

Female Urology, Urodynamics, Incontinence, and Pelvic Floor Reconstructive Surgery

Can Urethral Bulking Agents Salvage Failed Slings?



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OBJECTIVE	To evaluate the efficacy of urethral bulking agents for stress urinary incontinence (SUI) in the setting of prior failed sling.
METHODS	This is a retrospective review of patients who underwent urethral bulking agent injections for a primary complaint of SUI following prior failed sling surgery. The outcomes assessed were patient reported improvement, need for further interventions for incontinence and validated questionnaires. Values for questionnaires were obtained from the patient's preprocedure visit, at the first visit following their last injection and at their most recent visit within our system.
RESULTS	Over the study period, 73 patients underwent urethral bulking agent injection following failed sling. Thirty-eight patients received Macroplastique injections and 35 had collagen injections. On average, patients underwent 2.6 injections. Seventy-one percent of patient reported at least partial symptom resolution at first postinjection follow-up. Validated questionnaire responses also improved at short-term follow-up (mean difference in American Urological Association Symptom Index-3.8, Michigan Incontinence Symptom Index-5.1, $P < .01$). Forty patients had long-term follow-up data available (mean 39.6 months postinjection). Statistically significant improvement persisted on the stress incontinence and quality of life domains of the validated questionnaires.
CONCLUSION	In our cohort of patients with persistent or recurrent SUI following urethral sling procedure, 71% experienced short-term improvement or resolution of symptoms following urethral bulking agent injections, with SUI-specific improvement persisting at an average of 35 months in patients with available data. UROLOGY 124: 78–82, 2019. © 2018 Elsevier Inc.

Stress urinary incontinence (SUI), the loss of urine with effort or exertion, is a common urinary complaint, affecting approximately one-fourth of the female population and resulting in billions of dollars in health care expenditures annually.^{1,2} Synthetic mesh midurethral slings (MUS) have become the new gold standard for surgical treatment of SUI with excellent long-term subjective and objective cure rates.^{3–6} While equally robust data do not exist for autologous fascial pubovaginal slings, their outcomes appear to be comparable.⁷ Despite their efficacy, sling procedures are not infallible: 9.4% of patients are noted to be objective failures and 8.6% go on to have repeat incontinence surgeries.^{8,9} How to manage patients with recurrent or persistent stress incontinence following sling placement remains a controversial topic among specialists in the field. While many have advocated repeat sling procedures, not all patients desire, or are candidates for, further surgical interventions.

Urethral bulking agent injections were first attempted in the 1930s, but were not popularized until the 1990s with the development of glutaraldehyde cross-linked collagen (Contigen, C.R. Bard, Inc. Murray Hill, NJ).^{10,11} Eighty-six percent of patient with previously untreated SUI had short-term subjective success following transurethral collagen injections.¹² Unfortunately, a significant decrease in symptom relief is noted beyond 1 year.^{13,14} While Contigen was discontinued by its manufacturer in 2011, polydimethylsiloxane (Macroplastique, Cogentix, Minnetonka, MN), calcium hydroxyapatite (Coaptite, Boston Scientific, Marlborough, MA) and Pyrolytic carbon-coated beads (DurasphereEXP, Coloplast, Minneapolis, MN) remain available in the US, and a recent Cochrane review found no difference in outcomes between these agents and collagen.¹⁵ Few reports exist on the use of urethral bulking agents after prior failed SUI surgeries, and those that do are predominantly very small case series. The goal of our study is to evaluate the efficacy of urethral bulking agents (Macroplastique or Contigen) for SUI in the setting of prior failed sling (fascial or mesh).

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MATERIALS AND METHODS

Following Institutional Review Board approval, a retrospective review of our electronic medical record was performed of all female patients who underwent urethral bulking agent injections between March 2008 and March 2016 at our institution. Inclusion criteria were a primary diagnosis of SUI and a history of a prior mesh or autologous pubovaginal sling procedure.

Preinjection urologic symptoms were assessed using the American Urological Association Symptom Index (AUASI).¹⁶ Incontinence was assessed with the Michigan Incontinence Symptom Index (M-ISI), a validated questionnaire which evaluates urgency incontinence, stress incontinence, severity of incontinence and patient bother, with increasing score indicating worsening symptoms as well as daily incontinence pad use.¹⁷ Postinjection outcomes were taken from the first visit following the patient's final bulking agent injection, and included AUASI, M-ISI, number of incontinence pads used daily and subjective improvement. For patients with >10 months follow-up from last injection, long-term data from validated questionnaires completed at the patient's most recent visit were included when available. Demographic information, including age and body mass index, type of prior sling (mesh or fascial), number of injections, type of injectable used (Macroplastique, collagen or both), as well as subsequent operative interventions for SUI or urge urinary incontinence were also reported. Urethral bulking agent injections were performed in clinic using a topical anesthetic. Prior to injection, all patients were counselled on treatment options for recurrent/persistent SUI, including conservative management, continence pessaries, bulking agents, and repeat sling placement (if no contraindications to anesthesia present). Collagen injections were performed transurethraly, just distal to the bladder neck at 3- and 9-o'clock using 2.5-5 cc of collagen. Macroplastique injections were performed similarly, with 2.5cc injected at either 3- and 9-o'clock or 6-o'clock depending on

provider preference using a 21Fr Wolf cystoscope with the manufacturer injection needle system. As part of our standard protocol, antibiotic prophylaxis was administered prior to injection and postvoid residual volume was assessed after administration of bulking agent. Repeat injections were performed based on symptom response, and time between repeat injections determined by surgeon preference.

Statistical analysis was performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC). Categorical variables were analyzed using the chi-square test and paired *t* test and continuous variables using the Kruskal-Wallis test. *P* values <.05 were held to be statistically significant.

RESULTS

Between 2008 and 2016, 73 patients with a primary diagnosis of SUI and a history of prior urethral sling procedure underwent urethral bulking agent injections at our institution.

Mean age of the group was 65.1 years (range 37-91, SD 12.6), and approximately half of patients had a body mass index over 30. The majority of patients had a prior synthetic mesh MUS (65.8%; Table 1). Prior to urethral bulking agent, mean AUASI was 16.6 with a quality of life score (QOL) of 4.9 and M-ISI was 22.6 with a bother score of 5.2. Patients used an average of 3.2 incontinence pads per day preinjection (Table 2).

Thirty-eight patients received Macroplastique injections and 35 had collagen injections. On average, patients underwent 2.6 injections with first postinjection follow-up visit taking place 4.2 months after last injection. Seventy-one percent of patient reported at least partial symptom resolution at first follow-up, with 18 patients reporting total resolution of stress incontinence (Table 1). Improvement vs nonimprovement was not associated with demographic factors, prior sling type, or type of bulking agent used. Improvement was associated with a higher number

Table 1. Demographics and outcomes

Demographics	Total	Improved Incontinence	No Improvement	<i>P</i>
Age, Mean (SD)	65.1 (12.6)	–	–	–
<65 y	32 (43.8)	21 (65.6)	11 (34.4)	.35
≥65 y	41 (56.2)	31 (75.6)	10 (24.4)	–
BMI (SD)	30.1 (7.1)			
BMI <30	36 (49.3)	24 (66.7)	12 (33.3)	.40
BMI ≥30	37 (50.7)	28 (75.7)	9 (24.3)	–
Type of sling, no. (%)				
Mesh MUS	48 (65.8)	34 (70.8)	14 (29.2)	.57
Fascial sling	20 (27.4)	16 (80.0)	4 (20.0)	–
Both	5 (6.9)	2 (40.0)	3 (60.0)	–
Type of bulking agent (%)				
Collagen	35 (47.9)	27 (77.1)	8 (22.9)	.28
Macroplastique	38 (52.1)	25 (65.8)	13 (34.2)	–
No. of injections (SD)	2.6 (1.6)	2.9 (1.7)	1.9 (0.89)	.01
Symptom improvement (%)				
None	21 (28.8)	–	–	–
Partial	34 (46.6)	–	–	–
Complete resolution	18 (24.7)	–	–	–
Subsequent surgery for SUI (%)				
Yes	9 (12.3)	3 (33.3)	6 (66.7)	<.01
No	64 (87.7)	49 (76.6)	15 (23.4)	–
Subsequent procedure for UUI (%)				
Yes	13 (17.8)	6 (46.2)	7 (53.8)	.02
No	60 (82.2)	46 (76.7)	14 (23.3)	–

BMI, body mass index; MUS, midurethral slings; SUI, stress urinary incontinence; UUI, urge urinary incontinence.

Table 2. Validated questionnaire results

Results, Mean (SD, N)	Preinjection	Postinjection Follow-up	Final Cohort Follow-up
Follow-up time	N/A	4.2 (4.7, 73)	39.6 (23.6, 40)
AUA symptom score	16.6 (7.7, 65)	14.1 (8.5, 65)	18.9 (8.6, 24)
AUA QOL	4.9 (1.2, 64)	4.0 (1.8, 65)	4.4 (1.5, 24)
M-ISI symptom score	22.6 (7.3, 66)	18.5 (8.9, 66)	19.7 (7.5, 29)
Stress incontinence	8.3 (3.5, 64)	6.5 (4.5, 66)	6.9 (3.4, 29)
Urge incontinence	9.1 (3.9, 64)	7.4 (4.2, 66)	8.5 (3.6, 29)
M-ISI bother	5.2 (2.2, 65)	4.2 (2.7, 66)	4.3 (2.6, 29)
Incontinence pads per day	3.2 (1.9, 65)	2.1 (1.6, 70)	2.4 (1.9, 32)

M-ISI, Michigan Incontinence Symptom Index.

of injections received (2.9 vs 1.9, $P = .01$). Validated questionnaire responses improved at short-term follow-up (mean difference in AUASI-3.8, M-ISI-5.1, $P < .01$), as did incontinence pad use (-1.1 pads per day, $P < .01$; Table 3).

Nine patients (12.3%) had a subsequent surgical intervention for SUI (7 autologous fascial slings, 1 bladder neck closure, and 1 Burch procedure). While 3 of these women had short-term improvement following urethral bulking agent injections, they were all considered long-term failures. These patients were removed from long-term validated questionnaire outcomes analyses to avoid artificial improvement in SUI outcomes following these more effective SUI interventions. Thirteen patients underwent procedural interventions for urge incontinence. These patients remained in our analysis as urethral bulking agent injections are not designed to address urge incontinence.

Forty patients had long-term follow-up data available (mean 39.5 months postinjection, SD 23.6). Only 2 of these patients reported total resolution of SUI symptoms, however, when compared to baseline validated questionnaire scores, statistically significant improvement was seen in all categories with the exception of the AUA symptom score and the urge component of the M-ISI. There was also a trend towards decreased number of incontinence pads daily which did not reach statistical significance (Table 3).

DISCUSSION

In our study, more than two-thirds of patients reported subjective symptom improvement following urethral bulking agent injections. At short term follow-up, improvement in both M-ISI and AUASI met minimally important difference for the test, and reduction in incontinence continued at long-term follow-up as measured by the M-ISI.^{16,17} Our overall improvement, along with the drop off in benefit with time, is in line with pre-existing data on primary use of urethral bulking agents for SUI. A

meta-analysis of studies regarding the use of Macroplastique injections by Ghoneim et al gave a short-term (<6 month) improvement rate of 75%, with long-term (>18 months) improvement rates of 64%.¹⁸ Similar to our results, subjective improvement was associated with higher rates of reinjection. Comparable subjective short-term success rates have been noted with collagen injections (77% at 12 months).¹² Collagen has a known tendency to resorb and therefore poorer long-term success rates, although this trend could not be demonstrated on a recent meta-analysis.^{15,19}

Persistent or recurrent SUI following urethral sling placement poses a unique management challenge. Few reports exist regarding the use of urethral bulking agents in this setting. Lee et al conducted a retrospective review of 23 women undergoing either Macroplastique or Durasphere injection following failed MUS.²⁰ They reported a cure rate of 34.8% and a 92% improvement rate at a median follow-up of 10 months. The applicability of this study is limited by its small sample size and lack of long-term outcomes. Zimmern et al evaluated 31 women with a history of urethral surgery who underwent collagen injections for SUI.²¹ At 6 weeks, 93% of patients considered themselves improved or cured. Twenty-five patients were noted to be durable responders at 2 years, while 6 patients (19.4%) went on to undergo autologous fascial pubovaginal sling placement. The relevance of this study for patients with a history of failed slings is questionable, however, as only 4 of the patients in the cohort had a prior sling.

The most robust extant data comes from Gaddi et al, who performed a retrospective cohort study comparing 165 patients who underwent repeat synthetic MUS to 67 patients who had urethral bulking agent injections

Table 3. Change in urinary symptoms from baseline

Mean Difference (SD, N)	Postinjection	<i>P</i>	Final Follow-up	<i>P</i>
AUASI	-2.8 (-7.6, 59)	<.01	-1.6 (7.5, 22)	.32
AUA QOL	-1.0 (2.0, 58)	<.01	-0.7 (1.4, 21)	.04
M-ISI symptom score	-4.0 (8.1, 60)	<.01	-3.3 (6.6, 26)	.02
Stress incontinence	-1.8 (3.8, 58)	<.01	-1.4 (3.1, 24)	.04
Urge incontinence	-1.6 (4.4, 58)	<.01	-0.6 (3.6, 24)	.40
M-ISI bother	-1.1 (2.9, 59)	<.01	-1.0 (2.6, 25)	<.01
Incontinence pads per day	-1.1 (1.8, 63)	<.01	-0.8 (2.7, 29)	.13

AUASI, American Urological Association Symptom Index.

performed for recurrent or persistent SUI following prior mesh MUS.²² Their primary outcome was subjective or objective (positive cough stress test, urodynamic SUI, or retreatment for SUI) failure. They reported that 26/67 patients (38.8%) failed bulking agent injections, while 11/98 patients (11.2%) in the MUS sling group failed. However, 12/26 patients who were noted to be bulking agent “failures” actually reported improvement in their symptoms, giving an overall cured/improved rate of 79.1% for urethral bulking agents in their cohort. On multivariate analysis, they concluded that urethral bulking agents were associated with a higher risk of failure compared with midurethral sling (odds ratio 3.49). While this is a well-designed study, it has several drawbacks when generalizing to the entire population of urethral sling failures. The study is limited to patients who had prior MUS only and outcomes were only followed up to 1 year. Furthermore, validated questionnaires were not used to accurately characterize patients’ symptoms. Finally, repeat treatment for SUI was deemed a failure, which, as urethral bulking agents often require repeat injections, may have led to overreporting of failure in the bulking agent group.

There are limitations to our study which are inherent to the collection of retrospective data, such as selection bias. Objective measures such as cough stress test or urodynamic studies are not available in the majority of patient to verify cure. However, as SUI is a quality of life complaint, subjective improvement is more clinically relevant to patients. As previously mentioned, collagen is no longer available in the US market, but as parity with other bulking agents was demonstrated in the recent Cochrane review, we felt that data from the inclusion of collagen injections remained useful. Finally, only a third of patients have matched preinjection and long-term follow-up questionnaire responses available for statistical analysis. This drop-off is somewhat mitigated by the fact that over two-thirds of patients had at least 1 remote visit following injection, and of these patients only 9 went on to have subsequent surgery for SUI, implying an acceptable degree of satisfaction at 3-year follow-up.

CONCLUSION

In our cohort of patients with persistent or recurrent SUI following urethral sling procedure, 71% experienced short-term improvement or resolution of symptoms following urethral bulking agent injections, with SUI-specific improvement persisting at an average of 39 months in patients with available long-term data. Despite the decrease in efficacy with time, urethral bulking agents performed in the office setting are a viable option for women with this challenging problem who wish to avoid secondary operative interventions and the risks of anesthesia.

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