COLLAGEN INJECTION FOR INTRINSIC SPHINCTERIC DEFICIENCY IN MEN

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ABSTRACT

Purpose: We evaluated the efficacy of collagen injections in the treatment of male urinary incontinence due to intrinsic sphincteric deficiency.

Materials and Methods: A total of 88 men (mean age 68 years) with mild to severe intrinsic sphincter deficiency underwent a mean of 3.5 transurethral injections of collagen (mean total volume injected 25 ml.). Patients were subdivided into 2 groups based on use of more than 3 or 3 or fewer pads per day. Patient age, pad use before treatment, duration of leakage, number of injections, volume of collagen used and etiology of incontinence were compared for the 2 groups.

Results: Of the patients 42 became nearly completely dry, 19 had substantial improvement but still required 1 to 3 pads per day, 14 consistently used fewer pads but still more than 3 per day and 13 showed no improvement. Most injections were performed with the patient under local anesthesia and no significant morbidity occurred.

Conclusions: In select patients collagen injections appear to be effective, easy to deliver and safe. Pretreatment incontinence severity, concomitant detrusor abnormalities and etiology of intrinsic sphincteric deficiency other than radical retropubic prostatectomy were associated with a worse response to collagen therapy.

Key Words: urinary incontinence, collagen, urethra, urination disorders, injections

Endoscopic injection of materials into the urethral wall to increase urethral closure has been performed for many years. In 1938, Murless described injection of a sclerosing agent into the anterior vaginal wall of an incontinent woman to trigger an inflammatory response that would compress the incompetent urethra.1 Sporadic studies with sclerosing and bulk enhancing agents have been conducted but complications, unsatisfactory results and improper patient selection have delayed acceptance.2,3 In the early 1970s, Berg4 and Politano et al5 reported encouraging results with polytetrafluoroethylene (Polytef) paste injected endoscopically into the sphincteric area. Despite early enthusiasm and initially promising reports disadvantages, such as distant migration, difficulty with injecting polytetrafluoroethylene because of the high viscosity and difficulty performing subsequent operations, prevented this procedure from becoming popular. Polytetrafluoroethylene granuloma and emboli in the liver, lung and spleen caused concern about long-term sequelae.6

Glutaraldehyde cross-linked collagen has been developed for intrarectal use to treat intrinsic sphincteric deficiency. Histological examination of canine and human laryngeal specimens after collagen injection,7,8 as well as early results of collagen use in the urinary tract by Shortliffe et al9 have shown it to be associated with only a minimal inflammatory response and no tendency to migrate. Collagen was approved by the Food and Drug Administration in October 1993 for treatment of intrinsic sphincteric deficiency. We report our early experience with the treatment of male urinary incontinence secondary to intrinsic sphincteric deficiency.

PATIENTS AND METHODS

A total of 88 men (mean age 68 years, range 54 to 82) underwent transurethral injection of collagen for the treatment of urinary incontinence due to intrinsic sphincteric deficiency caused by prostatectomy in 85, trauma in 1, myelodyplasia in 1 and chondroma of the sacral roots in 1 (see table). All patients had been incontinent for at least 1 year and medical management had failed. Before collagen treatment, fluoroscopic urodynamic testing verified the presence of intrinsic sphincteric deficiency and detrusor abnormalities, such as poor compliance and an uninhibited detrusor, were detected and treated concomitantly. Intrinsic sphincter function was evaluated by measurement of the abdominal leak point pressure, which is the minimum abdominal pressure required to cause leakage in the absence of significant detrusor pressure. The risks and benefits associated with transurethral collagen injection as well as the major alternative procedure, the artificial urinary sphincter, were discussed.

All patients underwent skin testing with an intradermal injection of 0.1 ml. glutaraldehyde cross-linked collagen into the volar surface of the forearm and were observed for 4 weeks to rule out allergy or hypersensitivity. Injections were performed transurethrally through a 21F blunt end sheath with a 25 degree lens and a working element with a side channel through which a 22 gauge metal needle was inserted (fig. 1). Of the 88 patients 15 required general anesthesia for the initial injection. However, the remaining injections were performed under local anesthesia.
Response to collagen injections in 88 men with intrinsic sphincteric deficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (cured or improved)</th>
<th>Group 2 (no improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>61</td>
<td>27</td>
</tr>
<tr>
<td>Pt. age (range)</td>
<td>68.2 (64-82)</td>
<td>68.7 (62-79)</td>
</tr>
<tr>
<td>No. pads/day (range)</td>
<td>5.7 (1-10)</td>
<td>6.4 (4-10)</td>
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<tr>
<td>Msd. incontinent (range)</td>
<td>37.1 (12-130)</td>
<td>37.6 (15-130)</td>
</tr>
<tr>
<td>Cm. water leak point pressure (range)</td>
<td>76 (34-108)</td>
<td>39.6 (26-53)</td>
</tr>
<tr>
<td>No. treatments (range)</td>
<td>3.4 (1-7)</td>
<td>2.5 (2-5)</td>
</tr>
<tr>
<td>Total ml. injected (range)</td>
<td>22.7 (2.5-39)</td>
<td>25.5 (11-45)</td>
</tr>
<tr>
<td>Cause of sphincteric deficiency, No. pts. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical retropubic prostatectomy</td>
<td>31 (67)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Radical retropubic prostatectomy and radiation</td>
<td>4 (9)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Transurethral resection of the prostate and visual laser ablation of the prostate</td>
<td>3 (6)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Radical retropubic prostatectomy and anastomotic incision</td>
<td>2 (4)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Radical retropubic prostatectomy, anastomotic incision and radiation</td>
<td>1 (2)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Post-artificial sphincter implantation</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Radical retropubic prostatectomy and transurethral resection of the prostate</td>
<td>1 (2)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Cryotherapy and radiation with or without transurethral resection of the prostate</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Radiation and transurethral resection of the prostate</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chondroma of sacral roots</td>
<td>1 (2)</td>
<td>0 (0)</td>
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</tbody>
</table>

RESULTS

All 88 patients were available for evaluation at the time of this report. Mean followup was 10 months (range 6 to 12). Patients were divided into 2 groups according to the response to collagen injection. Group 1 consisted of 61 patients with normal bladder compliance who required 0 to 3 pads per day (0 to 1 pads in 42 and 1 to 3 pads in 19). Mean duration of incontinence was 37.6 months (range 12 to 7). Intrinsic sphincteric deficiency was the cause of leakage in every patient with a mean abdominal leak point pressure of 76 cm. water (range 34 to 108). Mean number of treatments required to achieve the maximal response was 3.4 (range 2 to 7) and mean total volume injected was 22.7 ml.

Group 2 consisted of 27 patients with severe incontinence requiring more than 4 pads per day before treatment (mean 6.4 pads per day). Pad use decreased to 3 to 5 pads per day in 13 patients and did not change in 13, although many in the latter group became continent overnight. Three patients had undergone complicated radical retropubic prostatectomy, with 2 requiring reexploration and reanastomosis, and 1 requiring symphysiotomy to control bleeding. Fewer had undergone radical prostatectomy as an isolated procedure, that is without ancillary radiation and/or an anastomotic incision. Mean abdominal leak point pressure was 39.6 cm. water (range 26 to 53). Mean number of injections was 3.5 (range 2 to 5).

The 2 groups did not differ in age, duration of incontinence, volume of collagen used or number of injections given. Group 2 patients had a significantly lower mean abdominal leak point pressure than those in group 1 (p < 0.01), indicating worse pretreatment intrinsic sphincteric deficiency. Intervention, such as radiation and/or anastomotic incision, was associated with a worse response, with 10 patients in group 2 having undergone radical prostatectomy plus anastomotic incision and/or radiation therapy.

Of note, 5 patients showed no improvement until 4 injections had been administered, when continence status improved dramatically. In these 5 patients leakage still clearly occurred in response to activity that increased abdominal pressure and all were dry at night. When leakage was associated with bladder symptoms, such as urge incontinence, frequency or nocturnal enuresis, a urodynamic study was repeated and the patients were treated accordingly. No man in group 1 had poor bladder compliance, whereas 3 in group 2 had poor compliance initially and in 3 this condition or overt detrusor instability developed during the course of collagen treatment. These disorders were treated with medication, usually imipramine and hyoscyamine.

Clean intermittent catheterization was required for 24 to 48 hours in 8 patients (11%). Urinary tract infection was noted in 6% of the patients and was easily controlled with antibiotics. Some patients experienced minor complications, such as dysuria and hematuria. No long-term urinary retention or other major complications occurred. Two patients had a vasovagal episode. The majority of injections were performed with the patient under local anesthesia (more than 95%). Only 3 patients preferred subsequent injections with sedation or general anesthesia (1 had had a vasovagal episode and 2 had experienced prior significant discomfort).
DISCUSSION

Treatment of urinary incontinence secondary to intrinsic sphincteric deficiency is a clinical challenge. Although in women the pubovaginal sling procedure is easily performed, durable and associated with a low complication rate, in men such a procedure is technically difficult, especially after radical pelvic surgery, and as yet it is rarely performed. The artificial urinary sphincter is an efficacious procedure for some men with intrinsic sphincteric deficiency, although despite improvements in technology it is associated with a risk of erosion, mechanical problems and an alteration in bladder compliance that may endanger the upper tracts. Our patients were offered an artificial urinary sphincter except for those who had undergone cryotherapy and radiation and, therefore, had a significantly greater risk of urethral erosion and upper tract deterioration.

Since the mechanism of post-prostatectomy incontinence is usually intrinsic sphincteric deficiency, the concept of endoscopic urethral injection with the patient under local anesthesia to improve proximal urethral closure is attractive. Collagen has been used extensively in cosmetic surgery and vocal cord rehabilitation with few side effects. Glutaraldehyde cross-linked collagen is a highly purified suspension of bovine dermal collagen containing at least 95% type 1 and 1 to 5% type 3 collagen. Cross-linking lessens its antigenicity and decreases the hypersensitivity to less than 1% that of bovine collagen. In addition, it makes collagen virtually resistant to the fibroblast-secreted collagenase, so that it is only slightly absorbed. By contrast the collagen commonly used in cosmetic surgery, lacking the cross-linkage, is sensitive to collagenase and is reabsorbed within approximately 2 years. Collagen currently used for transurethral injection is suspended in a phosphate buffered physiological saline solution to form a sterile nonpyrogenic paste of low viscosity, which results in better injectability than polytetrafluoroethylene. Because there is minimal inflammatory response, subsequent operations at the injection site are not jeopardized. The efficacy of glutaraldehyde cross-linked collagen in cosmetic surgery has not paralleled our experience with its transurethral use. Remacle et al attribute this loss of efficacy to a molding phenomenon that occurs when collagen is subject to the excessive muscular movement of the face or larynx. Although this is not applicable to the lumen of the urethra under normal circumstances, a molding phenomenon has been seen in patients with an indwelling Foley catheter.

Of our patients 85% gained some benefit from collagen therapy, with 47% being cured or nearly so and 19% showing marked improvement. These findings are better than early results and can be attributed to increasing experience with the material, development of improved instruments, technique and patient selection. No significant improvement was noted in 15% of the patients who were offered further collagen treatment or other treatment modalities. There are as yet minimal data about the long-term durability of collagen in this setting, although there are data indicating that a sustained response occurs in women with intrinsic sphincter deficiency. In addition, to date only 4 patients who became dry on collagen therapy have required reinjection because of diminished continence with time.

The most important determinants of the success of collagen injections were the pretreatment continence status and etiology of the sphincteric deficiency in patients who had undergone radical prostatectomy with no other intervention (67% of group 1). A complicated prostatectomy that resulted in extensive scarring, such as after multiple anastomotic incisions and especially radiation therapy to the anastomotic area, was associated with a worse response. Typically, these patients had a rigid urethra that tolerated collagen poorly, often resulting in collagen extravasation. Unfortunately, the patients with such poor tissue characteristics were also unsuitable candidates for artificial urinary sphincter implantation. For this reason, and because even after cryotherapy and radiotherapy some patients became dry, we still offer collagen treatment.

Apart from some studies of patients with post-prostatectomy incontinence, our patients predominantly had intrinsic sphincteric deficiency, although a small group had concomitant detrusor disorders. When internal sphincter function is quantified with abdominal leak point pressures...
or fluoroscopically guided proximal urethral pressures, intrinsic sphincteric deficiency is usually the cause of postprostatectomy incontinence.\textsuperscript{21} Detrusor causes in the absence of intrinsic sphincter deficiency are unusual in the setting of incontinence after radical prostatectomy.

CONCLUSIONS

Transurethral injection of collagen is effective in carefully selected patients with intrinsic sphincteric deficiency. Although followup is still relatively short and the long-term durability is not certain, the procedure is easy to perform with the patient under local anesthesia, has few complications and should be considered in men with intrinsic sphincteric deficiency. Further research is required to determine the predictors of outcome after collagen therapy in men with intrinsic sphincteric deficiency. The etiology and seventy of pretreatment incontinence are associated with a worse outcome. By contrast, many of the patients who were cured had undergone only uncomplicated radical retropubic prostatectomy without another procedure and had normal bladder function.

REFERENCES