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REVIEW

Injectable treatments for female stress urinary incontinence

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Core tip: While there are different types of injection materials available, it is unknown which one is superior as few head to head studies have been performed between the newer agents. It is important to inform patients that treatment with injectable agents is not as effective as surgical treatment, and that such agents might necessitate additional and repeated administrations in order to achieve the desired therapeutic effect.

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Abstract

The use of injectable agents for the treatment of stress urinary incontinence (SUI) is an option for female patients who are unwilling to undergo surgery, or have concurrent conditions or diseases that render surgical treatment unsuitable. To be effective for SUI, an injectable agent must be nonimmunogenic, hypoallergenic, biocompatible, permanent, nonerosive, nonmigratory and painless. It must also heal with minimal fibrosis, possess a long-term bulking effect, and be easily stored and handled. Glutaraldehyde cross-linked bovine collagen (Contigen), silicone polymers (Macroplastique), Durasphere, calcium hydroxyapatite (Coaptite), polyacrylamide hydrogel (Aquamid, Bulkamid), Permacol, and stem cell therapy have been used as injectable agents. Patients must be informed that treatment with injectable agents is not as effective as surgical treatment, and that such agents might necessitate additional and repeated administrations in order to achieve the desired therapeutic effect.

Key words: Stress urinary incontinence; Injectable treatment; Bulking agent; Outcomes; Adverse events

INTRODUCTION

Injection treatment for female stress urinary incontinence (SUI) is not new. Murless[1] reported the first results in 1938, followed by Quackles[2] in 1955 and by Sachse[3] in 1963. In the 1970s and 1980s, polytetrafluoroethylene (Teflon) was used extensively. However, safety concerns that included distant particulate migration, foreign body reaction, severe granulomatosis reaction and possibly carcinogenic effects inhibited its usage[4,5]. In 2001, autologous fat was studied in women with urethral hypermobility but serious adverse events including systemic embolization and death were reported[6-8]. Dextranomer/hyaluronic acid copolymer (Deflux) was another agent used as a bulking agent, and while short term results were satisfactory, long term durability was poor[9,10]. Ethylene vinyl alcohol copolymer (Tegress), a permanent, hypoallergenic, nonimmunogenic implant demonstrated equivalence in outcomes with collagen and was approved by the Food and Drug Administration (FDA) in 2004[11,12]. However, a high rate of urethral erosion was noted and as a result, the manufacturer voluntarily withdrew Tegress from the market in 2007[13].

After glutaraldehyde cross-linked bovine collagen

(GAX-collagen) was introduced in 1993, it was reported as a safe and reliable endoscopic treatment option of SUI. Currently, collagen is the gold standard method in SUI treatment modalities[14]. To be effective against SUI, an injectable agent must be nonimmunogenic, hypoallergenic, biocompatible, permanent, nonerosive, nonmigratory and painless. It must also heal with minimal fibrosis, possess a long-term bulking effect, and be easily stored and handled[15-17]. It is important that the components of these agents remain structurally stable following administration. In addition, to preclude any significant risk of migration, the microcrystalline or micro polymer particles of such agents must have nearly spherical shapes, with diameters greater than 110 micrometers[15]. No agent to date has satisfied all these requirements and research continues on additional bulking materials and modes of delivery.

RESEARCH

We searched the Medline database for published articles, reviews and case reports between 2000 and 2013. The key words "stress urinary incontinence", "injectable treatment" and "bulking agent" were used for literature research. Three hundred and ninety nine abstracts were viewed, and many of these articles were chosen for review and inclusion.

MECHANISM OF ACTION

Although the exact mechanism is not understood, it is thought to improve the urethral sphincter function. Urethral mucosal surface expands with injection, augments urethral coaptation and consequently post injection abdominal leak point pressure (ALPP) increases[17]. Though originally thought to be primarily an obstructive effect, Monga *et al*[18] showed that the mechanism of action might be related to an expanded urethral area and better pressure passage on the proximal urethra. The bladder neck opening during stress maneuvers could be prevented by injection of the proximal urethra and bladder neck[19]. Klarskov *et al*[20] introduced urethral pressure reflectometry, a technique for measuring pressure and cross sectional area in the urethra, which provides parameters useful for studying the mechanism of action of urethral injection therapy. The authors found that the group who showed subjective improvement after injection therapy had significantly higher squeezing opening pressure compared with the group that didn't improve. They concluded the bulking material might function as additional central filler volume which increase the length of the muscle fiber and thereby the power of the sphincter[20].

PATIENT SELECTION CRITERIA

Patients normally considered for intraurethral bulking include females with SUI attributed to intrinsic sphincter deficiency (ISD) and a urethral mobility below 30 degrees. However, various studies have demonstrated that intraurethral bulking is also effective for patients affected by urethral hypermobility[21]. Herschorn *et al*[22] previously demonstrated the absence of any significance difference between patients with urethral hypermobility and patients without urethral hypermobility. Overall, the dry rate at 1 year, 2 years and 3 years were 72%, 57% and 45%, respectively. Others have demonstrated similar results[23-25].

Intraurethral bulking agents are a good choice for patients who do not desire to undergo more invasive surgery and who comprehend that efficacy and durability are inferior to surgery[26]. Bulking agents should not be offered to patients who are seeking a permanent therapy for SUI[27]. Potential candidates for bulking agents are: the elderly; those who are a high anesthetic risk; those who are at an increased risk of urinary retention after a sling operation; those who are on anticoagulation therapy; those who desire to have children; those who have mild persistent SUI after an incontinence surgery; those who have SUI and insufficient bladder emptying; those who have mild SUI after exercise; those who don't want more invasive procedures; and those who are content with improvement instead of a cure[16].

For intraurethral bulking, exclusion criteria include urinary tract infections, hypersensitivity reactions to the bulking agent, and urinary incontinence caused by abnormal detrusor contractions[28].

INJECTION TECHNIQUES

Bulking agents are generally administered with cystoscopic assistance under local anesthesia. The implant can be administered *via* the urethral submucosa or lamina propria by transvaginal, transurethral or periurethral approaches. Currently the transurethral approach is the most preferred technique[28]. During implantation, it is very important to place the bulking material into the proximal urethral wall near the bladder neck. The amount of material needed for injection is the volume that achieves complete coaptation.

Before commencing the injection procedure, the patients are positioned in dorsal lithotomy, and prepared in accordance to the applicable sterile procedures. To prevent any infections, antibiotics are usually administered both before and after the procedure. During the procedure, a 20% benzocaine ointment can be applied to the vulvar vestibule as a local anesthetic. A 2% lidocaine jelly can also be administered intraurethrally. Perimeatal blebs are raised with 1% or 2% lidocaine at the 3- and 9-o'clock or 4- and 8-o'clock positions, 3 to 4 mm lateral to the urethral meatus using a 25-gauge needle, followed by 4 mL of 1% or 2% lidocaine injected periurethrally. The cystourethroscope is inserted and the bladder is inspected. After the bladder is emptied, the endoscope is backed to the mid-urethra with an irrigation rate just enough for visibility. Generally the 3- and 9-o'clock or 4- and 8-o'clock positions are preferred area for injection[29]. For the initial injection, the 6-o'clock position is often an ideal starting

Table 1 Level of evidence and grade of recommendation for injectable agents (b)

Evidence summary	LE
Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 mo), but not cure, in women with SUI	2a
Repeat injections to achieve therapeutic effect are often required	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI	2a
Adverse effect rates are lower compared to open surgery	2a
There is no evidence that one type of bulking agent is better than another type	1b
Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route	2b
Recommendations	GR
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence	A

LE: Level of evidence; GR: Grade of recommendation; SUI: Stress urinary incontinence.

point[28]. The needle diameter is dependent on the viscosity of the injected material. The patient can be instructed to perform a valsalva maneuver after injection and if urine leakage is still present, additional material may be injected[28-30].

Faerber *et al*[31] previously performed a review of the transurethral and periurethral techniques for ISD treatment and found both techniques were similar with respect to treatment outcome and the occurrence of adverse events. It was noted, however, that the transurethral technique involved the injection of smaller amounts of material[31]. Likewise, in a prospective and randomized study performed by Schulz *et al*[32], it was observed that the transurethral and periurethral techniques were similar with respect to efficacy however, it was also observed that the periurethral group required the injection of larger volumes of material as well as exhibited a higher rate of urinary retention[32]. Thus, the periurethral technique appears to require higher volumes of material than the transurethral technique, while also requiring more time to be learned effectively. This is important as higher volumes are associated with higher costs, and may increase the potential for postoperative complications.

INJECTABLE AGENTS

Many different agents have been studied for use as bulking material with varying success and adverse events. Patients should be informed that surgery is associated with greater improvement of symptoms, but at the expense of higher risks. Patients should also be informed that treatment with injectable agents is less durable and repeated injections will likely be needed to maintain effect. Cochrane systemic review did not show significant differences in clinical outcomes and complications between different injectable agents[33,34]. Table 1 list the level of evidence and grade of recommendation for injectable therapies for SUI in women by European Association of Urology guidelines[27].

Biomaterials

GAX-collagen: GAX-collagen is produced by cross-linking bovine collagen with glutaraldehyde. The resulting substance is a highly stable collagen complex with a fibrillar structure. This structure confers GAX-collagen resistance to enzymatic breakdown by collagenases, thus increasing the durability of the implant[35]. Contigen is composed of 1%-5% collagen type Ⅲ, and approximately 95% of collagen type Ⅰ [36]. It was available as pre-filled syringes containing 2.5 mL of agent and which needed storage in the refrigerator. Injection was performed with 23 G injection needle through the cystoscope. A volume of 30 mL injection material may be necessary to ensure enough urethral coaptation during the operation[29]. Since GAX-collagen is both biocompatible and biodegradable, only minimal inflammatory changes occur[37]. It is not known to migrate. Although the collagen in GAX-collagen begins to denature by the 12th week of application, it can persist for up to 19 mo[38].

GAX-collagen is a widely used injectable agent and there are numerous studies pertaining to its efficacy and safety[39,40]. It has been considered the gold standard of urethral bulking material such that the FDA required direct comparison to collagen for any new bulking agents in clinical trials[14]. In the North American study group, 382 patients were followed for 2 years, with improvement and cure rates determined as 45% and 33% respectively. The dryness rate at the end of the first-year was 52% but dropped to 38% in the second year[41]. Many patients required repeat injections to maintain efficacy[42]. In a study by Winters *et al*[17], it was observed that 45% of the treated elderly women showed discernible improvement up to 24.4 mo post treatment; however, more injections were required to maintain efficacy in 40% of the patients after an average of 7.9 mo. Corcos *et al*[43] reported that GAX-collagen cured approximately 30% of the women, while improving the condition of 40% of the women in a study group of 40 women at 50 mo of follow up. However, they also reported that four of the women who were cured and five of the women who showed improvement later required "maintenance" injections.

Only a limited number of side effects are associated with GAX-collagen treatment[44]. Clinical trials in the United States have reported transient urinary retention among 15% of the patients, urinary tract infections (UTIs) among 5% of the patients, and irritative voiding syndrome among 1% of the patients[45]. *De novo* urgency as high as 10% has also been reported in certain studies[43]. Due to the minute amounts of GAX-collagen injected to the patients during treatment, the substance is not associated with any signifi-

cant immunoreactivity and cytotoxicity[46]. For this reason, no previous cases of migration or foreign-body responses have been reported with the GAX-collagen.

Importantly, GAX-collagen has the potential to trigger an allergic reaction to bovine protein in patients. For this reason, all patients are required to undergo an allergy skin test 30 d prior to treatment. In general, 3% of the patients are expected to exhibit a positive allergy result. Nearly 70% of such patients will display an allergic reaction within 3 d following the test, which indicates that their allergy to bovine collagen is pre-existing through dietary exposure. The other 30% of the patients will take longer to display any reaction, which may take up to 4 wk. Patients who display a positive allergy test result will not be able to receive GAX-collagen treatment. However, it is still possibly for patients with a negative allergy test result to later display an allergic reaction during and after GAX-collagen administration[47].

Owing to its lack of migration, its degradability and its limited allergenic potential, GAX-collagen is the most popular and widely used intraurethral bulking agent for the treatment of urinary incontinence[14]. However, despite its long track record, although with modest results, the manufacturer ceased production in 2011 and the implant is no longer available.

Synthetic materials

Silicone polymers (macroplastique): Macroplastique (Uroplasty Inc, Minneapolis, MN, United States) is composed of vulcanized polydimethylsiloxane macroparticles suspended in a hydrogel of polyvinylpyrrolidone (povidone). This hydrogel also functions as a lubricant during injection[48]. It has been in use in Europe for SUI since 1996. The material consists of particulates of various shapes and sizes with marked variability but 99% of the particles are greater than 100 μm. However, the potential for migration is present, though remote. Henly *et al*[49] identified small macroplastique particles within the lymph nodes, kidneys, lungs and brain of dogs within 4 mo following administration. Large particles, on the other hand, were identified in the lungs of only one case but without associated reaction[49].

Marcoplastique can be injected with standard cystoscopic equipment but since the substance is fairly viscous, it requires a high pressure 18-gauge Uroplasty needle gun for administration. Alternatively, non-endoscopic transurethral injection device, the Macroplastique Implantation System (MIS) can be used. The MIS consists of a multichannel needle positioning device that is oriented at the 2-, 6-, and 10-o'clock positions for injection. Henalla *et al*[50] noted successful results (74.3%) at the three months follow-up. Tamanini *et al*[51] published the results of 21 patients treated with MIS and at the 12 mo follow-up, an improvement was reported in 57% of the patients, but 23% of patients were deemed failures. ter Meulen *et al*[52] analyzed the efficacy of MIS in women with SUI and urethral hypermobility after an unsuccessful conservative treatment. Twenty-four women received Macroplastique *via* MIS compared with 21 patients who underwent a pelvic floor muscle exercise program. Decreased pad usage and improved questionnaire scores were seen in the MIS group ($P = 0.017$, $P = 0.015$, respectively)[52].

A recent North American multicenter trial randomized 247 patients with ISD to transurethral injection of either Macroplastique or Contigen. After 12 mo, there were significant clinical improvement and dry/cure rates in 61.5% and 36.9% of patients treated with macroplastique *vs* 48% and 24.8% of patients treated with Contigen, respectively. This indicated that macroplastique was non-inferior to Contigen ($P < 0.001$)[53]. In a randomized study by Maher *et al*[54], macroplastique was compared with pubovaginal sling. At the 12 mo follow-up, subjective success rates were 90% in the sling group and 77% in Macroplastique group ($P = 0.41$), and there was no differences between the two groups in patient satisfaction. The authors emphasized the obvious advantages of macroplastique in terms of shorter operative time, less blood loss and shorter hospitalization time.

Complications associated with macroplastique use include urinary retention (5.9%-17.5% of cases), urinary frequency (0%-72.4%, of cases), dysuria (0%-100% of cases), and UTI (0%-6.25% of cases)[55].

Durasphere

Durasphere consists of nonabsorbable zirconium oxide beads coated with pyrolytic carbon, and suspended in a water-gel with 2.8% beta-glucan. It gained FDA approval for use in patients with ISD in 1999[28]. During administration, the zirconium oxide beads are encapsulated by the periurethral tissues[56], which allows it to have a long-lasting bulking effect. In contrast to GAX-collagen, Durasphere is nonimmunogenic and inert. Thus, skin testing with this agent is not necessary prior to administration. Durasphere was designed with larger caliber particles (> 80 μm) to prevent migration. The size of the beads varies between 212-500 μm which contributes to its higher viscosity. As a result, the injection of Durasphere is often more difficult. To overcome this difficulty, an alternative injection method was developed for Durasphere, which involves the injection of local anesthetic to raise a circumferential bleb into which agent was injected[57]. Additionally, as a way to remedy this, the manufacturer introduced Durasphere EXP (Injectable Bulking Agent from Carbon Medical Technologies Inc.) in 2006, whose smaller bead size (range 90 to 212 μm), facilitated injection. However, the size of these particles is still greater than the threshold for migration. As of late 2013, no clinical results have been published with this new formulation.

In a multicenter, randomized, controlled, double-blind study consisting of 355 patients, Lightner *et al*[56] reported that Durasphere was as effective as GAX-collagen. The authors emphasized that the Durasphere group required significantly less volume of injected material to obtain comparable clinical results (4.83 mL *vs* 6.23 mL, $P < 0.001$), and that the probability of achieving successful treatment

with a single injection was higher for the Durasphere group. At the one year follow-up, the ratio of patients that demonstrated an improvement of one Stamey grade or more in the Durasphere and the GAX-collagen groups were 80% and 69%, respectively[56]. Long-term data have been reported by Chrouser *et al*[58], and they observed a decrease in clinical success over time. For the Durasphere group, the success rate for treatment was 63% at one year, 33% in the second year, and 21% in the third year follow-up. For the collagen group, the success rate was 19% in the second year, and 9% in the third year follow-up[58].

In the clinical studies that served as the basis for the FDA approval, the most commonly observed adverse effects included acute retention for ≤ 7 (13% of subjects), dysuria (12% of subjects), UTI (9% of subjects), hematuria (6% of subjects), and retention for > 7 d (6% of subjects)[59]. In a randomized multicentre clinical study comparing Durasphere and GAX-collagen, adverse events were similar between the two groups, except for a higher incidence of urgency and acute retention in the Durasphere group (24.7% and 16.9%, respectively) than in the collagen group (11.9% and 3.4%, respectively)[56]. There have also been case reports of pseudo abscess formation and urethral prolapse[60,61]. Distant particle migration has been reported with the original Durasphere formulation, which raised concern since its bead sizes ranged from 212 to 500 μm, higher than the threshold thought to be critical for migration. With its smaller bead sizes (range 90 to 212 μm), it is unknown whether the risk for migration is increased with Durasphere EXP[62].

Calcium hydroxyapatite (Coaptite)

Calcium hydroxyapatite received its first approval for the treatment of SUI in women in 2005. Calcium hydroxyapatite is a synthetic substance composed of glycerin and carboxymethylcellulose, and which structurally forms an aqueous gel. The spherical calcium hydroxyapatite particles have an average diameter of 100 μm (75-125 μm), which is above the threshold for migration[28]. The gel facilitates injection and provides the initial bulking effect but is designed to degrade over time, and allowing for ingrowth of tissue around the particles. Calcium hydroxyapatite is a natural component of teeth and bones; it has hence been used in orthopedic and dental applications, and also in the ureteral orifice for vesicoureteral reflux, with excellent biocompatibility[63,64]. It is not antigenic, immunogenic or toxigenic and thus a pre-procedure skin test for hypersensitivity is not needed. Refrigeration or special handling are not required[63,64]. Because the material is not viscous, it can be performed with a 21 G injection needle. Since calcium hydroxyapatite is radiopaque, it can be seen on ultrasonography or fluoroscopy, which may aid in accurate localization and placement[14].

In the first pilot study with calcium hydroxyapatite, Mayer *et al*[65] reported a reduction in average pad weight, a reduction of 45% in pad usage, and an increase in average ALPP from 39 to 46 cm H_2O at the 12 mo follow-up. Seven patients needed a second injection after 8.4 mo[65]. In the data leading up to FDA approval, there was no significant difference in quality of life, pad weight or Stamey grade change between coaptite and collagen at a mean follow-up of 11.2 mo[66]. In a large multicenter randomized clinical study, Mayer *et al*[65] compared Coaptite *vs* collagen in 296 women with ISD and demonstrated, at the 12 mo follow-up, an improvement of one or more Stamey grade in 63.4% of the Coaptite group and 57% of the collagen group (P = 0.34). There was no difference in cure rates (39% Coaptite *vs* 37% collagen). More patients in the Coaptite group required only one injection (38%) compared with the collagen group (26.1%) (P = 0.03) and the mean injected volume was lower (4.0 mL *vs* 6.6 mL, $P < 0.0001$)[67].

Common adverse associated with calcium hydroxyapatite are urinary retention (41% of patients), hematuria (19.6% of patients), dysuria (15.2% of patients), UTI (8.3% of patients), urinary urgency (7.6% of patients), urinary frequency (7.0% of patients), and urge incontinence (5.7% of patients). The overall erosion rate was 1.3%[49]. Palma *et al*[68] published a case with urethral prolapse 3 mo after calcium hydroxyapatite injection therapy. The prolapsed nodule was surgically extracted and the resulting pathology reported lymphocytic infiltration, giant cells and granulomatous reaction characterized with macrophages[68].

Polyacrylamide hydrogel (Aquamid, Bulkamid)

Aquamid and Bulkamid are polyacrylamide hydrogels composed of 2.5% polyacrylamide that are nontoxigenic. They possess a homogeneous composition and texture, presenting elasticity and viscosity properties similar to tissue. They contain no solid particles, thereby eliminating any risk of particle migration[28]. Aquamid is used clinically as soft tissue filler in plastic surgery and reconstructive procedures[69]. Bulkamid is the corresponding product for the SUI indication. It does not need refrigeration or any special handling[16]. Bulkamid and Aquamid are currently not approved for use in the United States; however, randomized clinical studies involving numerous centers are currently being conducted in both Europe and North America. Toozs-Hobson *et al*[70] reported a noncomparative, multicenter case series of 135 women in 2010. Half the patients had mixed urinary incontinence. At 12 mo, two-thirds of the women reported being cured or improved, and there were significant reductions in incontinence episodes per 24 h and pad weight testing. Efficacy was similar between patients with pure SUI and those with mixed incontinence. There was a 35% reinjection rate. Minor adverse events were noted and included UTI (5%), transient urinary retention (3%), hematuria (1%), transient *de novo* urgency and urge incontinence (1%)[65]. In the 2 years follow up analysis of this cohort, there was durability of success with 64% of women cure/improved, which was not significantly different compared with the 12 mo data[70].

In a recent prospective, multicenter study Sokol *et al*[71] randomized 345 women with SUI or stress predominate

mixed incontinence to Bulkamid or Contigen and a > 50% reduction in leakage and incontinence episodes was seen in 53.2% of the Bulkamid group *vs* 55.4% of the Contigen group at 12 mo. Additionally, at 12 mo, 47.2% of the Bulkamid patients and 50% of the Contigen patients reported no SUI episodes. Seventy seven percent of the Bulkamid patients and 70% of the Collagen patients considered themselves cured or improved. The authors concluded that Bulkamid is not inferior to Contigen and is a promising new simple office based bulking agent for women with SUI, particularly since Contigen is no longer commercially available[71].

Permacol

Permacol is a dermal implant made from non-reconstituted collagen obtained from porcine skin. Until now, it has been mainly used for pelvic reconstruction and hernia repair. Non-collagenous material, except elastin, is removed and a cross linking process is performed. It maintains its 3-dimensional structure and when implanted, it allows for in-growth of new tissue, which can potentially be permanent. Permacol is non-allergenic, obviating the need for skin hypersensitivity testing[72].

Bano *et al*[73] compared Permacol and Macroplastique in a randomized controlled trial that included 50 women with urodynamic SUI. A great majority of the injections (84%) were performed peri-urethrally in the Permacol group. At 6 mo, 62.5% in the Permacol group were dry *vs* 37.5% in the Macroplastique group but no statistical analysis was reported. Rates of adverse events were similar between both groups[73].

Future directions

Stem cell therapy: Recently, within the context of tissue engineering strategies, stem cell therapy was evaluated for the experimental treatment of SUI[74,75]. The first report evaluating the safety and efficacy of cell therapy in humans yielded an 81.3% cure/improved rate at 12 mo[76]. Multiple small series have been published since but none generated as much excitement as the study by Strasser *et al*[77], which demonstrated very impressive outcomes from sphincteric injection of autologous myoblasts compared with collagen in a randomized trial[77]. This article was later retracted due to ethical violations and investigators question whether this trial as described ever existed. Most recently, Stangel-Wojcikiewicz *et al*[78] reported a case series of 16 women who had sphincteric injection of muscle derived stem cells with a cure/improved rate of 75% at 2 years of follow-up. There were no adverse events from either the deltoid muscle biopsy or from the injection[78]. Cook MyoSite, a part of Cook Medical, has two active clinical trials underway with intrasphincteric injections of autologous muscle-derived cells for the treatment of SUI. While still considered experimental, stem cell therapy holds great promise and in the near future may very well be an additional option in therapy for the treatment of SUI[79]. The clinical trials on injectable treatments for female SUI is shown on Table 2.

POSTOPERATIVE PERIOD

It is rare to observe postoperative complications immediately following the administration of injectable treatments. Once the injection procedure is completed, patients must be capable of voiding without difficulty. In the unlikely case of post operative urinary retention, a Foley catheter should be avoided, as is possible for the bulking agent to become molded around the catheter, and to thus lose its effectiveness. However, it should be noted that there is currently no data or findings indicating that short-term use of catheters might adversely affect intraurethral bulking. For patients that require catheterization for longer periods, it is preferable to use suprapubic catheters in order to prevent the bulking agent's position or efficacy from being affected.

For most patients, multiple treatments with injectable agents will be necessary before achieving the desired therapeutic effect. Each bulking agent requires different time intervals between successive treatments. For instance, GAX-collagen can be administered once every 7 d (although a 4 wk time interval was used in the initial clinical studies with GAX-collagen); however, in order to better evaluate the patient response to the injections, many physicians prefer to wait for 4 or more weeks before continuing with the next injection[23]. Teflon requires a 4-mo waiting period, while Macroplastique injections can be performed at 12-wk intervals. Durasphere injections require a minimum time interval of 7 d, while Coaptite can be injected once every month. In case erosion is observed within the bladder during repeat injections, the eroded side should not be reused for injection purposes until the epithelium recovers[23].

CONCLUSION

Injectable agents represent an effective and safe approach for treating SUI in women. They should especially be considered for female patients who are unwilling to undergo surgery, or have concurrent conditions or diseases that render surgical treatment unsuitable. It must be remembered that injection treatments will mainly serve to improve the patients' symptoms, and that they will not provide a definite cure for SUI. It is also important to inform patients that treatment with injectable agents is not as effective as surgical treatment, and that such agents might necessitate additional and repeated administrations in order to achieve the desired therapeutic effect. Although there are different types of injection materials with different properties, the superiority of one agent over another is not known. There is thus a continuous search for effective, inert, nonmigratory and nonimmunogenic materials that can be readily injected and incorporated into the patient's tissues, and that can maintain their structure for extended periods of time once injected.

Table 2 The clinical trials on injectable treatments for female stress urinary incontinence

Ref.	Bulking agents	Number of patients	Assessment methods	Outcomes
Lightner *et al*[56]	Durasphere *vs* Collagen	*n* = 61 (Durasphere) *n* = 68 (Collagen)	SUIS Standardized pad test	At the one year follow up, the Durasphere group achieved improvement in one Stamey grade or more in 80.3% of patients compared to 69.1% of patients in the Collagen group (P = 0.162)
Chrouser *et al*[58]	Durasphere *vs* Contigen	*n* = 43 (Durasphere) *n* = 43 (Contigen)	Patient satisfaction and continence were subjectively evaluated *via* telephone interview	Success rateswere reported in 33% of Durasphere group and 19% in Contigen at 24 mo; at 36 mo, 21% in Durasphere, 9% in Contigen No significant difference was observed in time to failure between the injection groups (P = 0.25)
Bano *et al*[73]	Permacol *vs* Macroplastique	*n* = 25 (Permacol) *n* = 25 (Macroplastique)	1-h pad test SUIS KCQ	At 6 mo, 62.5% in the Permacol group were dry *vs* 37.5% in the Macroplastique group but no statistical analysis was reported
Hurtado *et al*[13]	Tegress	*n* = 19	Physical exam Urodynamic findings Complications	A 58% of the patients had a complication related to the procedure with 37% experiencing urethral erosion 10.5% of the patients reported at least a 50% subjective improvement
Mayer *et al*[67]	Coaptite *vs* Collagen	*n* = 131 (Coaptite) *n* = 100 (Collagen)	SUIS	Improvement of one or more Stamey grade was showed 63.4% in Coaptite group and 57% in the Collagen group, at 12 mo follow-up (P = 0.34) More patients in the Coaptite group required only one injection (38%) compared with the Collagen group (26.1%) (P = 0.03)
Ghoniem *et al*[53]	Macroplastique *vs* Contigen	*n* = 122 (Macroplastique) *n* = 125 (Contigen)	SUIS 1-h pad test Urinary Incontinence QoL Scale scores	After 12 mo, improved 1 or more Stamey grade and dry/cure rates were determined in 61.5% and 36.9% of patients treated with Macroplastique, *vs* 48% and 24.8% of patients treated with Contigen, respectively (P < 0.05)
Toozs-Hobson *et al*[70]	Bulkamid	*n* = 135	24-h pad weighting test 3-d micturition diary ICIQ score QoL score VAS score	There was durability of success with 64% of women cure/improved, which was not significantly different compared with the 12 mo data
Sokol *et al*[71]	Bulkamid *vs* Contigen	*n* = 229 (Bulkamid) *n* = 116 (Contigen)	Bladder diaries QoL questionnaire Pad weight testing VLPP	47.2% of Bulkamid patients and 50% of Contigen patients reported no SUI episodes 77.1% of Bulkamid patients and 70% of Collagen patients reported improvement or cure

SUIS: Stamey urinary incontinence scale; KCQ: Kings college hospital quality of health questionnaire; QoL: Quality of life; SUI: Stress urinary incontinence; ICIQ: International consultation on incontinence questionnaire; VAS: Visual analogue scale; VLPP: Valsalva leak point pressure.

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