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ORIGINAL ARTICLE

Long-term results and patients' satisfaction after transurethral ethylene vinyl alcohol (Tegress®) injections: a two-centre study

Annette Kuhn · Werner Stadlmayr · Amara Sohail · Ash Monga

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Abstract Tegress is ethylene vinyl alcohol which is non-allergenic and permanent. The aim of the study was to evaluate efficacy, feasibility and safety of transurethral Tegress® in women with urodynamic stress incontinence in a two-centre setting. Approximately 33 female patients with urodynamic stress incontinence were prospectively included in the study. Preoperatively, the patient's history, gynaecological examination and multichannel urodynamics were performed. On follow-up, the patient was asked to use a visual analogue scale to measure her contentness and underwent uroflowmetry and a cough test. Median follow up was 51 months. About 15 women considered themselves as completely continent, and 23 (69%) were either satisfied or very satisfied. Pad test was positive in 18 (54.5%) patients, and cough test was positive in 20 (60.6%). Patients' satisfaction did not correlate with objective dryness. Ethylene vinyl alcohol is a bulking agent with a success rate of approximately 45% after 51 months.

Introduction

When conservative therapy for stress urinary incontinence fails, surgery is the mainstay of treatment. Urethral bulking agents, as an office or day-case procedure, are the most minimally invasive options available and are associated with minimal morbidity.

A. Kuhn (✉) · W. Stadlmayr
Frauenklinik, Inselspital,
CH-3010 Bern, Switzerland
e-mail: annette.kuhn@insel.ch

A. Sohail · A. Monga
Princess Anne Hospital,
Southampton, UK

According to a recent systematic review from the Cochrane Database [1], injection therapy may represent a useful option for short-term symptomatic relief amongst selected women with co-morbidity that precludes anaesthesia.

Peri-urethral injectable agents have been used for the treatment of urinary incontinence in women for more than a century. A variety of substances have been used, the most frequent being polytetrafluoroethylene (Teflon), polydimethylsiloxane elastomer (silicone), bovine glutaraldehyde cross linked (GAX) collagen, carbon-coated zirconium beads, hyaluronic acid/dextranomer and autologous tissues as fat and cartilage [2–6]. Initially, Teflon injections were used but were associated with migration, granuloma formation and even carcinogenesis, and this material has now been abandoned [15].

Collagen is one of the best-documented substances with good initial success rates associated with an average of 1.5–2 injections [7–13] however, long-term success rates are not satisfactory [14], with success rates as low as 26%.

The low success rates of collagen injections especially at long-term follow-up have been attributed to collagenase-induced biodegradation. Because of this, newer more durable substances have been investigated to try and improve the long-term outcome of injectable therapy. The other disadvantage of collagen is possible allergic reaction which occurs in about 3%, and patients require an intradermal allergy test at least 1 month prior to treatment [5].

Tegress® is ethylene vinyl alcohol, and within more than 150 publications, the substance has been successfully used to treat cerebral aneurysms, carotid-cavernous fistulas and esophagobronchial fistula in men [15–17]. It is a biocompatible polymer which is dissolved in an 8% dimethyl sulfoxide (DMSO) carrier to allow injection of a very low-viscosity fluid into tissue [17]. Once the material comes into contact with body tissue or fluid, the DMSO rapidly

dissipates from the polymer, which results in a precipitate of a coherent solid mass [17, 18] (Fig. 1). In contrast to collagen, this substance is durable, not biodegradable and non-allergenic. Animal studies in mini pigs demonstrated that Tegress encapsulated with tissue in-growth into the porous material structure, with no material migration to other sites as determined by macro- and microscopic specimen (Bard, data on file).

This study aimed to determine the feasibility and short- and long-term efficacy of Tegress® injection for female stress incontinence.

Fig. 1 Detailed view of Tegress®

Materials and methods

Between September 1999 and October 2003, 33 female patients with median age 69 (range 36–89) who were referred to the urogynaecology outpatient clinic either to Princess Anne Hospital, Southampton or to the urogynaecology clinic, Frauenklinik, Inselspital Bern were included in the study. Only women with urodynamic stress incontinence, proper understanding of the local language, age >18 years and safe contraception, who were not breast-feeding and who gave written informed consent were included. Women with more than stage 1 prolapse were excluded. Ethics committee consent was obtained in both centres.

All patients were asked to fill in the Bristol female lower urinary tract symptoms questionnaire (BFLUTS) [19] and to estimate their grade of satisfaction on a visual analogue scale of 1 to 10. A grade of 0–3 was considered not satisfied, 4–7 moderately satisfied and more than 8 as satisfied.

BFLUTS is a questionnaire, which is divided into the three domains voiding disorders, urinary incontinence and overactive bladder (OAB) symptoms. The severity of symptoms is divided in columns.

"I have this problem never, occasionally, sometimes, most of the time or always". We rated the problem as being present with at least sometimes being bothersome in at least 50% of the specific questions.

A complete history, clinical gynaecological examination to assess prolapse and a cough and pad test were performed. For the cough test, the patients were asked to cough in the upright position at bladder capacity to visualize leakage. Any visual leakage was noted as positive cough test.

A 45-min pad test was performed according to International Continence Society (ICS) recommendations and was considered positive if the difference in pad weighing before and after the test was 2 g or more.

Urodynamic investigations were done prior to surgery. Cystometry was performed in the sitting position with the patient in the 45° upright position with a six French microtip transducer, which was introduced into the bladder for intravesical pressure measurement, and a water-perfused balloon catheter was introduced into the rectum for intra-abdominal pressure measurement. Bladder was filled with a rate of 20 ml/min with saline solution at 37°. Filling was continued until the patient experienced a strong desire to void. A cough stress test was performed every 100 ml of filling. At bladder capacity, pressure-flow studies were performed. Urethra pressure profile was performed at rest three times repetitively and the maximum urethra closing pressure (MUCP) und functional urethral length (FUL).

At final follow-up, all women completed the BFLUTS questionnaire and a visual analogue scale and underwent uroflowmetry and cough test at bladder capacity. Residual urine was measured using abdominal post-void ultrasound.

Tegress® can be stored at room temperature. At contact with moisture, it forms a spongy non-absorbable mass (Fig. 1). Due to low viscosity, the material is easily injected, and it has no allergenic potential.

Injection was performed transurethrally under cystoscopic view. For injection, the patient was placed in lithotomy position. Cystoscopy using a 20° optic was performed prior to and during injection to visualize coaptation of the bladder neck. Approximately 1 ml was injected per injection site very slowly over 60 s; after injection, the needle remained in place for a further 60 s before it was withdrawn, twisting the needle to allow easy disconnection between the needle and the material. This allows the material to precipitate in contact with body fluids and prevents extravasation. The substance was injected at the four and eight o'clock positions, with a maximum total amount of 2 ml per session by two different surgeons (AK, AM) who were using exactly the same technique.

Patients were considered cured if there was no subjective or objective evidence of stress incontinence. Success was defined as subjective and objective improvement of stress incontinence, whereas failure was no change or worsening of symptoms.

Table 1 Previous surgery for stress incontinence and general gynaecologic surgery; some patients had more than one operation

	All patients (n=33)
Marshall Marchetti Burch	9
Pereyra needle suspension	8
Total abdominal hysterectomy	16
Vaginal hysterectomy	3
Anterior repair	3
Posterior repair	1
Wertheim	1
Hysteropexy	1

Statistics were performed using the InStat system version 4.0 for Windows. To test whether the median of the variable flow and residual urine differs between the two groups pre- and post-operatively, t test was used.

Results

Median follow-up was 51 months (range 35–68 months).

Twenty-nine patients had a history of previous surgery for stress incontinence and/or gynaecologic surgery (Table 1).

All patients had urodynamically proven stress incontinence (Table 2).

Twenty-four patients had one injection, while 9 patients (27.2%) required a second injection which was performed 6 weeks after the initial treatment. Table 3 demonstrates subjective and objective cure rates, and Table 4 shows the results of the BFLUTS questionnaire pre- and post-operatively.

Fifteen women (45%) reported themselves as completely continent, and 23 (69%) were either satisfied or very happy.

Flow rate and residual urine did not differ significantly pre- and post-operatively (p=0.99, two-tailed t test) with flow rates of 32 ml (range 27–43) preoperatively and 30 ml (range 26–39) post-operatively. Both groups followed a Gaussian distribution.

Table 2 Urodynamics prior to surgery

	Urodynamic findings
Bladder capacity (median, range)	312 (289–428)
First sensation to void (median, range)	188 (136–289)
Second sensation to void (median, range)	260 (212–310)
Detrusor pressure at maximum flow rate cm H2O (median, range)	28 (12–30)
MUCP cm H2o (median, range)	28 (12–31)
FUL mm (median, range)	23 (17–27)
Positive cough test n	33
Maximum flow rate (median, range)	32 (27–43)

Table 3 Cure rates and success

	Number of patients	%
Objective cure		
Pad test negative	15	45.5
Cough test negative	13	39.4
Subjective cure		
Dry on BFLUTS	15	55.5
Visual analogue scale		
0–3	10	31
4–7	18	54.4
8 or more	5	15
Cured overall	14	42.4
Success overall	18	54.4

The only post-operative complications were voiding difficulties or persistent stress incontinence. Voiding difficulties lasted for 1 day only and occurred in two patients; no patient suffered from long-term problems.

Discussion

To our knowledge, this is the first study of ethylene vinyl alcohol with long-term data. The subjective and objective cure rates were approximately 42%, and the patients' satisfaction reached 69% (visual analogue scale ≥4) which is comparable to Tamanini et al. [20], who demonstrated a 73% improvement/cure rate in 15 patients 60 months after Macroplastique® injection.

A multi-centre randomized study from the USA [21] showed a rate of 59% successfully treated patients defined by a negative pad test and a 59% dry and improved rate using the Stamey grade. In this study, 253 women were included, and follow-up was 12 months. Compared to our data, we can assume a slight decrease in continence of approximately 10% over the next 4 years. Most other studies with a short-term follow-up only of 12–24 months have slightly better results with success rates of 67–94%. The only study with long-term follow-up of more than 5 years showed a success rate of 26% [14]. In this study, collagen was applied peri-urethrally.

Another study [22] found 62% dryness after bulking agents with a follow-up of 32 months. However, this is a rather difficult comparison as those patients were injected

Table 4 BFLUTS results

	Voiding disorders (n)	OAB (n)	Urinary incontinence (n)
Pre-operatively	2	12	33
Post-operatively	2	9	8

after radical prostatectomy, and various bulking agents as collagen, silicone and hyaluronidase acid were used.

Technically, Tegress® is slightly more difficult to apply because the injection rate should be very slow to allow the substance to have adequate contact with the tissue and establish the spongy mass [17]. Safety of the substance, particularly the lack of a significant fibrotic response, has been demonstrated in animal studies [18], and this is undermined if we consider the few cystoscopy results of those study patients who required cystoscopy during the tension-free vaginal tape (TVT) procedure. In a recently published study [24], there was a concern about the safety of ethylene vinyl alcohol, as an erosion rate of 37% was noted. However, in this retrospective study of 19 patients, the recommendation of the amount of 1 ml ethylene vinyl alcohol per site was not respected, and injection was performed due to the degree of coaptation, which is not necessary according to the producer's recommendation. Another study by Erekson et al. [25] has presented some significant local complication of ethylene vinyl alcohol in two patients. Urethral erosion is a very serious complication, which has to be considered particularly when there is a deterioration of incontinence post-operatively or recurrent urinary tract infections occur. This is a severe potential downside of permanent urethral bulking agents, and the patient has to be informed about this complication prior to surgery. Removal of a permanent mass requires another intervention and may deteriorate continence, leaving urethral scar tissue behind resulting in a drainpipe urethra. Since initial injections, two patients have undergone a TVT for persistent urodynamic stress incontinence. At cystoscopy during the TVT procedure, no Tegress was visible inside the bladder or urethra.

All other patients requested no further treatment, although some of them were not completely dry.

The risks of permanent injectables as ethylene vinyl alcohol in stress-incontinent women have to be weighed against the short life of non-permanent materials like collagen.

Overall complication rate in our series is very low, mainly consisting of retention or persistent stress incontinence.

Peri-operative complications associated with peri-urethral injections are uncommon; transient urinary retention is approximately observed in 15% of patients [13] which was similar in our patients.

During injection, perforation and extravasation of the injected material can occur if the mucosa is disrupted. With both substances, this was generally not a problem because collagen is immediately flushed away and Tegress can easily be removed by the injection needle or the cystoscope.

Some authors report discomfort during the injection [7] but we did not experience this side effect during our study. This may be due to the transurethral injection technique in comparison to peri-urethral application.

It remains difficult to compare results of treatment for stress incontinence, as many authors do not differentiate between subjective and objective or between cure and success. In our series, we have a cure rate of 42% and a 54.4% success rate. Two patients still required further surgery despite improvement of symptoms. The decision about further surgery was based on the patients' wishes.

The cure rate may not seem excellent; however, when applying similar criteria, Ward et al. [26] found a 60% cure rate following TVT and Burch in patients with primary stress incontinence. These results were approximately 30% lower than the 5-year results published by Ulmsten et al. [27]. This is most likely attributable to the fact that all surgery was performed by one surgeon but also to the fact that there were no objective criteria to determine cure, and cure and success was not differentiated.

A weakness of the study is that we used our own scoring system for the BFLUTS questionnaire. As we qualified the bladder problems as such if the questions were at least positive in 50% starting from "sometimes a problem", we do not take the bothersomeness of occasional occurrence into account. However, to our knowledge, there is no published scoring system available which could be used.

A recent publication suggests the Symptom Severity Index and Symptom Impact Index (SSI/SII) as best patient-based outcome measures to assess urinary incontinence [28].

It must be recognized that in this group of negatively selected patients, success rates of other forms of treatment may well be comparable. It should also be taken into consideration that in general, transurethral injections can be applied under local anaesthesia, whereas other techniques are not only more invasive with a higher complication rate but often also require general anaesthesia. Success rates for recurrent urinary incontinence with intrinsic sphincter deficiency (ISD) are around 70% for TVT and Burch colposuspension which is slightly better; however, complication rates are noticeably higher.

In conclusion, ethylene vinyl alcohol copolymer is a permanent bulking agent with a patient satisfaction rate of 69% and a cure rate of 40% in women with urodynamic stress incontinence after 51 months follow-up. Despite the absence of urethral erosions in our series, we need to be cautious about this serious side effect in permanent bulking agents, and patients should be informed about this.

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