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Review Article

Update on Urethral Bulking Agents for Female Stress Urinary Incontinence due to Intrinsic Sphincter Deficiency

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Abstract

Urethral Bulking Agent (UBA) injection is currently the second most commonly performed procedure for the treatment of Stress Urinary Incontinence (SUI). It is second only to urethral sling placement. UBA injection is used for incontinence caused by Intrinsic Sphincter Deficiency (ISD). The search for an ideal bulking agent continues, however many agents have been proposed and tested while several of them have been removed from the market due to safety concerns. Currently, there are three UBAs available for use in the United States, with varied efficacy, durability, and location of administration that has been noted in the literature. This review provides an update of the current UBAs marketed in the United States while maintaining a clinical perspective on the injection procedure of UBAs in the outpatient office setting. Future directions and potential developments are discussed and demonstrate the promising future treatment of SUI due to ISD.

ABBREVIATIONS

SUI: Stress Urinary Incontinence; ISD: Intrinsic Sphincter Deficiency; UBA: Urethral Bulking Agent

INTRODUCTION

Background

Stress Urinary Incontinence (SUI) is a socially taxing condition that is the major type of involuntary urine loss in adult women [1,2]. SUI is caused by weakening of pelvic floor muscles, the urethra or the supporting ligaments of the urethra. Such weakness results in involuntary passing of the urine when intra-abdominal pressure increases, such as during coughing, laughing and sneezing. Using fluorourodynamics, McGuire recognized a different etiology to SUI due to dysfunction of the internal urethral sphincter and called it Type III. Intrinsic Sphincter Deficiency (ISD) or Type III is seen in patients who have little or absent motility of the urethra during the Valsalva maneuver, leakage at smaller increases in abdominal pressure, and often have abnormal opening of the proximal urethral sphincter [3]. The most common treatment methods for SUI due to ISD include urethral sling placement and Urethral Bulking Agents (UBAs). The latter treatment method was initially suggested as a salvage minimally invasive procedure for women with devastated bladder outlet, typically after undergoing many pelvic surgical procedures and/or pelvic radiation therapy. Because of its minimally invasive nature, it was also used in frail, elderly patients and patients experiencing complications with procedures requiring general anesthesia [4].

History

Injection of the urethra to treat urinary incontinence has been performed since 1938. A number of materials, including polytetrafluoroethylene (Polytef paste), glutaraldehyde cross-linked collagen, silicone and autologous fat, have been utilized following the initial substance injected, sodium morrhuate [5]. Many of these bulking agents fell out of favor secondary to their specific complications. Currently, there are three UBAs available in the United States: Durasphere®, Coaptite®, and Macroplastique®. Since their introduction to the United States market, UBAs have become increasingly used as a secondary method of treatment, mainly due to the greater effectiveness of sling surgeries [6].

USE OF UBAS IN THE MEDICARE POPULATION

Due to the fact that SUI affects 10%-35% of Americans over 65 years old, it is important to assess the change in surgical management of SUI in Medicare patients over the years [7]. In the past two decades, surgical procedures for the treatment of SUI have more than doubled [8,9]. Interestingly, the prevalence of specific procedures has fluctuated, from popularity in needle suspension in 1992 and 1995 to collagen injections in 1998 to

sling placement in 1995-2001 [8]. Despite the modest decline in use of UBAs to manage SUI from 2002-2007, injection of bulking agents was the most common procedure performed second only to urethral slings [9]. The reported prevalence of procedures among the Medicare population between 2002-2007 was 63.4% for pubovaginal slings, 24.0% for injectable bulking agents, 5.8% for hysterectomy with colpo-urethropexy, 4.1% for urethropexy, 1.2% for laparoscopic repair, 1% for Raz-type suspension, 0.3% for Kelly plication, and 0.2% for Pereyra procedure [9]. The treatment method chosen by patients seems to be affected by a number of factors including age, distress over SUI symptoms and quality of life. In their study on women's expectations for treatment of SUI, Langford et al found that older women (mean age of 61.7) more often chose to undergo a clinical procedure, such as injection of a bulking agent, despite the lower cure rate [1]. In the United States, rapid growth of the older population is expected to occur between 2010 and 2050 [10]. By 2050, the number of Americans aged 65 and older is anticipated to reach 88.5 million, doubling from 40.2 million in 2010. This increase in the older population is mainly attributed to the baby boomers (born between 1946 and 1964), who began entering into this category in 2011. This finding demonstrates the likelihood of UBAs remaining as one of the primary treatments among the older population.

THE IDEAL BULKING AGENT

The objective of UBA injections is to restore mucosal seal and coaptation and to increase urethral resistance in order to decrease urinary leakage. To achieve this end effectively, the UBA should increase the urethral closure while minimizing the effect on voiding pressures. It is also believed that UBA injection can increase the length of the posterior urethra, allowing more transmission of pressure to the urethra during stress. Increased abdominal leak point pressure after treatment was demonstrated in different studies [11]. Two main types of substances have been utilized as bulking agents. Biological UBAs are either cellular membranes that are from autologous, allogenic or xenogeneic sources or cellular, such as fat, chondrocytes and stem cells. Synthetic UBAs are commonly inert polymers. Whether biologically or synthetically based, the ideal bulking agent should be soft, easy to inject, nonimmunogenic, hypoallergenic, biocompatible and durable. In order to prevent its migration from the injected location, the particle size should be greater than 80μm and preferably over 110μm. It should also exhibit adequate wound-healing characteristics while minimizing fibrotic in growth and inflammatory response [5,12-13]. If the outcome of injection is not satisfactory, it should not interfere with subsequent surgical management of SUI.

Bulking agents

In the United States: Currently, there are three injectable bulking agents approved by the Food and Drug Administration (FDA) available on the market in the United States: carbon-coated beads (Durasphere®, American Medical Systems, MN), calcium hydroxylapatite particles in a gel carrier (Coaptite®, Boston Scientific, Boston, MA) and polydimethylsiloxane (silicone; Macroplastique®, Uroplasty, Inc., Minnetonka, MN). Two other UBAs were recently taken off the market. Although approved by the FDA for treatment of stress urinary incontinence due to internal sphincter deficiency, cross-linked collagen (Contigen®) was discontinued in 2011 by the manufacturer. Additionally, ethylene vinyl alcohol copolymer implants (Uryx®/Tegress, Bard Urological, Covington, GA) was voluntarily withdrawn from the market due to safety issues, specifically as it was found to increase dysuria and urethral sloughing at the site of injection [14]. A dextranomer/hyaluronic acid copolymer (Zuidex®) multicenter study was also voluntarily stopped in the United States secondary to increased incidence of sterile abscess formation [15].

Carbon-coated beads (Durasphere®): Durasphere is made of zirconium beads that are carbon-coated and suspended in a polysaccharide gel. Its durability and large particle diameter (more than 100m) has made it comparable to collagen as a UBA. In their randomized, double-blind study, Lightner et al compared the effectiveness and durability of treatment for stress urinary incontinence due to intrinsic sphincter deficiency [16]. They found that following 12 months of the last injection date, 80.3% of patients who received treatment with Durasphere showed improvement of continence while 69.1% of those treated with bovine collagen showed improved results. Of note however, patients treated with Durasphere had a greater risk of urgency and urinary retention [16].

Calcium hydroxylapatite (Coaptite®): Coaptite is a synthetic UBA that is made up of calcium hydroxylapatite bioceramic microspheres immersed in an aqueous gel. Coaptite is comparable to collagen in terms of improvement of patient continence symptoms, demonstrated in the 231-patient, randomized trial conducted by Mayer et al [17]. In this study, 63.4% of patients who received Coaptite injections demonstrated improved continence 12 months following the treatment compared to 57.0% of patients who received bovine collagen injections [17].

Silicone (Macroplastique®): Macroplastique is made up of silicone polymers, polydimethylsiloxane, that are immersed in a polyvinylpyrrolidone gel [18]. Its large particle diameter (>100μm) decreases the likelihood of particle migration, thereby lending itself to longer results for patients. A randomized trial by Ghoniem et al compared the cure rates of transurethral injection of Macroplastique or Contigen in 247 female patients with intrinsic sphincter deficiency [18]. Macroplastique proved to have greater improvement after their 12 months follow up (61.5%) versus patients who received Contigen injections (48%). Moreover, the 12-month follow up demonstrated a greater percentage of cured patients that had received Macroplastique injections (36.9%) versus patients injected with Contigen (24.8%) [18].

Around the world

Polyacrylamide hydrogel (Bulkamid®): Bulkamid is a synthetic hydrophilic gel made up of 2.5% cross-linked polyacrylamide with 97.5% non-pyrogenic water. It is biocompatible, durable, atoxic and has adequate viscosity when injected. A study measuring the durability of Bulkamid 24 months after the initial injection found that 94% of respondents had continued success rates [19]. A recent retrospective study assessed the effect of transurethral Bulkamid injection in

patients suffering from stress or mixed urinary incontinence. These patients had undergone surgery but the operation had failed to give them desired results. Retrospective evaluation showed that after 22 months following surgery, 45.1% of patients who had received Bulkamid injections experienced continued improvement or had no further complications and 15.7% of patients were completely dry [20].

INDICATIONS

Traditional

Despite the success of sling surgery for the treatment of SUI, UBAs are a beneficial treatment method for a number of patients who are not ideal candidates for surgery. Primary SUI patients may have comorbidities that do not make them good candidates for surgical repair of SUI. Such patients include the elderly who have a weakened urethra and women who have had vaginal deliveries. DeLancey explained this notion by demonstrating a progressive decrease in striated muscle cells in the urethra that reflected the decline in maximal urethral closure pressure as women age. Moreover, he noted that women who had two vaginal deliveries were over twice more likely to have SUI symptoms than their cesarean-section counterparts, strongly due to levator ani damage only occurring during vaginal birth [21]. Secondary SUI patients who have failed previous surgeries for SUI may also find relief by using UBAs. Moreover, patients of any age who are unwilling or not suitable to undergo surgery may also greatly benefit from UBAs as an alternative treatment of SUI symptoms.

Contemporary/Expanded

The fact that injection of UBAs is an office procedure makes it an appealing option for more contemporary patients. Potential candidates who may prefer the use of UBAs include women of childbearing age who wish to have more children so do not wish to undergo surgery and women under time constraints, such as athletes training for a specific event like a gymnastics competition. The use of UBAs does not stop here, as it can also serve as a supplemental technique for patients who have undergone a urethral sling procedure to correct urethral hypermobility but have incomplete results from continued ISD [18].

EVALUATION

The use of UBAs has been most effective for patients suffering from stress urinary incontinence due to intrinsic sphincter deficiency. In this condition, the bladder neck does not close properly; therefore, a high intraabdominal pressure can cause the contents of the bladder to leak involuntarily. Patients seeking relief for their incontinence symptoms undergo a physical assessment and may be asked to fill out a series of questionnaires to determine the duration and level of inconvenience of their symptoms. Objective assessment techniques characterize ISD by a very low or absent proximal urethral closure pressure (<15cmH_2O), low closing urethral pressure of 20cmH_2O and a Valsalva leak point pressure of <90mmHg [22-23], as determined by urodynamic studies. There is no standardized set of urodynamic values to diagnose SUI due to ISD; however, Pajoncini et al found that using both maximal urethral closure pressure and Valsalva leak point pressures as parameters to assess incontinence yields more accurate results in identifying patients with genuine stress incontinence [22].

Techniques

Transurethral injection: Once the patient has been diagnosed with ISD, UBAs can be utilized to alleviate stress incontinence symptoms. A common technique for injecting UBAs is transurethrally, which allows direct visualization of the urethra, thus theoretically leading to more accurate injection of the UBA using the tunneling technique [23]. As a result of this localization, less volume of bulking agent is needed for injection [24]. This technique may lend itself as being both more precise and more cost-effective in the long run. In transurethral injections, the cystoscope is placed midurethrally and the injection needle pierces the urethral wall at the proximal urethra about 1.5-2.0 cm distal to the bladder neck. Injection sites are often at the 3 o'clock, 6 o'clock and 9 o'clock positions in relation to the urethra. This technique allows the bulking agent to be localized at the bladder neck and proximal urethra [25]. The localized UBA increases the central filler volume of the urethra. Therefore, it elongates urethral striated muscle fiber length of the sphincter, thereby increasing the power with which the urethral lumen can close [26]. Shulz et al conducted a randomized comparison of transurethral versus periurethral injections of a bulking agent to determine which was more effective for the treatment of stress and mixed incontinence. They found that there was no significant difference in efficacy between the two techniques, however patients who received transurethral injections had a lower incidence of acute retention (5%) compared to periurethrally-injected patients (30%) [24]. This observation paralleled the findings of Faerger et al, who used collagen instead of dextran copolymer as the bulking agent [27].

Periurethral injection: Periurethral injection of bulking agents may seem more appealing than the transurethral technique due to its supposed evasion of mucosal leakage and less local trauma of the urethra [24]. In this technique, the injection needle that will deliver the UBA is inserted lateral to the urethral meatus with the assistance of a cystoscope. The needle is then moved within the urethral wall to the proximal urethra and bladder neck area and the UBA is injected, creating a bleb of raised mucosa. Similar injection is performed on the opposite side of the urethra laterally, often injected in the 3 o'clock and 9 o'clock positions. The desired outcome (coaptation of the blebs) is the same as that seen in the transurethral injection technique, excluding the fact that the number of injections and therefore blebs may differ. Injection of a methylene blue mixture before UBA injection has been proposed to be more accurate and less wasteful for the periurethral UBA injection technique [28]. Usage of a bent needle for injection has also been shown to enhance the ease and precision of periurethral injection [25,29].

Device-guided injection: Administration of the bulking agent has also been achieved via the usage of the Macroplastique implantation device, not yet approved for use in the United States. This device does not require an endoscope but rather, it allows administration of the UBA through three angled channel openings in the device. These equally-spaced channels open onto the appropriate location in the urethra where the UBA should be injected. As a result, when the implantation device is inserted into the urethra and the level of the bladder neck has been determined by fluid drainage, the UBA can be administered in

the correct urethral submucosal area. Henalla et al reported that the success rate using the Macroplastique implantation device was comparable to that in patients who used the endoscopic technique. Moreover, they determined that this procedure was more easily performed than its endoscopic counterpart and no prior experience with endoscopic injection was needed in order to perform the procedure successfully [30].

Perioperative care in an office setting

Before the UBA injection procedure, it is preferable for patients to be off anticoagulant medications for up to seven days prior to the procedure. They are also asked not to take ibuprofen for three days before the procedure. In addition, patients are commonly prescribed an oral broad-spectrum antibiotic three days following injection of the UBA, as a prophylactic measure. The patient is also instructed on how to perform self-catheterization, as temporary urinary retention may result following injection.

On the day of the procedure, avoided urine sample is taken to ensure the patient does not have an active urinary tract infection. Otherwise, the urethral bulking procedure must be postponed until after the infection has been treated. Injection of the bulking agent is performed under local anesthesia, typically with the injection of 1% lidocaine and 8.4% sodium bicarbonate [23]. Following the aforementioned cystoscopically-guided procedure of UBA injection either transurethrally or periurethrally, the patient is reassessed for urine leakage upon straining in order to ensure urethral coaptation is complete. The patient is then informed of the possible side effects or complications that may result due to the procedure and is instructed to drink six to eight glasses of water during the 24 hours following the procedure to prevent a urinary tract infection. Patients are also advised not to engage in sexual activity for at least one week to allow full healing of the urethral mucosa. A follow-up appointment is scheduled for one month after injection of the UBA.

Complications

The most commonly reported adverse effect following the injection of a UBA is urinary tract infections. Temporary urinary retention, urge incontinence and transient hematuria may also ensue [16-17,31]. Pain or discomfort in the urethra may follow the procedure and last for about 24 hours, while a slight burning sensation may also be sensed for 24 hours following the procedure [23]. Recurrent incontinence may occur, making it necessary for patients to be counseled on the repetitive nature of the UBA injection procedure.

Safety

In order for a bulking agent to be considered safe for use, there should be no indication of serious adverse effects such as the appearance of granulomas, abscesses, or erosion of urethral tissue. There should also be no migration of the bolus of bulking agent injected. Previous bulking agents were either withdrawn from the United States market or not approved by the FDA due to safety issues. Of these, autologous fat was discontinued due to evidence of migration of the particle, resulting in death of a patient due to pulmonary embolism [32]. Teflon (polytetrafluoroethylene), marketed under the name Polytef, was not approved by the FDA to be marketed due to evidence of particle migration to lymph nodes and distant organs, granuloma formation, and potential carcinogenic effects [33-34]. Urethral erosion due to injection of bulking agents has also been an issue that has caused the rejection of particular UBAs from being used. Tegress (also called Uryx), an ethylene vinyl alcohol copolymer, was one such agent that was discontinued in 2006. Rates of urethral erosion in subjects who had received Tegress injections were as high as 37% in female patients [35]. Zuidex, hyaluronic acid with dextranomer, also proved to cause formation of sterile abscesses and infections [15]. Two pivotal studies demonstrated that in addition to other complications, up to 15% of patients who were injected with Zuidex experienced pseudoabscess formation, due to the material itself rather than the injection technique or study design [36-37]. Unsurprisingly, it was withdrawn from the US market. Urethral prolapse is another complication of UBA injection found in previous literature, such as with the use of calcium hydroxylapatite and carbon beads [38]. However, although sparsely occurring, this complication has been noted with other bulking agents as well [39-40].

Effectiveness

In general, there is improved quality of life reported by patients who undergo urethral bulking agent injections for treatment of SUI due to intrinsic sphincter deficiency. Chapple et al found that reported levels of quality of life improvement following the procedure was comparable to that found in patients who had undergone surgery, despite the greater objective efficacy of surgery [41]. In general, open surgery for the treatment of SUI seems to have longer lasting effects 12 months after treatment compared to UBA injection therapy [42]. However, silicone particle injections have proven more beneficial than pelvic floor muscle training for improvement of incontinence symptoms [42].

Macroplastique is one of the most well studied urethral bulking agents currently available in the United States. Studies demonstrate that it has desirable durability for patients, as demonstrated by Ghoniem et al in their 2-year multicenter study results [43]. 84% of patients who were assessed for improvement after 12 months of receiving UBA injections were found to have continued improved results of incontinence. This result was reflected in sustained improvement results in Incontinence Quality of Life scores, pad weight, and in physician assessments of results after 24 months following treatment [43]. Ghoniem et al conducted a meta-analysis of the efficacy of Macroplastique for the treatment of SUI by reviewing the literature from 1990 to 2010 [31]. Their review, containing a total of 958 patients, demonstrated that 73% of patients showed improvement rates of their stress incontinence between 6-18 months following initial injection with the UBA. Furthermore, 64% of patients had continued improvement of symptoms at greater than 18 months follow-up from their initial injection [31]. The sustained improvement rates of the patients even after 18 months post-injection with Macroplastique validates the promising potential of this UBA as a durable agent.

To date, the effectiveness of Durasphere as a durable bulking agent has been variable. Results from a multicenter, randomized, double-blind study testing the carbon-coated zirconium agent demonstrated 80.3% improvement (improvement of 1 Stamey continence grade) 12 months following initial injection, among

the 61 women treated with this bulking agent [16]. These results were further supported by a long-term clinical trial that assessed the improvement of patients injected with Durasphere over the course of 2.6 years [44]. This clinical trial showed that 80% of those patients sustained an improvement of 1 continence grade or more. 40% of these patients were dry [44]. Nevertheless, Chrouser et al conducted a similar study over the course of over 4 years and found that only 33% of Durasphere patients remained effective 2 years after initial injection and merely 21% of patients showed continued improvement at 3 years follow-up [45]. Notably, there was an increased occurrence of transient urinary retention and urgency seen in Durasphere patients compared to the other test group who had been injected with bovine collagen [16].

The efficacy of calcium hydroxylapatite has also been tested. A multicenter randomized study followed 131 female patients with SUI due to intrinsic sphincter deficiency and without urethral hypermobility for 12 months following their injection with calcium hydroxylapatite (Coaptite) [17]. At 12 months follow-up of these patients, 63.4% of patients had sustained improvement and 39% remained cured (Stamey grade 0). These results were reaffirmed by decreased 24-hour pad weight at 12 months following the procedure. 62% of patients that received Coaptite injection had a 50% or greater decrease in their 24-hour pad weight [17], demonstrating the durability of this bulking agent. It is important to note however that patients were allowed additional injections of the bulking agents up until 6 months following the initial injection. Further investigational studies and long-term studies that measure the efficacy of calcium hydroxylapatite should be conducted to supplement the aforementioned results.

FUTURE DEVELOPMENTS

Despite the number of studies that have examined the efficacy, durability and complications of different UBAs, the 2012 Cochrane Review determined that additional comparative randomized clinical trials are needed to put UBA treatment at the forefront of SUI treatment [42]. Long-term comparative trials and placebo studies have also been recommended. Currently, there has been increased interest in autologous skeletal muscle-derived stem cell injections for the treatment of SUI specifically due to intrinsic urinary incontinence. This therapy involves obtaining a biopsy of the patient's skeletal muscle, which is then processed ex vivo to ensure a large quantity of myogenic cells in the product. The product is then injected into the urethral sphincter, transurethrally or periurethrally. Decreased stress leaks have been seen as early as within 1 month of treatment [46]. Peters et al recently reported that all groups that were injected, regardless of the dosage of myogenic product injected, showed some success in relief of incontinence symptoms. Notably, they found that groups receiving injections with higher doses had greater relief of incontinence symptoms, reflected in a larger number of patients exhibiting at least 50% decrease in pad weight at 1 year follow-up [46]. Carr et al has examined varied dosages of myogenic cell products, concluding that there is enhanced efficacy of incontinence symptoms with doses of 32 x 10^6 cells or higher [47]. The current proposed mechanism of action of this therapy is an augmentation in urethral sphincter function, possibly with innervation of the newly formed myotubes and myofibers following injection [47]. More simple procedures, such as the use of autologous minced skeletal muscle cells have also been reported to be effective in the treatment of SUI due to ISD [48], however further studies should be performed to confirm this.

Other treatment methods, such as alpha-agonist medications showed potential for treating SUI symptoms but were not FDA-approved due to their side effects, most notably hypertension. Recently, Chen et al examined the effect of the main component of *Ramulus Cinnamomi*, which makes up a Chinese herbal medication used for incontinence among other symptoms [49]. The main component of this herb, cinnamaldehyde, proved to cause elevated contractility of the urethra and decreased contractility of blood vessels in SUI-model mice that had induced vaginal distension. Moreover, this substance greatly lowered the blood pressure of the SUI-model mice, demonstrating that it has the benefits of alpha-agonists on alleviation of SUI symptoms without the side effect of hypertension [49].

The use of balloons, as demonstrated by Ghoniem (1994) [50], and micro balloons (UroVive®) has also been tested in patients suffering from ISD but are now unavailable. Other adjustable balloons are used on a limited scale in the United States, such as ACT® therapy. This technique involves the injection of microballoons periurethrally, followed by inflation of the balloon. The result is coaptation of the urethral mucosa, much like that seen in the injection of UBAs. The microballoons are usually implanted at the 3 o'clock and 9 o'clock positions periurethrally. The noted advantage of this procedure is its stability and the added ability of being able to move or rupture the balloon in case of obstruction. Accidental extrusion of the implanted balloons has been noted however it is very rare [50-52]. Additional studies should be conducted to confirm these results and ensure its reproducibility; however, these new treatment methods reflect a promising future for the treatment of SUI via injection therapy.

CONCLUSION

The use of bulking agents for SUI secondary to ISD is an important proven addition to the armamentarium of the practicing urologist and urogynecologist. Its current use is less prevalent than minimally invasive sling procedures but comprises a significant percentage of treatment techniques (over 20%) for patients suffering from this condition. In the last few years, the use of UBAs has plateaued, secondary to minimally invasive mid-urethral sling placements. However, its use may expand as contemporary indications in patients continue to increase and the elderly population further enlarges. The search for the ideal injectable agent continues, tampered by the high rate of introduction of new UBAs and the subsequent withdrawal of many bulking agents. Stricter criteria for introduction of newer UBAs should be implemented. Moreover, high quality long-term studies are lacking and further studies are suggested to determine and confirm the efficacy and durability of each available UBA.

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