2023 ACVS Surgery Summit
Louisville KY, October 12-14, 2023

Evaluating the benefit and tolerability of an intra-articular injection of a collagen-elastin hydrogel microparticle (CEHM) into the stifle joint of dogs with suspected cruciate ligament rupture

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BACKGROUND

Cranial cruciate disease (or CCD) remains one of the most common causes of canine pelvic limb lameness observed in clinical practice today. Surgery remains the treatment of choice for the best return to function. Several intra-articular injection products are currently being investigated to maintain patient comfort and quality of life for non-surgical patients. CEHM, a collagen-elastin biomatrix on a heparin scaffold, has shown to be effective when utilized for osteoarthritis and degenerative joint disease.

BIOMATERIAL

Collagen-Elastin Hydrogel Microparticles (CEHM) is commercially available as Spryng with OsteoCushion Technology and was previously referred to as Mastergel Hydrophilic Biomaterial (MHB). CEHM product is formulated with a collagen, elastin bio-matrix on a heparin scaffold and is classified as a medical device, NOT a therapeutic. The biomaterial has already been proven to be effective when utilized for osteoarthritis and degenerative joint disease.

STUDY OBJECTIVE

Determine if CEHM injection will help alleviate acute pain and loss of function associated with partial or complete unilateral cranial cruciate disease, despite the kinematic disadvantages of lacking a surgically altering procedure to the stifle.

METHODS AND EXPERIMENTAL DESIGN

Inclusionary criteria

- > 6 mo with unilateral partial or complete CCD, determined by physical and orthopedic examination, Stifle radiographs to confirm CCD.

Null hypothesis

- The true response rate is 10% will be tested against a one-sided alternative that the true response rate is 25% of the study population.

Simon's Two Stage Study Design (Simon, 1989)

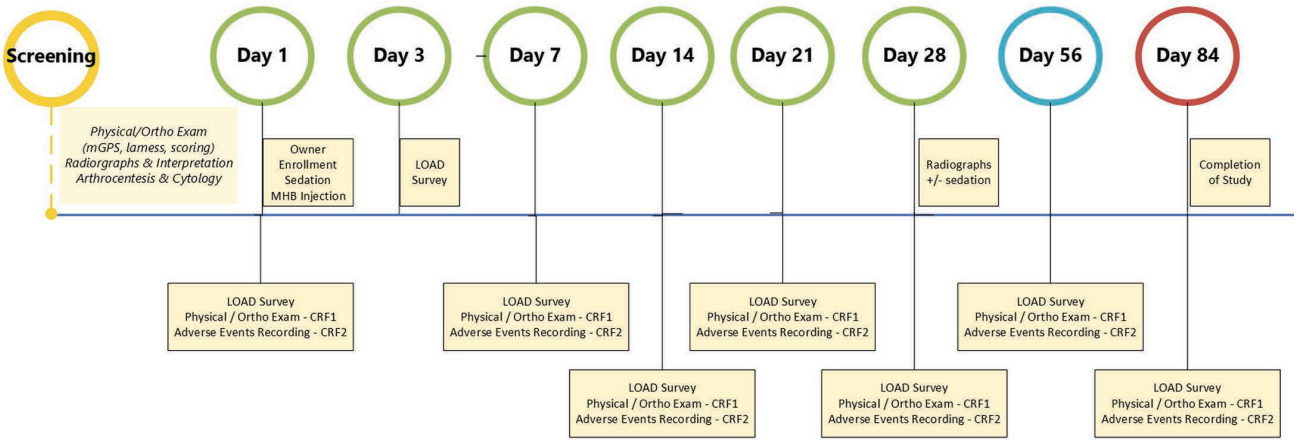
- Initial cohort: 22 patients with unilateral CCD.
- Second cohort: additional 18 patients enlisted (total of 40) if proven effective.

Primary endpoint

- Response rate from day 1 to day 28 as measured by the modified Glasgow Composite Pain Score (mGCPS), in which a reduction in the mGCPS by 25% or greater would be considered a beneficial response.

Secondary endpoints

- Change in mGCPS from Day 1 to all subsequent study days.
- Change in visual lameness score (VLS) and the Liverpool Osteoarthritis in Dogs (LOAD) survey score from Day 1 to all other subsequent study days.



Lameness Grade	Definition
0	Normal
1	Mild subtle lameness with partial weight bearing
2	Obvious lameness with partial weight bearing
3	Obvious lameness with intermittent weight bearing
4	Full non-weight bearing

Score Variable	Grade Range
Posture	0 – 3
Lameness at walk	0 – 4
Lameness at trot	0 – 4
Willingness to raise contralateral limb	0 – 4
Cranial drawer	0 – 3
Tibial thrust	0 – 3
Pain on extension	0 – 3
Pain on full flexion	0 – 3
Meniscal click	0 – 1
Pain following orthopedic exam	0 – 3

RESULTS

On average there was significant improvement in all of the clinical variables throughout the study period (Table 1). The table notes the range for the gradual improvement of mGCPS, VLS and LOAD scores were statistically significant throughout the study.

Table 1: mGCPS Day 1 to subsequent study days

Clinical Variable	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Day 56	Day 84	P-value
n	43	41	41	41	41	40	35	24	
Average mGCPS (Range)	4 (1 – 10)	N/A	3 (1 – 10)	3 (0 – 8)	3 (0 – 8)	3 (1 – 10)	3 (0 – 7)	2 (0 – 7)	**0.0063**
Average VLS (Range)	16 (5 – 32)	N/A	14 (2 – 23)	14 (2 – 27)	12 (2 – 30)	13 (3 – 27)	12 (0– 27)	10 (0 – 26)	**<0.0001**
Average LOAD (Range)	19 (0 – 32)	20 (0 – 36)	17 (1 - 31)	17 (0 – 32)	15 (0 – 27)	13 (0 – 25)	14 (0 – 37)	12 (0 – 37)	**<0.0001**

P-values calculated using general linear mixed models

Table 2: Multiple comparisons of mGCPS

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 7	-0.65	-1.29 to -0.01	**0.0430**
Day 1 vs. Day 14	-0.74	-1.56 to +0.08	0.0896
Day 1 vs. Day 21	-0.61	-1.36 to +0.13	0.1384
Day 1 vs. Day 28	-1.11	-1.97 to -0.26	**0.0060**
Day 1 vs. Day 56	-0.72	-1.71 to +0.27	0.2294
Day 1 vs. Day 84	-1.57	-2.52 to -0.61	**0.0006**

P-values calculated using Dunnett's multiple comparison test

Table 3: Multiple comparisons of VLS

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 7	-2.54	-5.26 to +0.44	**0.0030**
Day 1 vs. Day 14	-2.47	-5.87 to +1.53	**0.0361**
Day 1 vs. Day 21	-3.69	-5.95 to -0.44	**0.0002**
Day 1 vs. Day 28	-3.59	-6.89 to +0.34	**0.0018**
Day 1 vs. Day 56	-4.51	-11.12 to -1.16	**0.0004**
Day 1 vs. Day 84	-6.57	-13.95 to -2.63	**<0.0001**

P-values calculated using Dunnett's multiple comparison test

RESULTS (CONT.)

Table 4: Multiple comparisons of LOAD

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 3	+0.1310	-2.335 to +2.60	>0.9999
Day 1 vs. Day 7	-2.883	-5.535 to -0.23	**0.0279**
Day 1 vs. Day 14	-2.784	-5.346 to -0.22	**0.0281**
Day 1 vs. Day 21	-4.869	-7.473 to -2.27	**<0.0001**
Day 1 vs. Day 28	-6.006	-9.059 to -2.95	**<0.0001**
Day 1 vs. Day 56	-5.750	-9.515 to -1.99	**0.0012**
Day 1 vs. Day 84	-6.929	-11.28 to -2.58	**0.0007**

P-values calculated using Dunnett's multiple comparison test

CONCLUSIONS AND FUTURE STUDIES

- Final combined cohort's response rate: 22/40 (55%, 95% CI: 40%-69%)
- Null hypothesis: Rejected, Alternate hypothesis: Accepted
- The CEHM injection appears to be a reasonable, non-invasive alternative for patients with CCD when patient and/or owner factors preclude surgical intervention.
  - The study noted a reduction in all of the measured parameters (mGCPS, VLS, and LOAD scores) for responders resulting in clinical improvement across all time points.
  - The CEHM injection appears to be a reasonable, non-invasive alternative for patients with CCD, where owners are not pursuing surgical intervention.
- This preliminary data supports additional, larger prospective trials and studies to evaluate Spryng injections for medically managing patients with CCD.

ACKNOWLEDGEMENTS
Ethos – Wisconsin Veterinary Referral Center
Samuel Stewart DVM, DACVECC – Ethos Veterinary Healthy Science Consultancy
Garrett Tougas – Ethos Veterinary Healthy Science Consultancy
PetVivo, Inc.
Bridger Veterinary Specialists