SUBMUCOSAL BLADDER NECK INJECTIONS FOR MANAGEMENT OF STRESS URINARY INCONTINENCE

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ABSTRACT

Submucosal deposition of bulking agents is increasingly used for the treatment of intrinsic stress urinary incontinence both in male and female patients. Bulking agents should ideally be non-immunogenic, biocompatible, non-migratory, injectable, cause a minimal inflammatory reaction, retain the submucosal bulging effect, and reasonably cheap. None of the agents available to date fully meets these criteria. The rationale and clinical results of artificial, heterologous and autologous agents currently used for treatment are analyzed and the technique of transurethral submucosal injection applied by the authors is described. Perioperative imaging using transrectal or transvaginal ultrasonography is important for the exact placement of the injected material, and is one of the key factors for a satisfactory result.

Depending on length of follow-up, the route of application (transurethral, antegrade transvesical, periurethral), the etiology of the patients, the amount of injected material, the number of procedures and the bulking agent used continence and improvement rates vary from 21-83% and 40-100%, respectively.

A future outlook describes new agents and techniques that may be promising for broad clinical use.

Key words: incontinence, bulking agents, urethra, injectables, submucosal injection, ultrasonography. 
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INTRODUCTION

The concept of using injectables to increase urethral resistance and thus treat urinary incontinence was already known more than sixty years ago (1). The first agents, such as paraffin or Dondren, actually worked as sclerosing medium causing a difficult to control urethral stenosis. In the early seventies the first bulking agent in the actual sense – polytetrafluoroethylene (Teflon®) – was introduced as a possible means for treating incontinence (2). Several encouraging reports (3,4) were soon followed by reports about disappointing long-term results (5) and complications, especially migration of substance particles into the lungs (6,7) and brain (8) causing at times severe morbidity. More recently developed alloplastic injectables for the urethra which have a bulging effect onto the urethral mucosa are collagen, suspended silicone particles and newer potential substances like polyvinyl alcohol foam (9), dextranomers in hyaluronan (10), and bioglass (11). Potential long-term immunogenic side effects (12) and possible migration of these substances have led to the developments of techniques whereby autologous materials such as the patients’ own fat (13), collagen (14), smooth muscle cells, or chondrocytes (15) are used for suburethral injection. The problem with non-vascularized free tissue transplants is a significant loss of implant volume over time. This may be overcome by the use of precursor cells such as stem cells, myoblasts (16) or chondrocytes (17), which according to recent preliminary results induce new tissue formation at the injection site, rendering uniform and stable implants after several months.
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RELEVANT ANATOMY

Female

The goal of injectables is to restore the relatively thick, highly vascular submucosa, which contributes coaptation and mucosal seal to the continence mechanism. In female patients coaptation and mucosal seal is most effective in the proximal urethra where it is supported by urethral smooth muscle tone and dense fascial structures supporting the bladder neck and adjacent urethra (18). Smooth musculature extends along the entire length of the urethra, whereas the striated fibers of the rhabdosphincter are located only in the mid and distal portion (19,20). These are the sites where the greatest increase in intraurethral pressure occurs. The rhabdosphincter together with the surrounding extrinsic striated muscles contribute to the resting tone but also to the pressure rise that precedes coughing and Valsalve maneuvers and which is exerted when inhibiting micturition. These zones of increased intraluminal pressures therefore less depend on the sealing effect of a thick submucosa.

Male

A lack of watertightness in male patients in the majority of cases is a consequence of either lower urinary tract surgery or trauma. During transurethral and radical prostatectomy almost all of the relevant smooth muscle sphincter is removed or destroyed and continence depends on the omega-shaped layer of the rhabdosphincter (21). Inadvertent cutting, deep bites during placement of the anastomotic sutures, hematoma, or extensive inflammation may cause scars and functional impairment of the rhabdosphincter. In addition some of the various amounts of fibers that extend ventrally to the base of the bladder will also be eradicated during open surgery. Anatomical studies have shown that the striated sphincter is not a ring-like structure but a complex interdigitating system intimately connected to the prostatic smooth musculature.

INDICATIONS

It is evident that bulking agents will restore neither a weakened pelvic floor nor a damaged sphincter. Its presumed mode of action is the restoration of the submucosal cushion in the urethra, which has been lost either due to age, previous surgery or chronic disease. In female patients therapy with injectables is therefore best indicated in pure intrinsic sphincter deficiency, but may be combined with reconstructive pelvic floor surgery as an adjuvant (22). In male patients a contractile external sphincter damaged by previous surgery or trauma is the most rewarding indication. Endoscopically visible indentations may in these cases delineate the site of preferred injection.

MECHANISM OF ACTION

The first injected substances used led to a sclerosis with destruction of the urethral musculature and non-compliance of the urethral wall instead of a submucosal bulge. It was only more recently that inert substances applied into the submucosa resulted in its actual bulging at and above the level of the maximum sphincter pressure.

Polytetrafluoroethylene (Teflon® paste is usually encapsulated but not penetrated by vascular and fibrous tissue creating at times sequester in the urethral wall (23,24). Commercially available collagen preparations consist of sterile, nonpyrogenic bovine dermal collagen cross-linked with glutaraldehyde and dispersed in phosphate-buffered physiologic saline (25). Glutaraldehyde cross-linked (GAX) collagen starts to degrade within 12 weeks. At the same time neovascularization and deposition of fibroblasts and autologous collagen takes place inside the implant (26). A similar albeit more rapid process is assumed after injection of autologous fat. Experimental studies have shown, however, that in the long term up to 90% of the fat implant is lost (27).

Silicone preparations consist of biphasic copolymers of fully polymerized and vulcanized particles of polydimethylsiloxane compounds suspended in a hydrogel carrier (28). The size of the particles ranges from 100 to 600mm (average 150mm), which makes particle migration practically impossible. After absorption of the hydrogel carrier within the first few days the innumerous irregularly
shaped silicone particles are solidly encapsulated by collagenous tissue thus creating the therapeutic mucous bulge.

**TECHNIQUE OF TRANSURETHRAL INJECTION**

In order to achieve our current success rate we developed a standardized transurethral technique using three-dimensional ultrasound (29).

Implantations were performed using three dimensional, transrectal ultrasound with a 7.5 MHz Voluson 3D multiplanar endorectal transducer (30) before, during and after the procedure. Intraoperative transrectal ultrasound will show the position of the needle and subsequently the position of the injected material. This may also be useful for any additional procedures to show which deposits remained inside and which ones may have been lost.

The bulking agent initially was a collagen preparation and consists now of solid textured silicone particles suspended in a carrier gel (31).

**Technique in Male Patients**

In patients with stress urinary incontinence after radical prostatectomy the external sphincter zone needs to be outlined. This can be done by scoping the patient under local anesthesia during which the patient is asked to contract the sphincter. In addition transrectal ultrasound may delineate the morphology of the rhabdosphincter and sometimes sonographically scars can be depicted (Figure-1). The needle is then inserted in the bladder, drawn back into the proximal urethra, turned appropriately and injected at an angle of at least 45°.

A regular rigid cystoscope with an Albarran deflector, a 0° to 30° lens and a 5F working channel are used. First the defect is visualized endoscopically and its relationship to the external sphincter zone is clarified. The endoscope is advanced into the bladder, the bladder is filled, and an 18g needle is inserted through the working channel of the scope until it can be seen through the lens thereby avoiding any lacerations of urethral or vesical mucosa. After turning the needle it is brought to the location of the desired injection, angled at least 45° from the urethral axis, and inserted into the submucosa for approximately 1 cm or any visible marking of the needle, e.g., beginning of a white coating. If transrectal sonography is used during the procedure the insertion of the needle and its exact position can be followed on the ultrasound screen.

Whenever a defect in the sphincter zone is apparent, the endoscopically visible defect is undermined and cushioned with 1 to 2.5 cc of the agent (Figure-2). In addition or in cases where there is no apparent defect, the material is injected at the 3, 9

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**Figure 1** - Depiction of a scar (arrow) in the rhabdosphincter of a patient with stress incontinence after radical retropubic prostatectomy. Transverse plane, three dimensional, transrectal ultrasound using a 7.5 MHz Voluson 3D multiplanar endorectal transducer.

**Figure 2** - Endoscopic appearance after submucosal injection of bulking agents. The area of the external sphincter shows good coaptation, the arrows depict the sites where the needle was inserted.
and if possible 6 o’clock position. After each injection the needle should be left in place for at least one minute to allow the material to settle.

Three-dimensional transrectal sonography improves the exact transurethral deposition of the implants. After injection the suspended collagen or polydimethylsiloxane particles present as hyperechogenic structures which can be depicted in all three dimensions (Figure-3).

Usually patients where the rhabdosphincter can be outlined fare better than those where this is sonographically not possible. The goal of the procedure is to restore the coaptation of the mucosa from the level of the external sphincter cranially (Figure-4). After the injections the cystoscope should not be passed beyond the area of injection nor should any catheter be inserted afterwards. The immediate success of the injection can be tested with a simple trick. When the sphincteric zone is sufficiently closed, irrigation fluid of the scope placed in the urethra will not be able to advance into the bladder but instead will be seen coming out along side the cystoscope shaft at the tip of the penis.

**Technique in Female Patients**

The injection technique in female patients is slightly different because no distinct sphincteric zone can be seen (Figure-5), and due to the length of the urethra injections in the caudal part of the urethra are difficult because of insufficient irrigation.

A rigid cystoscope with an Albarran deflector, a 5F working channel, but a 30° to 70° lens are therefore advisable. A specially designed short endoscope where the working channel opening is at the level of the optical lens is currently developed.

The injection procedure is basically the same with the exception of the location and the number of deposits. Smaller but more deposits (usually four) are placed at the bladder neck and cranial third of the urethra at the 3, 6, 9 and 12 o’clock position.
Follow-up

Catheterizations should be avoided in the early postoperative period. If urinary retention occurs or may be anticipated at the time of injection, a 10 Fr. suprapubic catheter should be inserted until the patient resumes spontaneous voiding. Patients should receive oral antibiotics for 1 week. Mechanic pressure to the perineum such as hard seat covers, hard stools, etc. should be avoided for 2 weeks, bicycling should be avoided for 6 weeks. If a second or third injection is necessary, it should be performed after an interval of at least 3 months to allow the previous implant to heal in.

Pitfalls

The needle can be inserted in the urethra too far cranially resulting in a partial or total loss of material into the bladder lumen. It may not always be visible endoscopically, but could definitely be seen if ultrasound were used during the procedure. If the needle perforates the entire urethral wall the bulking agent will be placed periurethrally where its effect regarding closure is minimal (Figure-6).

It is important to remember to outline sphincteric defects when injecting bulking agents transurethrally. Injections into the remaining rhabdosphincter in male patients may even aggravate incontinence postoperatively.

The insertion of the needle in the urethra may cause lacerations of the urethral mucosa with subsequent bleeding and blurred vision.

RESULTS

Many urologists have abandoned the use of Teflon in recent years due to disappointing long-term results and severe co-morbidity related to distant migration end ensuing embolization of the particles (5,7). Collagen has replaced Teflon over the last 10 years, and has definitely increased the safety of submucosal urethral injections (25). In a multicenter trial injection related transient urinary retention in women was observed in 8%, urinary tract infection in 6%, hematoma formation at the injection site in 2%, and pain in 1% (25). Hypersensitivity reaction to the collagen material, however, is possible, and a skin test prior to the injection is mandated (12).
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 Cure and improvement rates with submucous collagen in male patients with stress incontinence due to exstrophy/epispadias complex or prior radical prostatectomy ranges from 21-25% and 53-70%, respectively (32-34). In female patients 23 – 48% and 40 – 68% are being reported as cured and improved, respectively (25, 35-37) (Table).

 Due to an average silicone particle size of 150 µm in the clinically used preparation neither migration nor any migratory-related adverse effects have been observed.

 Whether dextranomer microspheres suspended in a sodium hyaluronan solution (10) are going to be superior to any currently used agent with regard to continence, durability and side effects, needs to be demonstrated in larger studies.

 The most extensively studied autologous substance to date is fat (13,27,43,44). Its advantages are that autologous fat is absolutely biocompatible, readily available, and inexpensive. The drawback is that in the long-term 10-50% of the injected fat will survive, repeated injections may become necessary, and extensive periurethral scarring may result.

 Table - Results of most recent studies of various bulking agents used in male and female patients with stress urinary incontinence. F = female, M = male, LA = local anesthesia, RP = radical prostatectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Agent</th>
<th>Sex</th>
<th># of pts.</th>
<th>follow-up (months)</th>
<th>% cured</th>
<th>% improved</th>
<th>Technique</th>
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<tr>
<td>Monga et al. (36)</td>
<td>1995</td>
<td>Collagen</td>
<td>F</td>
<td>60</td>
<td>&gt;24</td>
<td>48</td>
<td>68</td>
<td>LA, periurethral</td>
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<td>Collagen</td>
<td>M</td>
<td>19</td>
<td>26</td>
<td>53</td>
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<td>Exstrophy / epispadias pts.</td>
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<td>F</td>
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<td>23</td>
<td>52</td>
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</tr>
<tr>
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<td>Collagen</td>
<td>M</td>
<td>20</td>
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<td>25</td>
<td>70</td>
<td>Antegrade transvesical injection, prior RP</td>
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<td>19</td>
<td>10.4</td>
<td>21</td>
<td>58</td>
<td>Prior RP</td>
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<tr>
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<td>Collagen</td>
<td>F</td>
<td>111</td>
<td>&gt;24</td>
<td>25</td>
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<tr>
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<td>1999</td>
<td>Dextranomers</td>
<td>F</td>
<td>20</td>
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<td>85</td>
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<tr>
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<td>Autologous fat</td>
<td>M+F</td>
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<tr>
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<td>F</td>
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<td>50</td>
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<td>46</td>
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<td>M</td>
<td>12</td>
<td>11</td>
<td>25</td>
<td>75</td>
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FUTURE OUTLOOK

In order to overcome the problem of biocompatibility, migration, and short and long-term immunogenic reactions, the use of autologous tissues and cells was the focus of recent experimental studies (15). As outlined above autologous fat despite promising experimental results did not prove to be as good clinically.

A better option is apparently chondrocytes (17), which possess the ability to form viable cartilage. Chondrocytes are harvested from the patient’s auricular surfaces, submersed in an alginate polymer delivery vehicle, and injected submucosally into the urethra, where they are supposed to act as a stable bulking material. Its clinical applicability is currently assessed in a multicenter clinical trial in the United States.

Combining the technique of submucosal urethral injection with tissue engineering principles (45) may be an interesting variant. A possible advantage might not only be a permanent, perfectly biocompatible bulking material, but also a periurethral expansion of the injected cells. A further step could be to make bulking agents functional by provoking, e.g., nerve ingrowth. To date animal studies using autologous smooth muscle cells, myoblasts (16), and stem cells have been performed using various carrier substances. Stability of the implants, and surprising differentiation into viable muscle cells when using precursor cells, could be demonstrated. The material in which the cells are suspended prior to injection has to be carefully selected regarding a possible immunogenic reaction, maintenance of cell viability, and viscosity necessary for injection through a reasonably small needle. Whether bulking agents need to be injected through a needle at all is also a matter of debate. The authors of this paper currently undertake experiments with new injection modalities.

CONCLUSION

Treatment of intrinsic stress incontinence with endoscopic submucosal injection is an effective method and is the least invasive of all surgical procedures. New developments, especially in combination with tissue engineering, may render it as one of the primary treatment modalities for stress urinary incontinence in the future.

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