

STANDARD ARTICLE

Evaluation of cross-linked gelatin as a bulking agent for the management of urinary sphincter mechanism incompetence in female dogs

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Abstract

Background: Bulking agent implantation is a minimally invasive intervention for the management of urethral sphincter mechanism incompetence (USMI).

Hypothesis/Objectives: To evaluate the efficacy and safety of the novel bulking agent VetFoam for the management of urinary incontinence in female dogs diagnosed with USMI.

Animals: Fifteen client-owned female dogs.

Methods: Prospective study. Female dogs diagnosed with USMI, refractory, or unamenable to medical treatment were included. VetFoam was injected under endoscopic guidance into the urethral submucosa. Continence score was evaluated before and after the procedure and monthly thereafter.

Results: Twenty-two injection procedures were performed in 15 dogs (5 dogs underwent >1 procedure). Median age of all dogs at the time of the procedure was 111 months (range, 18-180). Median continence score significantly increased after, compared with before bulking agent injection (1.5; range, 1.0-3.5 versus 4.0; range, 1.5-5 respectively; $P < .001$; effect size, 2.6). Continence was achieved in 13/15 (87%) dogs after the first procedure and in 7/7 (100%) repeated procedures. Overall, 20/22 (91%) procedures resulted in high (≥ 4) continence scores at time of first follow-up. Mean duration of continence was 11.1 months (SD, 10.7) after the first injection. One dog (7%) developed self-limiting stranguria, pollakiuria, and tenesmus while no other apparent adverse effects were recognized in the other dogs.

Conclusions and Clinical Importance: VetFoam is an apparently safe, effective novel bulking agent, which can be used as an alternative for the management of USMI.

KEYWORDS

collagen, cystoscopy, incontinence, urethral injection

Abbreviations: CS, continence score; EU, ectopic ureters; GAX, bovine glutaraldehyde cross-linked collagen; USMI, urethral sphincter mechanism incompetence.

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1 | INTRODUCTION

Urethral sphincter mechanism incompetence (USMI) is the most common cause of acquired incontinence in dogs.¹ Urinary incontinence caused by USMI is most prevalent in spayed female dogs with a reported incidence of as high as 20%.² Despite the high response rate, medical treatment has several limitations, including adverse effects (such as hypertension, restlessness, anxiety, and tachycardia),^{2,3} refractoriness to treatment,¹ and the need for life-long treatment, which requires owner compliance and on-going expenses.

Refractory cases could be treated with a variety of surgical interventions in an attempt to increase urethral sphincter resistance, urethral functional length, and to achieve intra-abdominal positioning of the bladder.⁴ Colposuspension and urethropexy are associated with approximately 55% success rate and 10 to 21% complication rate,⁵⁻⁷ with combined urethropexy and colposuspension yielding 70% success rate.⁸ The use of trans-obturator vaginal tapes has long-term success rates of 80%, but half of the dogs require additional medical treatment to restore continence.⁹⁻¹¹

Bulking agent implantation under endoscopic guidance is another potential therapeutic intervention.¹² The advantages of this procedure include high continence rate, minimal invasiveness, and low risk of complications,^{12,13} however, the effect is relatively short-lived and repeated injections are often necessary to maintain continence.^{12,14} Bovine glutaraldehyde cross-linked collagen (GAX) is the most commonly used bulking agent, with reported success rate of 68% and a mean continence duration of about 17 months.^{12,14} Continence is achieved in 83% of dogs after collagen injection with the addition of medical treatment.¹² Mild adverse effects are reported in 15% of dogs including stranguria, hematuria, and vaginitis.¹² In a more recent study with up to 10 years follow-up, mean continence duration after GAX implantation was 45.8 months.¹⁵ Despite its advantages, collagen had become unavailable in many countries; therefore, there is a need for an alternative, cost effective bulking agent.

This study describes the use of a cross-linked gelatin for the management of USMI. Gelatin is a protein produced by the denaturation process of collagen while preserving most of its cellular binding sites. These sites play an important role in signal transduction and regulation of cell activity,¹⁶⁻¹⁸ promoting its function as a tissue scaffold. Its biocompatibility, adhesiveness, plasticity, and low immunogenicity makes it an ideal biomaterial for use as a bulking agent.^{19,20} Gelatin serves as a good substrate for transglutaminase and the combination of gelatin polymer with the enzyme leads to cross-linking, thereby creating a stable scaffold, which allows migration of surrounding cells and stimulates tissue growth (ie, procollagen secretion).^{16,21,22} "VetFoam" (BioChange Ltd, Kibuts Nahsholim, Israel) is a biomaterial made of a medical grade porcine gelatin crosslinked by the enzyme into a porous injectable scaffold.

The objective of this study is to evaluate the efficacy and safety of the novel bulking agent VetFoam in the treatment of urinary incontinence due to USMI in female dogs.

2 | MATERIALS AND METHODS

2.1 | Animals

Dogs diagnosed with USMI, refractory or unamenable to medical treatment were prospectively enrolled. This research was approved by the Research Committee of the Hebrew University Veterinary Teaching Hospital (KSVM-VTH/01_2016), and dogs were included after the owners signed a consent form. Diagnosis was based on compatible history, clinical signs (eg, urinary incontinence with normal micturition), normal neurologic exam, clinicopathologic data, imaging, and response to previous treatment, if administered. Diagnosis was further supported in 2 dogs that underwent urodynamic testing. Female dogs with anatomical causes for incontinence such as ectopic ureters (EU) were excluded unless the anatomic abnormality was previously corrected.

Preprocedural testing also included CBC, serum biochemistry, urinalysis and culture, abdominal ultrasound, and cystoscopy, during which other causes for incontinence were excluded and appropriate correction of EUs was confirmed. Dogs included in the study either had a negative bacterial culture or were treated for urinary tract infection before the procedure.

2.2 | Procedure

Dogs were premedicated with an opioid (of the anesthesiologist's discretion); induction and maintenance of anesthesia were achieved using Propofol (Ripol, Corden Pharma, Caponago, Italy), midazolam (Midolam, Rafa Laboratories Ltd, Jerusalem, Israel), and isoflurane (Isoflurane, USP, Terrell, Piramal Critical Care, Inc, Bethlehem, Pennsylvania), respectively. Dogs were placed in a right lateral recumbency. The area around the vulva was clipped and aseptically prepared. Cystoscopic examination with a rigid cystoscope (Karl Storz, Tuttlingen, Germany) (2.7 or 4 mm, depending on the dog's size) was performed before injection. Immediately before use, 1.6 to 2 mL (during subsequent procedures a constant volume of 1.8 mLs was used) of sterile saline was injected into a prepackaged syringe containing 500 mg VetFoam powder, and this solution was mixed by passing the mixture between 2 syringes attached by a 3-way stopcock, 10 to 15 times. A flexible 21 G (Urotech FIN-06-380 injection needle, GmbH, Rohrdorf, Germany) or 22 G (BoNee Dedicated Needle for bladder injection, Coloplast A/S, Hølsted, Denmark) needle was used to inject 2 to 4 bulges (1-2 mLs of VetFoam in each bulge) into the submucosa of the proximal urethra, 1 to 3 cm caudal to the trigone, in a circumferential arrangement. The number of bulges was based upon the amount of urethral coaptation. Bulges were added to achieve at least 80% decrease in the urethral lumen diameter. The needle was left in place after injection for approximately 60 seconds to allow material stabilization and prevent backflow leakage of the foam to the urethra (Figure 1). The dogs were discharged on the day of the procedure, after voluntary urination ability was confirmed. All dogs were treated with amoxicillin clavulanate (or other antibiotic, if indicated by results



FIGURE 1 Cystoscopic image of the urethra after the submucosal injection of VetFoam

of urine culture and sensitivity before the procedure) for 3 to 5 days after procedure.

2.3 | Continence score

A continence score (CS) was assigned to each dog by the owners (the Appendix).^{14,23} The score was recorded before the procedure, within the first week after the procedure ("first follow up") and at 1-month intervals for the rest of the follow-up period (36 months). The procedure was considered successful, if CS was ≥ 4 at time of first follow-up and the duration of continence was defined as the time during which the CS was ≥ 4 .

2.4 | Statistical analysis

The Wilcoxon signed-rank test was used to compare CSs before and after the procedure. $P < .05$ was considered statistically significant. Effect size was calculated using the Cohen's *d* statistics. Statistical analysis was performed using a statistical software (SPSS for Windows, Chicago, Illinois).

3 | RESULTS

Fifteen client-owned spayed female dogs with USMI were enrolled. Breeds included were mixed breeds (10 dogs), Labrador retrievers (2 dogs), Dog De Bordeaux, Doberman, and a Pitbull Terrier (1 dog each). Median age of all dogs was 111 months (range, 18-180). Three of the dogs were previously diagnosed and treated for EU; their median age at the time of the injection was 36 months (range,

24-48). Median body weight of all dogs was 25.8 kg (range, 14.4-45).

The median incontinence duration before the procedure was 36 months (range, 2-108) and median CS before the first injection procedure was 1.5 (range, 1.0-3.5). Twenty-two injection procedures were performed during the study period: 5 dogs underwent >1 procedure (4 dogs had 1 additional procedure, and 1 dog had 3 additional procedures), whereas 10 dogs underwent only 1 procedure. Repeated procedures were performed because of either unsatisfactory result (CS < 4) after the first procedure (in 2 dogs CS before the procedure was 1.5 and 1.0 and after the procedure 1.5 and 2.0) or because of recurrence of incontinence (3 dogs, at 4, 6 and 13 months). Mean procedure time was 30 minutes (SD 3.2) (available for 9/22 procedures).

Overall, 20/22 (91%) procedures resulted in a CS ≥ 4 at time of first follow up. Satisfactory CS (≥ 4) was achieved in 13/15 (87%) dogs after the first procedure. In dogs requiring >1 procedure, 7/7 (100%) had CS of ≥ 4 after treatment. Median CS significantly ($P < .001$, effect size 2.6) increased to 4.0 (range, 1.5-5) within the first week after the procedure, without any addition of medical treatment. In 5 dogs, medical treatment was added to maintain continence; phenylpropanolamine with or without Diethylstilbestrol was initiated at 2 weeks (2 dogs with CS 3 and 1.5), 4 months (2 dogs with CS 2.5 and 2), and 8 months (1 dog with CS 4) after the procedure.

The mean continence duration of dogs undergoing successful procedure (CS ≥ 4) was 11.1 months (SD, 10.7), whereas 3 dogs were still continent at the time of writing the manuscript (21, 22, and 36 months). These 3 dogs had undergone only 1 injection procedure. In 2 of the 3 dogs, medical treatment was added at 4 and 8 months after the procedure because recurrence of incontinence, of which 1 dog was previously unresponsive to medical management. Dogs requiring additional medical treatment to remain continent had mean continence duration of 4.1 months (SD, 3.2) before medical treatment was added. Two of the 5 dogs receiving medical treatment remained incontinent (CS 2 and 3) despite the addition of medication and therefore bulking agent implantation was repeated.

In 5 dogs, the procedure was repeated at 3 months (2 dogs), and at 4, 6, and 13 months (1 dog each) after the first procedure because of recurrence of incontinence (3 dogs) or failure to achieve continence after the first injection (2 dogs). Median CS before the second procedure was 2.0 (range, 1.0-3.0) and it increased to 5.0 (range, 4.0-5.0) after the procedure. One dog, which was not treated medically at any time point, underwent 3 additional procedures at 3, 15, and 21 months after the first procedure. The CSs of this dog before repeated injections were 3.0, 2.0, and 2.0, respectively, and increased to 5.0 after each procedure.

One dog developed self-limiting stranguria, pollakiuria, and tenesmus for 2 days after the procedure. No clinically apparent adverse effects or clinicopathologic changes were documented in any of the other dogs. In 1 of the dogs that underwent >1 procedure, a 2 to 3 mm mucosal defect and a submucosal blind diverticulum was observed during cystoscopy in the proximal urethra, but the mucosal defect was not associated with any clinical signs. In all dogs undergoing repeated procedures, complete flattening of the submucosal

bulges was observed and no signs of inflammation or scarring of the mucosa were evident.

Four dogs died during the study period because of unrelated reasons. One dog died of pulmonary neoplasia 3 months after the second injection, 1 dog presented with hemoperitoneum and pulmonary metastasis secondary to hepatic neoplasia 3 months after the procedure, 1 dog died 6 months after the procedure because of unknown cause, and another dog died of multiple myeloma 11 months after the procedure.

4 | DISCUSSION

We have shown that the noncommercial version of VetFoam, a novel injectable tissue scaffold, is a good alternative for management of USMI.

Bulking agents have been used in the management of urinary incontinence in dogs for over 20 years.²⁴ Bovine glutaraldehyde cross-linked collagen was first evaluated as a bulking agent in 1996 and since then it was reevaluated with consistently satisfying results.^{12,14,24} In recent years, GAX became unavailable in many countries and its unavailability as well as its associated cost created the need for alternatives.

The temporary effect of bulking agents is a major drawback, especially in young dogs, for the abovementioned reasons. Preliminary studies in pigs (Chen H, Sinik K, Sherbo S, et al. Urethral tissue engineering for canine urinary incontinence. Proceedings of the 2020 ACVIM Forum On Demand, 2020; P-476) support the proposed advantage of VetFoam as a scaffold for fibroblasts growth, which over time replaces the matrix and produces a natural scaffold with a volumetric and functional effect of its own. Therefore, this agent has the potential to provide a long-lasting solution. This hypothesis will have to be tested in additional studies; however, it might be supported by the fact that some dogs in this study were still continent at 21, 22, and 36 months after the procedure. The prolonged time period of maintaining continence in some dogs outstayed the expected degradation phase of the biomaterial is encouraging and warrants further prospective evaluation of VetFoam for the maintenance of long-term continence. In addition, assessment of VetFoam's long-term remodeling effect on the urethral mucosa needs further evaluation, including histopathology and longer follow-up period.

Two dogs (13%) failed to achieve continence (CS <4) in our study. One of these dogs was the first dog recruited to the study and as continence was not achieved, a second procedure was performed 3 months later, with good outcome (CS of 5.0 for 9.5 months). It is possible, that lack of experience with the new material influenced the results of the first injections. The other dog failing to achieve continence had concurrent congenital abnormalities including bilateral EU and severe unilateral hydronephrosis, which were treated before the injection procedure (nephrectomy of the nonfunctional kidney and laser ablation of the contralateral EU). Implantation of bulking agents is considered technically more challenging in dogs after laser ablation of an EU because of scarring of the urethral mucosa and concurrent

urinary abnormalities such as short and wide urethra.¹⁴ Therefore, the outcome of this dog might have been influenced by the anatomical abnormalities and previous interventions performed. Yet, the other 2 dogs which were previously treated for EU had good outcomes (5.5 and >31 months of continence). With the exception of the 2 aforementioned dogs, all other dogs were continent at the time of first follow-up, with an increase of their median CS from 1.0 to 4.0. These results are comparable to the results of 2 studies evaluating GAX as a bulking agent,^{12,14} supporting the potential use of VetFoam as an alternative.

Three of the 15 dogs were still continent (CS \geq 4) at time of last follow-up, therefore, the mean continence duration is underestimated. The duration of continence was highly variable (0.5 to >36 months) similar to the findings of studies evaluating GAX as a bulking agent.^{12,14} Currently, there are no predicting factors to indicate the duration of continence after GAX implantation in dogs,¹⁴ and the same seem to apply to VetFoam.

Adverse effects were uncommon in this study, with only 1 dog presenting minor, self-limiting adverse effects including stranguria, pollakiuria, and tenesmus, which resolved spontaneously 48 hours after the procedure. A urethral mucosal defect was observed in 1 of the dogs during cystoscopy before a repeated injection procedure. The defect was observed in the proximal urethra, consistent with the location of the previous injection site and appeared to create a small diverticulum, which is unlikely to be associated with any clinical manifestations. We assume the lesion is a consequence of the previous VetFoam injection, possibly because of backflow leakage of the material from the injection site before full stabilization, precluding normal mucosal healing. Mucosal erosion was reported as a complication of bulking agent injections in humans,^{25,26} and may cause a wide range of clinical signs, from none to severe dysuria.²⁵ Pseudodiverticulum formation in people is believed to occur as a sequela of spontaneous pseudoabscess drainage into the urethral lumen after bulking agent implantation,^{26,27} and might have accounted for the formation of the lesion in this dog too. The dog in our study had no apparent clinical signs and the lesion did not seem erosive. The mucosal lesion was not biopsied and follow-up cystoscopy of the lesion was not performed. However, owing to the lack of clinical signs and further complications and because of its low incidence in our study (only 1 injection site), it is likely not a common scenario and was considered as a clinically insignificant complication. In the other 4 dogs undergoing repeated procedures, no mucosal defects were evident.

This study has several limitations. The relatively small number of dogs prevented a true estimation of VetFoam's effectivity in managing varying degrees of incontinence accompanied by other comorbidities (eg, EU). The follow-up period was limited (3 years) which is shorter compared with other studies,^{12,14} thus, further studies with longer follow-up period are warranted. Another limitation is the lack of uniformity of the procedure, namely mixing the VetFoam powder with saline before the injection was perfected during the study period, including different dilution ratios until a desired consistency was achieved. In addition, needle type was replaced during the study period. Reevaluation of the injection site after the procedure was not

routinely performed to avoid clinically unnecessary anesthetic procedures and complications. Finally, the degree of urethral wall coaptation after VetFoam implantation was not compared, either quantitatively nor qualitatively, between individual dogs, however, degree of coaptation was not a significant factor for successful outcome in dogs,¹⁴ and did not change the long-term outcome in people.²⁸

In conclusion, the results of this study suggest VetFoam is a safe and effective bulking agent, which can potentially be used as an alternative treatment option for dogs with USMI. However, as has been the case with previously utilized bulking agents, it has a temporary effect.

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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

This research was approved by the Research Committee of the Hebrew University Veterinary Teaching Hospital (KSVM-VTH/01_2016).

HUMAN ETHICS APPROVAL DECLARATION

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

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APPENDIX A.

Continence score:

1. Dog is never continent. Dribbles urine when awake as well as when sleeping. Constantly leaves urine on surfaces when getting up from a sitting or recumbent position.
2. Poorly continent. Dog urine soils where it has been sleeping >50% of the time. Dribbles urine or has a wet perineum when awake 25 to 75% of the time.
3. Dog urine soils where it has been sleeping >50% of the time. Dribbles urine or has a wet perineum when awake up to 25% of the time.
4. Dog urine soils where it has been sleeping up to 50% of the time, but does not dribble or have a wet perineum when awake.
5. Dog is always continent.