with Cosequin® produced an antiinflammatory effect in dogs with chemically induced synovitis.[11]

Glucosamine, chondroitin sulfate, and manganese are considered dietary supplements in the United States; and their manufacture, sale, and use are not closely regulated by any government agency. In fact, the purity, quality, and quantity of glucosamine and chondroitin sulfate can vary greatly from product to prod-

uct, depending on the technology used to extract them from their animal tissue sources and other factors.[22,38–40] Certainly, any of these factors is capable of affecting efficacy and safety of the product. The present study, as well as others previously mentioned,[11,14–16,18,36,37] were all performed using Cosequin®, a patented product of verified purity, content, and uniformity; it is not the intent of the authors to extrapolate findings to other "similar" compounds.

The study targeted horses in early, milder stages of the disease; whether these results can be extrapolated to more severe, long-standing cases is unknown. No significant improvement of standardized and subjective navicular radiographic scores was evident in this study. Alternative imaging techniques, such as nuclear scintigraphy, computed tomography, and magnetic resonance imaging would have been useful for assessing degenerative changes in the navicular bone; however, clinical diagnosis, based on established criteria for lameness, was found to be adequate for measurements of improvement after treatment because the level of disease was considered mild and subacute. Intraarticular anesthesia of the coffin joint was not used to assist with identification and standardization of these clinical cases because of the poor correlation of differentiating coffin joint disease from navicular syndrome and the risk of hemarthrosis exacerbating clinical signs of lameness and skewing the clinical trial data.[41] More studies with larger number of horses and a longer follow-up period are needed to assess the biochemical and structural responses of animal tissues to purported structure-modifying compounds.

CONCLUSION

Lameness and clinical condition scores were significantly improved ($P \leq .05$) for horses treated with the nutraceutical Cosequin® for 8 weeks, as compared with horses treated with placebo for the same period. Radiographic scores were not significantly different between the groups after treatment ($P > .05$).

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