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OUTCOME RESULTS OF TRANSURETHRAL COLLAGEN INJECTION FOR FEMALE STRESS INCONTINENCE: ASSESSMENT BY URINARY INCONTINENCE SCORE

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ABSTRACT

Purpose: We assessed the results of collagen injection for female sphincteric incontinence using strict subjective and objective criteria.

Materials and Methods: We evaluated 63 consecutive women with sphincteric incontinence who underwent a total of 131 transurethral collagen injections. Sphincteric incontinence was confirmed by urodynamics. All patients were treated with 1 to 5 transurethral collagen injections and treatment outcome was classified according to a new outcome score. Cure was defined as no urinary loss due to urge or stress incontinence documented by a 24-hour diary and pad test, and patient assessment that cure was achieved. Failure was defined as poor objective results and patient assessment that treatment failed. Cases that did not fulfill these cure and failure criteria were considered improved and further classified as a good, fair or poor response.

Results: Mean patient age plus or minus standard deviation was 67.7 ± 12.8 years. All women had a long history of severe stress urinary incontinence, 18 (29%) underwent previous anti-incontinence surgery, and 41% had combined stress and urge incontinence. Preoperatively diary and pad tests revealed a mean of 7.5 ± 4.6 incontinence episodes and 152 ± 172 gm. of urine lost per 24 hours. Overall 1 to 5 injections were given in 26, 17, 13, 3 and 4 patients, respectively. Mean interval between injections was 4.4 ± 5.7 months, mean followup was 12 ± 9.6 months, and mean interval between the final injection and outcome assessment was 6.4 ± 4.9 months. There was a statistically significant decrease in the total number of incontinence episodes per 24-hour voiding diary after each injection session. Although there was a clear trend toward decreased urinary loss per 24-hour pad test, statistical significance was not established. Using the strict criteria of our outcome score overall 13% of procedures were classified as cure, 10%, 17% and 42% as good, fair and poor, respectively, and 18% as failure.

Conclusions: As defined by strict subjective and objective criteria, we noted a low short-term cure rate after collagen injection in women with severe sphincteric incontinence. It remains to be determined how patients with less severe incontinence would fare using our outcome assessment instruments.

KEY WORDS: urethra; urinary incontinence, stress; collagen; outcome assessment (health care)

Injection therapy for female sphincteric incontinence has been done for decades. Although the American Urological Association Female Stress Urinary Incontinence Clinical Guidelines Panel concluded that retropubic suspension and sling surgery are the most efficacious therapy for stress incontinence,[1] injection is still occasionally indicated or preferred. The main indications for injection are the high risk of major surgery, previous surgical failure and patient preference.

Injected bulking agents cause passive occlusion of the urethra, and are presumed to enhance mucosal sealing and coaptation. Injected collagen is also known to create a fibrous network that develops the appearance of normal host tissue with time.[2] Although early studies of collagen injection showed a short-term to mid-term cure or improvement rate of 48% to 95%, long-term outcome has been much less favorable.[2,3]

Outcome results of anti-incontinence procedures are usually reported as cure, improvement or failure. However, to date there are no standard definitions of these terms and no standard, widely accepted clinical tools for assessing outcome after anti-incontinence therapy. Recently we presented a new outcome score incorporating the popular clinical tools of a 24-hour diary, 24-hour pad test and patient questionnaire (see Appendix).[4] The new score was constructed in a simple format that is easy to remember. It is divided into the categories of cure, good response, fair response, poor response and failure. We previously used this score to evaluate the long-term outcome of pubovaginal sling surgery and it seemed to reflect the surgical results more accurately. In the

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current study we used this new outcome score to assess the results of collagen injection for female sphincteric incontinence.

METHODS

We evaluated 63 consecutive women with a mean age of 67. ± 12.8 years who underwent a total of 131 transurethral collagen injections using a Contigen§ collagen implant for sphincteric incontinence. In all cases a long history of stress urinary incontinence was the main complaint and previous anti-incontinence surgery had been done in 18 (29%). About half of the patients had combined stress and urge incontinence. The latter component had been managed by medication, behavioral modification, pelvic floor exercise and so forth. Sphincteric incontinence was confirmed by urodynamics in all patients. Of 8 patients with concomitant urethral hypermobility 5 also had grade 3 urogenital prolapse. Table 1 lists patient characteristics.

All patients underwent collagen skin testing 1 month before treatment. Contraindications to injection therapy included hypersensitivity to collagen and urinary tract infection. Additional injections were performed as needed during followup.

All patients underwent a meticulous baseline evaluation, including a complete history and physical examination, standard urinary questionnaire, 24-hour voiding diary, 24-hour pad test, urine culture, noninvasive uroflowmetry, post-void residual urine volume measurement, video urodynamics and urethrocystoscopy. Methods, definitions and units conformed to the standards recommended by the International Continence Society except as specifically noted.[5] Multichannel video urodynamics were performed according to the recommendations of the International Continence Society except for cystometry. Contrary to these recommendations patients were not instructed to inhibit voiding during the filling phase, but rather to report sensations to the examiner. Cystometrography was performed using radiographic contrast material and a 7Fr double lumen catheter via constant infusion at a medium fill rate with rectal pressure monitoring. Sphincteric incontinence was defined as visible urinary leakage during increased abdominal pressure with absent detrusor overactivity.

The collagen implant syringe contained 2.5 ml. of sterile purified bovine dermal glutaraldehyde cross-linked collagen dispersed in phosphate buffered physiological saline. All injections were done transurethrally using an 18Fr hysteroscope. The needle was advanced into the urethral wall just below the bladder neck and the implant was injected submucosally until urethral coaptation was observed at the needle penetration site. Injections were repeated at multiple sites as needed until closure of the proximal urethral lumen was achieved. Postoperatively evaluation was scheduled at 1, 3, 6 and 12 months, and annually thereafter. At each visit a history, 24-hour voiding diary and 24-hour pad test were obtained, uroflowmetry and focused physical examination with a full bladder were done, and post-void residual urine volume was measured.

§ C. R. Bard, Inc., Covington, Georgia.

TABLE 1. *Patient characteristics*

No. pts.	63
Mean age ± SD	67.7 ± 12.8
Mean parity ± SD	2.1 ± 1.4
No. menopause (%)	59 (94)
No. estrogen replacement (%)	25 (42)
No. previous hysterectomy (%)	29 (46)
No. previous anti-incontinence surgery (%)	18 (29)
No. genital prolapse (%)	5 (8)
No. 24-hr. incontinence episode diary ± SD	7.5 ± 4.6
Mean 24-hr. pad test ± SD (gm.)	152 ± 172
Mean peak flow rate ± SD (ml./sec.)	22.6 ± 14.0
Mean Valsalva leak point pressure (cm. H_2O)	73 ± 33
No. concomitant detrusor instability (%)	26 (41)

Treatment outcome was classified according to our new outcome score (see Appendix). Briefly, the outcome score has a possible total of 6 points. Cure (a total score of 0) was defined by certain strict criteria, including a 24-hour voiding diary showing no urge or stress urinary incontinence episodes, a 24-hour pad test demonstrating a weight gain of less than 8 gm. and a questionnaire indicating patient assessment that cure was achieved. Failure (a total score of 6) was defined as poor objective results and patient assessment of treatment as a failure. Cases that did not fulfill these cure and failure criteria were considered improved and further classified as a good, fair or poor response with a total score of 1 or 2, 3 or 4, or 5, respectively. Results were analyzed statistically using Student's t and the chi-square tests with values considered significant at $p < 0.05$.[6] Data are presented as the mean plus or minus standard deviation or a percent according to the variables.

RESULTS

We evaluated 63 consecutive patients. Mean followup was 12 ± 9.6 months (range 1 to 32). One to 5 injections were administered in 26, 17, 13, 3 and 4 cases, respectively. Thus, a total of 131 injection procedures were available for outcome analysis. An average volume of 3.1 ± 1.4 ml. of collagen was injected per patient. The mean interval between injections, and between the final injection and outcome assessment was 4.4 ± 5.7 and 6.4 ± 4.9 months, respectively. We noted no statistically significant correlation of patient characteristics or baseline findings with the total number of injections.

Table 2 shows treatment characteristics and results. We analyzed results separately for each of the 5 injection sessions. Thus, 63, 37, 20, 7 and 4 patients were available for outcome analysis after injections 1 to 5, respectively. There was a statistically significant decrease in the total number of incontinence episodes per 24-hour voiding diary after each of the 5 injection sessions. In addition, there was a clear trend toward decreased urinary loss per 24-hour pad test, although statistical significance was not established.

We also analyzed outcome results of persistent stress or urge incontinence separately for each of the 5 injection sessions (table 2). Results were documented by the questionnaire, 24-hour diary and pad studies, and stress test with a comfortably full bladder. Determination of the prevalence of persistent stress or urge incontinence was based on the definitive urodynamic diagnosis of sphincteric incontinence or detrusor instability at the baseline evaluation. Persistent stress incontinence was noted in 50% to 75% of patients, while in most persistent urge incontinence was associated with preexisting mixed incontinence. New onset urge incontinence developed in only 1 case after injection 2. In 3 cases transient urinary retention required intermittent self-catheterization for up to 3 days. No other complications or side effects were associated with injection therapy.

Table 3 lists the outcome results of 131 injection procedures, as classified by our new outcome score. Overall 13%, 10%, 17%, 42% and 18% of procedures resulted in short-term to mid-term cure, a good, fair or poor response, and failure, respectively. Pubovaginal sling surgery was eventually performed in 7 patients (11% of the study population). These women were significantly younger with a mean age of 57 ± 18.8 versus 69 ± 11.5 years ($p = 0.01$) and they initially underwent collagen injection electively. Preoperatively a mean of 2.0 ± 0.9 injections per patient were done (range 1 to 3) and the mean interval from injection 1 to surgery was 11.1 ± 15.4 months (range 1 to 48). Postoperatively 6 of 7 women were considered cured and 1 had persistent urge incontinence.

TABLE 2. *Treatment characteristics and results*

	Injection				
	1	2	3	4	5
No. pts.	63	37	20	7	4
Mean mos. between injections ± SD		3.6 ± 5.7	5.2 ± 6.6	4.4 ± 2.3	4 ± 2.5
Mean injected vol. ± SD (ml.)	3.2 ± 1.3	3.2 ± 1.6	3.1 ± 1.3	2.9 ± 0.9	2.2 ± 0.9
Mean 24-hr. incontinence episodes ± SD:					
Baseline	7.5 ± 4.6	8.8 ± 5	10.5 ± 5.2	14.8 ± 4.8	15.7 ± 5.2
After treatment	3.7 ± 4.3*	4.8 ± 3.7*	6.1 ± 3.6*	6.4 ± 3.9*	10 ± 1
Mean 24-hr. urinary loss ± SD (gm.):					
Baseline	152 ± 172	167 ± 165	227 ± 174	188 ± 175	265 ± 189
After treatment	87 ± 153	101 ± 133	123 ± 126	75 ± 76	118 ± 161
No. incontinence (%):					
Persistent stress	40 (63)	20 (54)	10 (50)	5 (71)	3 (75)
Persistent urge	24 (92)	13 (72)	10 (100)	3 (60)	1 (33)
New onset urge		1 (6)			

* Significantly lower than baseline ($p < 0.05$).

TABLE 3. *Outcomes classified by urinary incontinence outcome score*

	Injection				
	1	2	3	4	5
No. pts.	63	37	20	7	4
% Cure	16	8	12	0	25
% Good response	11	16	0	20	0
% Fair response	18	12	19	20	25
% Poor response	33	52	50	60	25
% Failure	22	12	19	0	25

DISCUSSION

Our patients did not fare as well as others in the peer reviewed literature. We believe there are 2 reasons for these results. 1) Our patients had severe incontinence with a mean of 7.5 ± 4.6 incontinence episodes and 152 ± 172 gm. of urine lost per 24 hours, and 41% had concomitant urge incontinence. 2) We used very stringent objective and subjective outcome criteria, including no stress or urge incontinence per 24-hour diary, a negative 24-hour pad test and subjective cure by patient questionnaire. In our series only 13% of injection procedures resulted in cure, whereas 10% were classified as good, 17% fair and 42% poor response, and 18% as failure.

The reported success rate of collagen injection varies considerably according to patient selection, duration of followup and investigator definition of cure, improvement and failure. Previously others assessed collagen outcome by direct patient questioning on symptom severity and pad requirements.[7–10] The outcome was reportedly cure in 23% to 74% of cases, improvement in 20% to 52% and failure in 6% to 33%. Our results primarily differ from those in regard to the cure and improvement rates. We believe that most cases reported as cured in previous studies would be reclassified as improved by our strict criteria. Moreover, cure should imply the reestablishment of normal voiding patterns but in most studies cure denotes that the patient no longer had stress incontinence. However, persistent or new onset urge incontinence, urinary urgency or difficult voiding may have been present. Fulford et al noted that only 80% of their patients were satisfied with the results despite symptomatic control of stress urinary incontinence in 97% after sling surgery, mainly because the urge syndrome persisted.[11] Therefore, we believe that urge and stress incontinence should be considered when evaluating the outcome of any anti-incontinence procedure. Of course, for those with persistent incontinence it is important to determine whether the condition is sphincteric or vesical in origin. Furthermore, gross classification into cure, improvement and failure may fail to reflect accurately true clinical status. Strict criteria for cure and failure as well as the detailed differentiation of various degrees of improvement (good, fair and poor response) indicated by our new response score may provide a more meaningful tool for assessing outcome.

The relatively low cure rate in our series concurs with the recent series of 99 patients of Tschopp et al, who performed time to failure analysis.[12] In their study failure was considered as patient dissatisfaction with results or surgeon assessment of the degree of incontinence as worse or no better than preoperative status based on postoperative symptoms and/or pad use. The median duration of success was 4.7 months. Statistical analysis using a survival curve indicated only a 13% probability of success 18 months after injection. We further analyzed our results according to the total number of collagen injections and observed a similar rate of cure and various degrees of improvement or failure after 1 to 5 injections. This finding is also in accordance with the results of Tschopp[12] and Khullar[13] et al, who reported similar success rates of injections 1 and 2.

Pubovaginal sling surgery was eventually done in 7 of our patients (11% overall), of whom 6 were cured and 1 had persistent urge incontinence postoperatively. Pubovaginal sling surgery is the most effective and durable operation for urinary incontinence due to urethral hypermobility or intrinsic sphincter deficiency.[14] In a previous study we assessed long-term outcome in 94 consecutive women with sphincteric incontinence who underwent this procedure.[4] Using the strict criteria of our new response score 44.7% of cases were classified as cured and 40.5% as either good (26.6%) or fair (13.9%) response.

Contrary to these long-term favorable results, collagen injection is not considered to be a durable procedure and most patients need additional treatment sessions to achieve and maintain improvement or cure. Recently Gorton et al reported 5-year followup results of periurethral collagen injection.[3] Of 14 patients (26% of the study population) who considered the condition subjectively improved 7 had daily incontinence and only 1 was completely dry. Thus, not only are the short-term results of collagen injection controversial, but long-term results are definitely disappointing. In our opinion periurethral injection is rarely curative. Therefore, we recommend periurethral injection in patients at high surgical risk or those who understand and accept the cyclical nature of the treatment process. We also perform periurethral injection as a substitute for surgery in patients with mixed incontinence or an uncertain diagnosis. When periurethral injection is temporarily effective, it is likely that a definitive surgical procedure would also be effective.

CONCLUSIONS

In our series only 13% of injection procedures resulted in cure, whereas 10% were classified as good, 17% fair and 42% poor, and 18% as failure. We believe that these relative low cure and good response rates are due to severe incontinence in our patients, and the stringent objective and subjective

criteria used to define outcome. It remains to be determined how patients with less severe incontinence would fare using our outcome assessment instruments.

APPENDIX: SIMPLIFIED URINARY INCONTINENCE SCORE FOR EVALUATING TREATMENT OUTCOME[4]

Postoperative 24-hour voiding diary:
- 0—No urge or stress urinary incontinence episodes
- 1—One or 2 incontinence episodes
- 2—Three or more incontinence episodes

Postoperative 24-hour pad test:
- 0—Total weight gain of the pads 8 gm. or less
- 1—Total weight gain of the pads 9 to 20 gm.
- 2—Total weight gain of the pads greater than 20 gm.

Patient questionnaire:
- 0—The patient considers herself cured
- 1—The patient considers herself improved
- 2—The patient considers that treatment failed

Total score and outcome:
- 0—Cure
- 1–2—Good response
- 3–4—Fair response
- 5—Poor response
- 6—Failure

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