

Periurethral Collagen Injection for Stress Incontinence With and Without Urethral Hypermobility

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Objective: To compare the use of periurethral collagen injection in the treatment of female stress urinary incontinence due to intrinsic sphincter deficiency in women with and without urethral hypermobility.

Methods: A retrospective review was performed of 60 periurethral collagen injections performed on 40 consecutive women from January 1996 to December 1997. A review of the office chart and operative notes was performed to obtain demographic, urodynamic, and procedural data. Outcome data were obtained by personal or telephone interview, using patients' subjective assessments including an analog satisfaction scale.

Results: Nine of 40 patients (23%) had urethral hypermobility. Compared with patients without hypermobility, patients with hypermobility required a similar number of procedures (a mean of 1.9 compared with 1.4, $P = .13$) and required similar amounts of collagen on the first injection (5.6 mL compared with 5.3 mL, $P = .69$). Preoperative urodynamic parameters were similar in both groups. Rates of subjective dryness were equivalent in patients with and without hypermobility at 1 month (76% and 46%, $P = .24$) and at 6 months (71% and 32%, $P = .09$) following initial injection. A post hoc power analysis was performed to evaluate the primary study measures of continence at 1 and 6 months, and number of collagen injections. This revealed that a sample size of 40 patients would be sufficient to detect a 2.5-fold difference in number of injections and a 3-fold difference in subjective dryness.

Conclusion: Coexisting urethral hypermobility should not preclude the use of collagen injections in women with stress urinary incontinence. (*Obstet Gynecol* 2000;95:327-31. © 2000 by The American College of Obstetricians and Gynecologists.)

Urethral bulking for female stress urinary incontinence has been in use since the 1970s, when Berg first described the use of polytetrafluoroethylene for incontinence.¹ Polytetrafluoroethylene was succeeded by other materials with less reactivity, including autologous fat.² Glutaraldehyde cross-linked bovine collagen is currently the only bulk-enhancing agent approved by the Food and Drug Administration after studies confirmed its safety and efficacy.³ It functions by preventing the bladder neck from opening during stress, leading to improved urinary continence.⁴

Current recommendations as well as Medicare reimbursement guidelines have limited collagen use in women to those patients with stress incontinence caused by intrinsic sphincter deficiency without urethral hypermobility.⁵⁻⁷ There is little data to support the distinction between women with and without hypermobility. Further, several studies have anecdotally noted good results of collagen injection in patients with some degree of urethral hypermobility.^{8,9} Given the efficacy, ease, and safety^{10,11} of periurethral collagen injection, recommendations that limit its use to patients without hypermobility may deny this effective option to women who cannot or do not wish to undergo a more aggressive surgical approach. The goal of this study was to review our experience with periurethral collagen injections in women with and without urethral hypermobility.

Materials and Methods

Forty consecutive patients who underwent periurethral collagen injections between January 1, 1996 and December 31, 1997 were identified. A detailed chart review was performed and included review of operative notes and follow-up data. Further evaluation when appropriate was by telephone follow-up with questions about

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current amount of urine loss, overall satisfaction with the procedure, and duration of success of the injection.

All patients underwent a detailed initial evaluation at the Division of Urogynecology at Good Samaritan Hospital, a tertiary referral center in Cincinnati, Ohio. The initial evaluation included a comprehensive medical history and physical examination; urinary evaluation by dipstick, microscopic and culture analysis as indicated; and single-channel water-fill cystometry.

Urethral excursion at rest and at maximumValsalva was recorded for each patient using a cotton swab placed at the urethral-vesical junction, as described by Karram and Bhatia.¹² A change of over 30 degrees from rest to maximumValsalva was used to define urethral hypermobility.¹³

Patients were then offered appropriate conservative therapies including pelvic floor muscle exercises, timed voids, physical therapy, pessary fitting, and medications. Patients were specifically identified for multichannel urodynamics if their history or physical examination suggested intrinsic sphincter deficiency, they were contemplating surgical correction, or they had health problems that would make them poor surgical candidates.

Multichannel urodynamics were performed with the patient in the sitting position using the UD-2000 system (Medical Measurement Systems USA, Inc., Wheaton, IL) with a filling rate of 80–100 mL/minute. Data collection included volumes at first urge, strong urge, and capacity; evaluation of the detrusor during filling; andValsalva leak point pressures at 150 mL and capacity. Urethral pressure profiles were performed using a mechanical puller at a rate of 1 cm/minute. Uroflowmetry and pressure-flow studies were also performed.

Patients were diagnosed with intrinsic sphincter deficiency and selected for therapy with collagen based on objective and historical findings. Objective criteria included a maximum urethral closure pressure less than or equal to 20 cm H₂O and/or aValsalva leak point pressure less than 60 cm H₂O. Additional subjective evidence included the presence of an immobile urethra, severe stress incontinence, a history of pelvic irradiation, or a history of previous unsuccessful anti-incontinence procedures. Further, the patients' ability to medically tolerate an aggressive repair procedure was taken into account when selecting collagen therapy. Urethral hypermobility was not an exclusion criterion for collagen therapy. All patients had a negative collagen skin test placed at least 30 days prior to the procedure and no evidence of cystitis at the time of injection.

Following multichannel urodynamics, informed consent was obtained from all patients. Local anesthesia included topically applied 2% lidocaine jelly (Xylocaine

jelly; Astra Pharmaceuticals, Westborough, MA) and periurethral injections of 1% lidocaine solution (Xylocaine solution; Astra Pharmaceuticals). Bulking of the proximal urethra was performed under cystoscopic guidance utilizing glutaraldehyde cross-linked collagen (Contigen; C.R. Bard Inc., Covington, GA) placed periurethrally with a 22-gauge spinal needle. Appropriate coaptation of the proximal urethra was used as a marker for adequate placement of the collagen.¹⁴ Patients' ability to void following the procedure was documented by catheterization for postvoid residual volume. Those patients with a postvoid residual of more than 25% of their functional bladder capacity postprocedure were instructed in intermittent self-catheterization. They were to perform intermittent self-catheterization on a regular basis until their postvoid residuals were persistently below 25% of their functional bladder capacity. All patients were given a 1-day course of antibiotic prophylaxis. In those patients who were unable to adequately empty their bladder postprocedure, the prophylaxis was continued for the duration of self-catheterization.

Data collection was performed initially by reviewing the subject's outpatient record. In addition to demographic, examination, and urodynamic data, operative data was collected including the number of injections performed on each patient and the amount of collagen used at each injection. Further telephone follow-up was utilized as necessary to obtain subjective outcomes data. An intent-to-treat methodology was utilized, and patient's subjective dryness at 1 and 6 months following the initiation of collagen therapy was evaluated, even if the patient had had other intervening collagen injections. No patient had other intervening surgical procedures that might have affected their continence status. In addition to the subject's subjective dryness following the procedure, a measure of the overall satisfaction with the use of collagen was obtained. This was quantified on a 1–3 scale with "1" being dissatisfied and "3" being very satisfied.

Data analysis was performed using the EpiInfo version 6 database and biostatistical software package (Centers for Disease Control and Prevention, Atlanta, GA). Qualitative data were analyzed using the chi-square, Mantel-Haenszel chi-square, and Fisher exact test as appropriate. All normally distributed quantitative data were analyzed utilizing Bartlett's test for homogeneity of variance. The variances of the samples differed in all cases, so the Kruskal-Wallis test was utilized for analysis of continuous data.

A post hoc power analysis was performed to evaluate the primary measures of the study—the number of collagen injections required to achieve continence, and the percentage of patients dry at 1 and 6 months. We

Table 1. Demographic and Urodynamic Parameters in Patients With and Without Urethral Hypermobility

| | Urethral hypermobility | | P |
|------------------------------------|------------------------|------------|------|
| | Present | Absent | |
| Mean age (y) | 60 ± 12.3 | 65 ± 10.1 | .29 |
| Estrogen exposure* | 63% | 67% | >.99 |
| Mean weight (lb) | 160 ± 52.4 | 170 ± 47.0 | .35 |
| VLPP@150 mL (cm H ₂ O) | 54 ± 13.5 | 56 ± 25.7 | >.99 |
| VLPP average (cm H ₂ O) | 70 ± 20.6 | 59 ± 27.3 | .29 |
| MUCP (cm H ₂ O) | 47 ± 21.8 | 38 ± 20.8 | .19 |

VLPP = valsalva leak point pressure; VLPP average = average of VLPP measurements at 150 mL and capacity; MUCP = maximal urethral closure pressure.

Data presented as the mean ± standard error or %.

*Includes cycling premenopausal patients and postmenopausal patients on oral estrogen replacement therapy.

assumed a success rate of 75% in patients without hypermobility based on an approximation of reported rates in the literature.^{3,11} This revealed that an overall sample size of 40 patients would have been sufficient to detect a 2.5-fold difference in number of collagen injections, and a 3-fold difference in the percentage of patients dry at 1 and 6 months, given a beta error of 20% and an alpha error of 5%.

Results

A total of 60 collagen injections were performed on 40 women from January 1996 to December 1997. Of these patients, nine (23%) had urethral hypermobility. Patients with urethral hypermobility had a change in cotton swab deflection of 43 degrees with maximum valsalva, compared with only 6 degrees of change in patients without hypermobility ($P < .001$). Patients with and without hypermobility were similar with regard to age, estrogen status, and weight. One patient without hypermobility was black, while all other patients were white. Further mean maximum urethral closure pressures or valsalva leak point pressures did not differ between the two groups (Table 1).

One patient with hypermobility and three patients without had previously undergone pelvic irradiation (11% compared with 10%, $P = 1.00$). The average number of previous bladder repairs in each group was also similar (1.5 compared with 1.0, $P = .11$).

Patient follow-up extended from 1 to 21 months. Patients with hypermobility had a mean follow-up of 8.4 months, compared with a mean follow-up of 8.2 months in those without hypermobility ($P = .94$). One patient in the group without hypermobility was unavailable for follow-up. This patient had had her initial collagen procedure discontinued almost immediately,

Table 2. Outcomes of Periurethral Collagen Injection in Patients With and Without Urethral Hypermobility

| Outcomes | Urethral hypermobility | | P |
|--|------------------------|-----------|-----|
| | Present | Absent | |
| 1 mo | | | |
| Dry (%) | 76 | 46 | .24 |
| Median satisfaction (range) | 3.0 (1-3) | 2.0 (1-3) | .08 |
| 6 mo | | | |
| Dry (%) | 71 | 32 | .09 |
| Median satisfaction (range) | 2.0 (1-3) | 2.0 (1-3) | .27 |
| Amount of collagen used on 1st injection (mL; mean ± SE) | 5.6 ± 2.2 | 5.3 ± 2.8 | .69 |
| Number of collagen injections | | | |
| Mean | 1.9 | 1.4 | .13 |
| Median (range) | 2 (1-4) | 1 (1-4) | |

Dry = percentage of patients subjectively free of incontinence from any cause at 1 and 6 months postinjection; SE = standard error.

Median overall satisfaction is based on a scale of 1-3, for which 1 = not satisfied, and 3 = completely satisfied.

due to discomfort with the injections. This subject was analyzed based on the intent-to-treat and was considered a failure at 1 and 6 months. All other patients were followed through 1 month postprocedure, while 25 (64%) were followed for 6 months or longer. Similar percentages of patients in both study groups had follow-up for 6 months or more following the initial procedure, with six of nine patients with hypermobility (67%) and 19 of 30 patients without hypermobility (63%) followed up for 6 months or more.

Rates of subjective dryness were equivalent in patients with and without hypermobility at both 1 and 6 months. There was no difference in number of collagen injections required or amount of collagen used on the first attempt in either group. Median overall satisfaction with the procedure at 1 month postinjection was similar in patients with or without hypermobility (Table 2). Based on stratified analysis of patients with and without hypermobility, neither current estrogen status nor prior anti-incontinence procedures were found to affect the rates of dryness at 1 and 6 months.

There were few complications in either group. One patient in the hypermobility group developed unexplained low-grade fever after each of her collagen injections. While initially thought to be due to urinary tract infection, subsequent cultures were negative. These fevers may have represented a minor reaction to the collagen injection. No long-term sequelae were noted. In the group with hypermobility, one patient died of a brain tumor during follow-up, and one patient was unable to tolerate the procedure due to pain during the injection. A third patient underwent a total of four collagen injections at our center following an unsuccessful

ful suburethral sling. She subsequently transferred her care to another center where she underwent several more collagen injections followed by the development of a urethral-vaginal fistula. Approximately 50% of patients in both groups developed some degree of de novo bladder overactivity following the collagen injection ($P = 1.00$). Thirty-eight percent of patients with hypermobility complained of at least one urinary tract infection following the initial collagen injection, compared with 24% of those without ($P = .65$).

Discussion

Current recommendations and Medicare reimbursements limit the use of collagen injections to women with intrinsic sphincter deficiency without hypermobility, based in part on work done comparing the suburethral sling procedure to a single collagen injection. Kreder and Austin¹⁵ reported cure rates of 81% with the suburethral sling in women with intrinsic sphincter deficiency and hypermobility, compared with 25% cure rates following a single collagen injection. Based on these data, the authors concluded that patients with intrinsic sphincter deficiency and hypermobility should not undergo periurethral collagen injection. However, this recommendation fails to take two issues into account. First, previous research has found that patients require an average of two injections to achieve continence.³ Rather than compare a single collagen injection with the suburethral sling, we chose to analyze the intent-to-treat with collagen and assessed whether urethral hypermobility had a deleterious effect on outcomes. Second, there is a significant difference in complexity and morbidity between the two procedures. In Kreder and Austin's work, for example, the suburethral sling group had a 7% prolonged retention rate, a patient who developed a thigh hematoma after the fascial harvest, and a patient who died in the perioperative period from a massive myocardial infarction. No complications were reported in the collagen group. We are currently performing collagen injections under local anesthesia in an office setting, and have noted a significant complication in only one patient.

Several recent studies have anecdotally noted good results of collagen injections in patients with some degree of urethral hypermobility.^{8,9} Our findings appear to confirm these reports.

Strict inclusion criteria for intrinsic sphincter deficiency were not applied to the dataset in our series. The diagnosis of intrinsic sphincter deficiency was based on the overall clinical presentation, as recommended by the recent Agency for Health Care Policy and Research guidelines.⁵ There is no exclusive single measure or set

of measures that defines intrinsic sphincter deficiency. Since clinicians tend to use this nonrestrictive approach in assessing the need for collagen therapy, we chose to analyze all data rather than limit the available information by setting stringent inclusion criteria. Additionally, our study showed little correlation between valsalva leak point pressure and maximum urethral closure pressure. This confirms the findings of other authors that suggest that the two studies tend to correlate poorly.¹⁶ Because of this lack of correlation, there was heterogeneity in the urodynamic values of individual patients that would have severely limited any single set of strict inclusion criteria. Since overall measures of urethral function did not vary significantly between groups, there should not be a selection bias with regard to disease severity, regardless of each patient's individual diagnostic criteria for intrinsic sphincter deficiency.

Limitations of this study include the relatively short follow-up of patients and the small sample size. Longer-term studies are needed to assess the duration of effectiveness in women who have undergone collagen injection. Additionally, larger studies could detect smaller differences in outcomes between the groups, although the clinical significance of these differences is unknown. The sample size in this study is consistent with other published reports.^{10,15}

Further, the study may be limited by the subjective nature of the outcome data, though the subjective component of pelvic floor dysfunction is a major part of the initial indication for, and overall satisfaction with, surgical therapy.

The distribution of patients without and with urethral hypermobility was 3:1. As this was a cohort study, evaluating all patients undergoing collagen treatment in a 2-year period, we did not attempt to balance numbers of cases and controls. Adjustment of the power analysis to account for this ratio found that the study still had adequate power to detect large clinical differences.

Expansion of the indications for collagen urethral bulking is necessary because of the low complication rate of this procedure, the ability to perform injections in an office setting, and the ability to expand the treatment options of women who do not desire or are unable to tolerate more aggressive surgical repairs. Collagen injection is an appropriate method of therapy for women with genuine stress incontinence and urethral hypermobility, with success rates similar to those seen in patients without hypermobility. Collagen may be used as a primary method of treatment in women with hypermobility who cannot tolerate or do not desire more aggressive surgical correction.

References

1. Berg S. Polytef augmentation urethroplasty. *Arch Surg* 1973;379-81.
2. Haab F, Zimmern PE, Leach G. Urinary stress incontinence due to intrinsic sphincter deficiency: Experience with fat and collagen periurethral injections. *J Urol* 1997;157:1283-6.
3. Smith DN, Appell RA, Winters JC, Rackley RR. Collagen injection therapy for female intrinsic sphincter deficiency. *J Urol* 1997;157:1275-8.
4. Monga AK, Stanton SL. Urodynamics: Prediction, outcome, and analysis of mechanism for cure of stress incontinence by periurethral collagen. *Br J Obstet Gynaecol* 1997;104:158-62.
5. Agency for Health Care Policy and Research. Urinary incontinence in adults: Acute and chronic management. Clinical practice guideline no. 2. Rockville, Maryland: U.S. Department of Health and Human Services 1996:57-8.
6. McGuire EJ, Appell RA. Transurethral collagen injection for urinary incontinence. *Urology* 1994;43:413-5.
7. Health Care Financing Administration. Medicare coverage issues manual. Baltimore, Maryland: U.S. Department of Health and Human Services. 1996:65-9.
8. O'Connell HE, McGuire EJ, Aboseif S, Usui A. Transurethral collagen therapy in women. *J Urol* 1995;154:1463-5.
9. Monga AK, Robinson D, Stanton SL. Periurethral collagen injections for genuine stress incontinence: A 2-year follow-up. *Br J Urol* 1995;76:156-60.
10. Khullar V, Cardozo LD, Abbott D, Anders K. GAX collagen in the treatment of urinary incontinence in elderly women: A two year follow-up. *Br J Obstet Gynaecol* 1997;104:96-9.
11. Stanton SL, Monga AK. Incontinence in elderly women: Is periurethral collagen an advance? *Br J Obstet Gynaecol* 1997;104:154-7.
12. Karram MM, Bhatia NN. The Q-tip test: Standardization of the technique and its interpretation in women with urinary incontinence. *Obstet Gynecol* 1988;71:807-11.
13. Bergman A, Koonings PP, Ballard CA. Negative Q-tip test as a risk factor for failed incontinence surgery in women. *J Reprod Med* 1989;34:193-7.
14. Kim YH, Kattan MW, Boone TB. Correlation of urodynamic results and urethral coaptation with success after transurethral collagen injection. *Urology* 1997;50:941-8.
15. Kreder KJ, Austin JC. Treatment of stress urinary incontinence in women with urethral hypermobility and intrinsic sphincter deficiency. *J Urol* 1996;156:1995-8.
16. Bump RC, Coates KW, Cundiff GW, Harris RL, Weidner AC. Diagnosing intrinsic sphincter deficiency: Comparing urethral closure pressure, urethral axis, and valsalva leak point pressures. *Am J Obstet Gynecol* 1997;177:303-10.

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