Short Communication

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Intravesical glycosaminoglycans for obstructive feline idiopathic cystitis: a pilot study

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Abstract

Feline idiopathic cystitis is a common condition, often resulting in repeated episodes of life-threatening urethral obstruction. Defective urinary bladder glycosaminoglycans have been implicated as a causal factor. In this report, a commercially available glycosaminoglycan product was infused into the urinary bladders of cats with urethral obstruction from idiopathic cystitis to study the effect on repeated obstruction. In this randomized, blind, placebo-controlled clinical trial, the therapeutic protocol was well tolerated with no adverse effects. Whereas no glycosaminoglycan-treated cats (n = 9) developed repeated urethral obstruction during the 7 day follow-up period, 3/7 placebo-treated cats developed repeated obstructions. Approaching statistical significance (P = 0.06), these data suggest that further investigation of this new treatment option is warranted.

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Feline idiopathic cystitis (FIC) is a common condition affecting an estimated 250,000–500,000 cats in the USA every year.[1] There have been many theories regarding the cause of FIC, and it is likely that the syndrome is multifactorial.[2] Many cats develop hematuria, and some develop urethral plugs that can result in urethral obstruction, which is over-represented in males because of the narrow penile urethra.[2,3] Urethral obstruction in cats can be life-threatening and expensive to manage; thus, avoiding repeated obstruction is desirable, as it often results in euthanasia.[4] Repeat urethral obstruction rates in male cats vary by the report and the cause of obstruction, but were 36% and 58% in two recent studies.[4,5]

A defective glycosaminoglycan (GAG) layer lining the urinary bladder mucosa has been proposed as both a cause and effect of FIC, as well as being involved in interstitial cystitis in humans.[2,6–8] Urothelial permeability increases with defects in surface GAGs, which could lead to increased contact of urine with bladder wall tissues, resulting in the induction of immune-mediated or neurogenic inflammation, mast cell activation and sensory afferent nerve stimulation.[2] Abnormalities in urinary system GAGs and bladder permeability have been documented in cats with FIC.[6,9,10] Exogenously-administered GAGs adhere to damaged bladder uroepithelium, and promising data exist for their use in experimental models and human interstitial cystitis, particularly when administered by intravesical infusion.[7,8,11,12] Recently, a new formulation of GAGs for intravesical administration (A-CYST; Dechra Veterinary Products) became available in the USA and was shown to be safe when administered parenterally several times to normal research cats.[13] In the pilot study described here, we hypothesized that this product would be safe when administered to cats by intravesical infusion, and the protocol assessed would lessen the short-term repeat urethral obstruction rate in client-owned cats when compared with a placebo group.

Local veterinary clinics were informed of the protocol and asked to refer client-owned cats with urethral obstruction from suspected FIC to the James L. Voss Veterinary Teaching Hospital at Colorado State University. The study was provided free of charge to the owners to encourage case recruitment. The primary care veterinarians and veterinary nurses at the Veterinary Teaching Hospital were provided with the protocol and client consent forms that were approved by the Institutional Animal Care and Use Committee. On

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admission, a scanning urinary bladder ultrasound, a serum biochemical panel, a urinalysis and an aerobic bacterial culture were performed. Cats with prior treatment for the current episode of urethral obstruction, a serum creatinine level of >5.0 mg/dl (442 mmol/l), a serum potassium level of >6.0 mEq/l (6.0 mmol/l), urolithiasis, neoplasia or uroabdomen were excluded from the study.

The clinicians and veterinary nurses in the Critical Care Unit at the Veterinary Teaching Hospital were asked to use standardized protocols as consistently as possible. Protocols provided included pain scoring, sedation (or anesthesia) for urinary catheter placement, sterile saline lavage to remove sediment from the bladder after the initial catheter placement, intravenous fluid therapy, buprenorphine analgesia and phenoxybenzamine administration. In addition, all cats were fed a canned urinary diet when their appetites returned. Deviations from the suggested protocols were noted, and, ultimately, the major difference in the management of the two groups of cats was whether intravesical GAG infusions were performed.

On admission to the study, each cat was randomized to be administered intravesical GAGs or an intravesical saline placebo at the time of catheter placement, and again 12 and 24 h later (n = 7 in each group). The primary clinician and patient care personnel were blinded to the assigned treatment group. At each GAG infusion time point, the bladder was first confirmed to be empty and then 2.5 ml of the product was infused via the urinary catheter followed by a 1 ml flush of sterile saline. The urinary catheter was then clamped for 1 h to ensure retention of the GAGs within the bladder. During this time, the bladder was gently palpated every 20 mins to monitor for over-distension. The placebo group was infused with 3.5 ml of sterile saline following the same protocol. All cats were followed for 7 days from the time of obstruction. Cats enrolled in the placebo group were crossed over to the treatment group if they developed a repeat urethral obstruction within seven days of initial presentation. With the exception of the treatments administered for their initial obstruction, the inclusion criteria for cats with repeat obstruction were the same as upon initial obstruction.

Outcomes assessed included urinalysis at days 0, 3 and 7, aerobic bacterial urine culture at days 0 and 7, daily standardized pain scoring while hospitalized and at recheck on days 3 and 7, and incidence of repeated urethral obstruction within the 7-day follow-up period. Binomial variables were compared using a Fischer's exact test, and the remainder of the comparisons was made using an unpaired *t*-test with significance defined as $P < 0.05$.

Repeat urethral obstruction occurred within the 7-day observation period in three placebo-treated cats and none of the GAG-infused cats. Owners of two of three cats with repeat obstruction allowed cross over into the GAG treatment group, and repeated obstruction was not observed in the subsequent 7-day monitoring period. When the two placebo treated cats that crossed over

Table 1 Comparison of select clinical and laboratory parameters in cats with urethral obstruction treated with intravesical infusion of a glycosaminoglycan (GAG) product or saline placebo

	Placebo group (n = 7)	Intravesical GAG treatment group (n = 9)*	*P*
Mean serum potassium (mEq/l) (normal range 3.5–5.2 mEq/l, SI: 3.5–5.2 mmol/l)	4.11	4.19¶	0.81
Mean serum creatinine (mg/dl) (normal range 0.8–2.4 mg/dl, SI: 70.7–212.2 µmol/l)†	2.11 (SI: 186.5)	3.14 (SI: 277.6)¶	0.29
Mean urine specific gravity	1.043	1.028¶	0.02
Mean urine protein content (0–4)‡	1.57	2.86¶	0.03
Mean presenting pain score (0–4)	1.85	1.99¶	0.71
Mean percentage decrease in pain score from days 0 to 2	68%	78%¶	0.58
Number of cats that developed bacteriuria	1 (of 5)§	2 (of 9)*	1.00
Number of cats with repeat urethral obstruction	3 (of 7)	0 (of 9)*	0.06

SI = International System of Units

*This group includes two cats from the placebo group that developed repeated obstruction and were entered into the treatment group

†For one cat in each group, the serum creatinine was measured by the referring veterinarian's laboratory and has a slightly different normal range. In the placebo group one cat had a creatinine of 2.2 mg/dl (normal range 0.6–2.0 mg/dl), and in the treatment group one cat had a creatinine of 7.2 (normal range 0.3–2.1 mg/dl)

‡The semiquantitative urine protein content is based on the sulfosalicylic acid precipitation assay with possible values of 0, trace (assigned a score of 0.5) and 1–4. In the one case (placebo) in which this confirmatory assay was not available, the dipstick protein value of 2+ was used in the analysis

§These data do not include the two cats with repeated obstruction prior to the 7 day recheck culture

¶These data do not include the two cats with repeated obstruction, as the fluid diuresis and analgesia they received immediately prior to repeat obstruction may have confounded their new baseline values

were included in the GAG infusion group, the overall repeat obstruction rates were 3/7 (42.9%) placebo-treated cats and 0/9 (0%) GAG-infused cats ($P = 0.06$).

There was no clinically significant difference in the majority of clinical or laboratory parameters between the groups on entry to the study, including potassium and creatinine concentrations and pain scores (Table 1). In addition, there were no differences in pain scores between the groups over time. However, on entry to the study, the mean urine specific gravity of the treatment group was 1.028 vs 1.043 for the placebo group ($P = 0.02$) and the mean urine protein content of the treatment group was 2.9 vs 1.6 for the placebo group ($P = 0.03$). While the more concentrated urine of the placebo group could be considered a marker for increased likelihood of urethral obstruction, the same could be said for the higher urine protein content of the treatment group. Additionally, all cats were obstructed on admission, all underwent bladder lavage, and all were rehydrated and administered fluid diuresis as indicated. Thus, while these were statistically significant differences between the treatment groups, these factors seem unlikely to have played a clinically significant role in differences in treatment outcome. Following completion of this study, prazosin therapy was associated with lower urethral obstruction recurrence rates than phenoxybenzamine;[14] however, because phenoxybenzamine treatment was standardized across all cats in the current study, it was not thought to be a factor in any difference in treatment outcomes.

Similar to the previously reported study of the parenteral administration of this GAG product to healthy cats, the intravesical infusion was apparently well-tolerated with no adverse effects observed.[13] There was no difference in incidence of bacteriuria between the treatment and placebo groups on the day 7 recheck. All cats demonstrated improved pain scores, and, subjectively, urine sediment became more benign in all cats over time, as would be expected with analgesia and bladder irrigation and drainage.

The three placebo group cats with repeat obstruction (42.9%) in the study described here had a time of occurrence that varied from 2 to 5 days after the original obstruction (approximately 12–72 h after catheter removal). This repeat obstruction rate was similar to the 57% within 1–2 days (median = 1 day) in the control group of a recent study assessing lidocaine and sodium bicarbonate delivered by intravesical infusion.[5] However, in contrast to the 0% repeat obstruction rate in the GAG infused cats described here, the repeat short-term obstruction rate in the lidocaine and sodium bicarbonate infused cats in the other study was 58% within 1–14 days (median = 3 days).[5] While the studies should not be directly compared, the information gathered in the study described here suggests that intravesical infusion of this GAG product using this protocol may lessen the short-term potential for repeat obstruction in males with urethral obstruction suspected to be related to FIC. However, as has been the case in clinical trials for interstitial cystitis interventions in humans, independent large-scale studies may fail to recapitulate the findings of smaller pilot studies. Accordingly, a study with larger numbers of cats per group should be considered to further evaluate for a treatment effect associated with intravesical infusion of the GAG product.

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

References

1 Kalkstein T, Kruger J and Osborne C. **Feline idiopathic lower urinary tract disease: part I. Clinical manifestations**. *Compend Contin Educ Prac Vet* 1999; 21: 15–26.
2 Kruger J, Osborne C and Lulich J. **Changing paradigms of feline idiopathic cystitis**. *Vet Clin Small Anim* 2008; 39: 15–40.
3 Defauw P, Van de Maele I, Duchateau L, et al. **Risk factors and clinical presentation of cats with feline idiopathic cystitis**. *J Feline Med Surg* 2011; 13: 967–975.
4 Gerber B, Eichenberger S and Reusch C. **Guarded long-term prognosis in male cats with urethral obstruction**. *J Feline Med Surg* 2008; 10: 16–23.
5 Zezza L, Reusch C and Gerber B. **Intravesical application of lidocaine and sodium bicarbonate in the treatment of obstructive idiopathic lower urinary tract disease in cats**. *J Vet Intern Med* 2012; 26: 526–531.
6 Pereira D, Aguiar J, Hagiwara M, et al. **Changes in cat urinary glycosaminoglycans with age and in feline urologic syndrome**. *Biochim Biophys Acta* 2004; 1672: 1–11.
7 Nickel J, Egerdie B, Downey J, et al. **A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis**. *BJU Int* 2008; 103: 56–60.
8 Nordling J and van Ophoven A. **Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis**. *Drug Res* 2008; 58: 328–335.
9 Press S, Moldwin R, Kushner L, et al. **Decreased expression of GP-51 glycosaminoglycan in cats afflicted with feline interstitial cystitis**. *J Urol* 1995; 153: 288A.
10 Westropp J, Kass P and Buffington C. **Evaluation of the effects of stress in cats with idiopathic cystitis**. *Am J Vet Res* 2006; 67: 731–736.
11 Bassi P, Costantini E, Foley S, et al. **Glycosaminoglycan therapy for bladder diseases: emerging new treatments**. *Eur Urol Suppl* 2011; 10: 451–455.
12 Nickel J, Egerdie R, Steinhoff G, et al. **A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome**. *Urology* 2010; 76: 804–809.
13 Veir J, Webb C and Lappin M. **Systemic effects of a commercial preparation of chondroitin sulfate, hyaluronic acid and N acetyl-D-glucosamine when administered parenterally to healthy cats**. *Intern J Appl Res Vet Med* 2013; 11: 91–95.
14 Hetrick P and Davidow E. **Initial treatment factors associated with feline urethral obstruction recurrence rate: 192 cases (2004–2010)**. *J Am Vet Med Assoc* 2013; 243: 512–519.