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Periurethral Collagen Implant: Ultrasound Assessment and Prediction of Outcome

G. Elia and A. Bergman

[1]Department of Obstetrics and Gynecology, State University of New York, Syracuse, New York; [2]Department Of Obstetrics and Gynecology, University of Southern California, Los Angeles, California, USA

Abstract: The objective of this study was to identify sonographic parameters that could predict successful outcome in women after periurethral collagen implant. Thirty-one women with a diagnosis of stress urinary incontinence with intrinsic sphincteric deficiency underwent one periurethral collagen implant between January and December 1994. Three months after the procedure ultrasound evaluation was performed using a 5 MHz probe placed at the vaginal introitus. Subjective assessment and cough stress test were used to measure outcomes. Twenty-five women were available for evaluation 1 year after the procedure. A successful outcome was found in 18 of the 25 women subjectively (72%) and in 16 objectively (64%). A distance of the collagen from the bladder neck of less than 7 mm was found to be associated with a positive outcome. This threshold was found to have a sensitivity of 83.3%, specificity of 85.7%, a positive predictive value of 93.7% and a negative predictive value of 66.6%.

Keywords: Bladder ultrasound; Collagen; Intrinsic Sphincteric Deficiency; Stress Urinary Incontinence

Introduction

Stress urinary incontinence with intrinsic sphincteric deficiency (ISD) is diagnosed when leakage from the urethra is observed at a bladder pressure equal to or less than 65 cmH_2O. This diagnostic parameter was first introduced by Wan [1] to describe the condition in myelodysplastic children. The same diagnostic tool has been subsequently used to assess urethral competence in adults [2–4]. Numerous procedures have been proposed for the treatment of stress urinary incontinence and ISD. Among these, bulking agents have been growing in popularity because of their ease of use and low morbidity. In past years periurethral injections have been performed, using different materials such as sclerosing agents, teflon, silicone, autologous fat and bovine collagen [5–9]. Because of its higher safety, glutaraldehyde cross-linked collagen (GAX) has been the one most extensively used in the treatment of women with stress urinary incontinence and ISD; the reported success rate range between 83% and 48% [4,10]. This big discrepancy is partly explained by the different criteria that have been used to define success; in addition, it is obvious that we have not definite knowledge of the mechanism of action of the collagen in restoring continence.

The purpose of this study was to try to identify by ultrasound the location of the collagen and to find out whether the distance of the material from the bladder neck affected the outcome.

Materials and Methods

Between January and December 1994, 31 women underwent periurethral collagen injection at the Los Angeles County University of Southern California Women's Hospital and at the State University of New York University Hospital facilities. They all had a diagnosis of stress urinary incontinence with intrinsic urethral sphincter deficiency (ISD) type III. The pretreatment evaluation consisted of history and physi-

Correspondence and offprint requests to: Professor G. Elia, Department of Obstetrics and Gynecology, State University of New York, 736 Irving Ave., Room 3654 West Tower, Syracuse, NY13210, USA.

cal examination (with special emphasis on neurologic screening tests of the S2–S4 central micturition center); negative urine culture; measurement of postvoid residual volume; cotton swab test (change of cotton swab angle between resting and straining, measured with an orthopedic goniometer, with the patient in the lithotomy position); dynamic water urethrocystoscopy; standing provocative water urethrocystometry (at a filling rate of 60 ml/min); Valsalva leak-point pressure in the sitting position at maximum cystometric capacity; urethral pressure profile in the sitting position at rest and during repeat coughing, with the bladder at maximum cystometric capacity; and uroflowmetry. Pressure in the abdomen (approximated by vaginal recording), bladder and urethra were measured simultaneously using two 8 Fr microtip pressure transducers (6 Fr in diameter, models 20K 60 and 20K 62, Dantec Electronics, Skovlunde, Denmark) and recorded on a six-channel electrophysiologic recorder (model Menuet, Dantec Electronics, Skovlunde, Denmark). Prior to the evaluation each patient was given a questionnaire addressing pertinent information; they also completed a 48-hour voiding diary. The patients were re-evaluated 1 year after the first injection, using the same workup as preoperatively except of the cystoscopy. The injection of collagen was performed by the two authors in the office or in the operating room as an outpatient procedure. The anaesthesia used was local only or local with intravenous sedation, for the office and the operative room respectively. A 0° or 30° cystoscope was used to visualize the site(s) of the injection(s), which were performed periurethrally inserting a 20 gauge spinal needle at 3 and 9 o'clock at the urethral orifice and injecting the material at 3 and 9 o'clock at the bladder neck. Cross-linked bovine collagen (Contigen, Bard) was used as provided by the manufacturer in 2.5 ml syringes. The collagen was injected on each side until complete captions of the urethral mucosa was obtained. The number of syringes used was recorded. After 3 months, ultrasound was performed using a vaginal probe applied at the level of the introitus. Special care was taken not to apply pressure on the introitus that would distort the anatomy of the urethra and bladder neck. The ultrasound was performed with a 5 MHz prober (General Electric RT 3600, Rancho Cordova, California), after filling the bladder with 150 ml of sterile saline and after insertion of a lubricated Q-tip into the urethra, with the cotton end well applied to the bladder neck (Figs 1 and 2). The collagen appeared as a hypoechoic area with round margins. The cotton swab was necessary to identify the urethra and the bladder neck. In a pilot evaluation performed both with and without the Q-tip in a separate group of patients, it was noted that the cotton swab enhanced and anatomical landmarks without altering them. Subjective outcome was measured as described by the patient on a scale of 1–10. The patients were interviewed by the nurse not directly involved in the study: she used questions on routine daily, activities and a general question on satisfaction about the outcome.

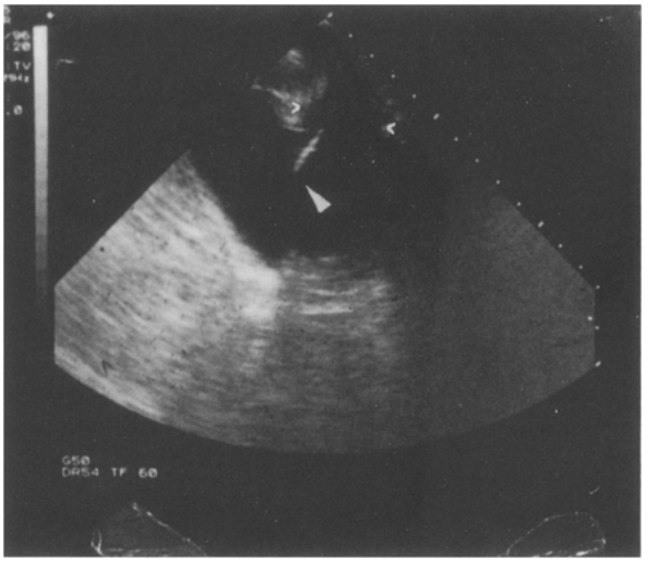

Fig. 1. Ultrasonographic imaging of periurethral collagen. Open arrows: collagen; closed arrow: Q-tip.

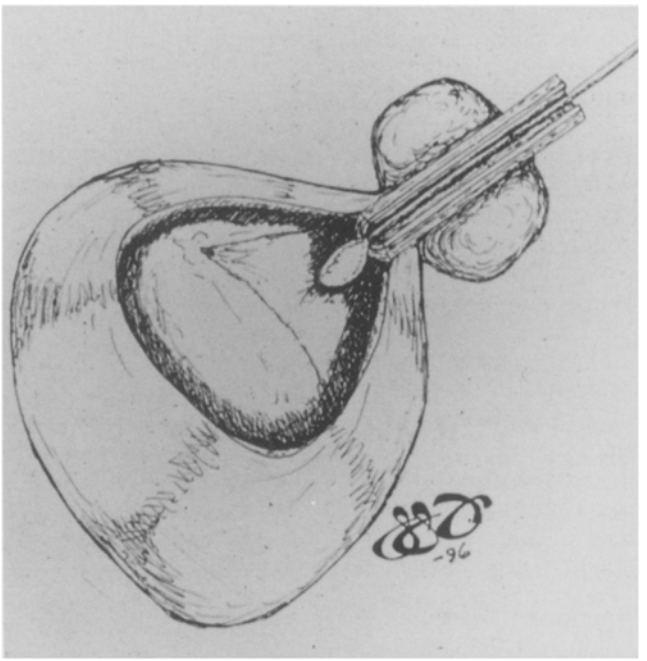

Fig. 2. Simplified drawing to help identify landmarks on ultrasonographic imaging.

As objective measurements we used the cough stress test in the supine position with the bladder filled to maximum cytometric capacity; if no incontinence was noted, the patient was then placed in the sitting position. Subjective success was empirically defined as a perception of improvement of 6 or more; objective success was defined as absence of urinary leakage on cough stress testing.

Statistical analysis was performed using the paired *t*-test, Fisher's exact test and the receiver operating

characteristic (ROC) curve [11]. The terminology conforms to that proposed by the International Continence Society [12], except where specifically stated.

Results

Of 31 subjects who underwent collagen injection, 25 were available for follow-up. Mean age was 57 years, mean parity 3; 17 were postmenopausal, 15 were on estrogen replacement therapy (1 patient with a prior history of breast cancer and 1 that refused the therapy were not on hormone replacement). Of the 25 patients, 18 (72%) were subjectively cured, 16 (64%) had a negative cough stress test, and 23 (92%) had a Valsalva leak-point pressure higher than 65 cmH_2O after the injection. One patient developed de novo detrusor instability, which was completely controlled with anticholinergic therapy. Two patients developed postprocedure cystitis. No urinary retention persisted more than 24 hours after the procedure.

Each patient received a total of 5–15 ml of collagen. No statistically significant differences were found as regards urodynamic parameters before and after the injection, except for the Valsalva leak-point pressure (Table 1). The insertion of a Q-tip in the urethra greatly enhanced visualization of the anatomical landmarks. The measurements of the distance of the most proximal margin of the collagen implant from the bladder mucosa at the bladder mucosa at the bladder neck (Fig. 1) was plotted for each patient on a ROC curve; the value of less than 7 mm was found to be located at the point of change of angle on the curve. This threshold was found to have a sensitivity of 83.3%, specificity of 85.7%, a positive predictive value of 93.7% and a negative predictive value of 66.6% (Table 2).

Table 1. Urodynamic parameters

	Pre Mean (±SE)	Post Mean (±SE)	
MUCP (cmH_2O)	26.3 (±3.1)	22.6 (±1.8)	NS
MCC (ml)	414.2 (±23.4)	418.6 (±21.5)	NS
PTR 1/3 proximal (%)	74.1 (±4.3)	83.9 (3.3)	NS
PTR midurethra (%)	74.6 (±4.3)	83.8 (±3.5)	NS
PVR (ml)	34.3 (±5.1)	31.6 (±4.0)	NS
Max flow (ml/s)	23.8 (±2.1)	22.6 (±2.2)	NS
	Pre (*n*)	Post (*n*)	
VLPP (<65 cmH_2O)	25	2	<0.05

MUCP, maximum urethral closure pressure; MCC, maximum cystometric capacity; PTR, pressure–transmission ratio; PVR, postvoid residual; VLPP, Valsalva leak-point pressure

Table 2. Table of outcome

	Success	Failure	
< 7 mm	15	1	16
≥ 7 mm	3	6	9
	18	7	25

Discussion

The concept of Valsalva or stress leak-point pressure was first introduced by Wan to diagnose and follow up, after collagen injection, myelodysplastic incontinent children with ISD [1]. When the bladder neck is well suspended, bulking agents are considered the most successful and less morbid treatment [2]. The purpose of injecting bulking agents around the urethra is to increase the coaptation of the urethral mucosa at the level of the bladder neck. In the past several materials were studied for this purpose, for sclerosing agents to teflon [5–8]. The success rate with these materials has been somewhat low in the long term, but more importantly, emboli, carcinogenicity and several local reactions have raised significant concern. Recently GAX collagen has been considered for its low local reaction, safety and longer persistence in the tissues (no migration of collagen to distant sites has been reported) [5,13,14]. This is collagen derived from cows and is cross-linked for higher stability. Allergic reactions have been reported in 2.6% of individuals exposed [3]. To avoid this complication the manufacturer has prepared a skin test that is injected 1 month prior to the procedure.

The success rate of the collagen implants has been reported in the initial studies as 80% [3], but a more recent study has reported success rates of 54% and 48% after 1 and 2 years respectively [10]. Our study, with a success rate of 72% at 12 months, is within the reported range. Most of the authors have identified several factors involved in the success of the treatment: injection at the bladder neck; injection in the lateral walls of the urethra at the 3 and 9 o'clock positions; hypomobility of the bladder neck; and absence of collagen leakage during the procedure [10,15].

Only Khullar in 1993 [15] and Stanton in 1995 [10] have reported on post injection evaluation by ultrasound. They found that the collagen was not well visualized after 6 months and was not visible at all at the 2-year evaluation. Khullar and colleagues concluded that continence appeared to be related to the height of the 'bumps' on either side of the bladder neck; they also noted that continence was not achieved if the 'bumps' were not located less than 10 mm from the bladder neck. The present study confirms that the distance from the bladder neck may be a factor in the success of collagen injections. We also suggest that there may be a cutoff point of 7 mm, beyond which continence is not achieved and reinjection is warranted. Doubt persists as whether to perform a reinjection in incontinent patients with the collagen located within 7 mm from the bladder neck. According to Khullar's observation it would be the height of the bump that determined the usefulness of a

repeat procedure, thus implying that augmentation of well placed collagen may improve the outcome. In our experience we also noted that a Q-tip placed in the urethra gives a better visualization of important anatomical landmarks. Further studies are necessary to better understand the issues discussed above in order to use this relatively simple and safe new procedure in the best way.

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EDITORIAL COMMENT: We know very little about why collagen injection at the bladder neck works or what makes it produce continence, especially in the long term. The height of the 'bumps', the location of the injection as determined by ultrasound, and finally the degree of vascularization of the material may all be important. Further studies are needed to elucidate these points in greater detail, especially at 1 year or more. It is difficult in this study to determine whether the patients had a well supported bladder neck, as the results of the Q-tip test are not given: Q-tip results should always be reported in terms of degrees from the horizontal, as an angle change of 60°–70° is only 10° and could indicate hypomobility. But isn't a resting angle of 60° from the horizontal already indicative of urethral *hypermobility*? As a final point, we know that Valsalva leak-point pressures are useful in determining the need for collagen injection in patients with ISD and urethral hypermobility, and that a value of less than 65 cmH_2O has validity. Where does the new figure of 100 cmH_2O fit in, as was recently announced by the manufacturer of the collagen implant? Valsalva leak-point pressure usefulness in selecting other forms of surgical procedures for continence remains to be proven, and this test should not be given the same significance as low urethral close pressure, whose clinical predictive value is well established, when other surgical procedures are considered.