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Bulking Agents in the Management of Urinary Incontinence: Dead or Alive?

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Abstract
Purpose of Review Although urethral bulking therapy has been available for more than 50 years, the ideal agent is still lacking and its result is considered inferior to surgery. In this review, we summarize the latest advances and evidences in the field of urethral bulking agents for treatment of stress urinary incontinence (SUI).
Recent Findings The use of ultrasound evaluation post-urethral bulking provides insights for the optimal position and configuration of the bulking agent. Novel agents are available and show promising results in pre-clinical and clinical studies. More clinical data is available for currently available agent, e.g., Bulkamid. The field of cell-based urethral injection and regenerative medicine provides exciting future in treatment of SUI.
Summary Urethral bulking therapy remains important in the treatment of SUI especially in high medical risk group or patients with recurrent SUI post-surgery. Further researches in novel bulking agents and regenerative medicine may further enhance its role and eliminate its current limitations.

Keywords Stress urinary incontinence · Urethral bulking agents · Urethral hypermobility · Intrinsic sphincter deficiency · Urethral injection

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Introduction

The use of urethral bulking agents for treatment of incontinence started from early twentieth century. At that time, paraffin oil [1], morrhuate sodium [2], or other sclerosing agents were used. They were associated with significant morbidities including embolization and urethral sloughing. Therefore, the widespread use of urethral bulking agents only started since 1993 with the introduction of glutaraldehyde cross-linked collagen. Collagen injection therapy rapidly popularized and became the most common anti-incontinence procedure in women with stress urinary incontinence (SUI) in 1998 [3]. Use of urethral bulking therapy declined gradually since then due to lack of long-term efficacy and the advent of other minimal invasive surgical options [4]. The ideal bulking agent should be non-migratory, biocompatible, non-antigenic, non-carcinogenic, easily injectable, and prepared. It should cause minimal inflammatory or fibrotic reaction, while maintaining its volume over time [5, 6]. Over the last 50 years, there has been development of different bulking agents in search of the ideal one. Currently, none of them fulfills all the criteria yet. Table 1 lists the past and current injectable agents for treatment of SUI.

Previously, urethral bulking agents were considered to be effective only in patients with intrinsic sphincter deficiency (ISD) alone. Different studies have demonstrated their clinical efficacy in patients with urethral hypermobility as well [7, 8]. For patient selection, urethral bulking therapy can be a valuable option for patients with high anesthetic risks, on anticoagulants, with poor bladder emptying, planning for childbirth, or residual mild SUI post-incontinence surgery. Patients undergoing urethral bulking injection should be well informed that the efficacy and duration are inferior to surgery, repeated injection may be required, and there may only be improvement instead of cure [9]. Although surgical treatment, e.g.,

Table 1 Types of injectable agents for treatment of SUI

Biologic agents
Bulking agents:
No longer used: bovine collagen (Contigen), porcine collagen (Permacol), autologous fat
Cell-based therapy:
Autologous muscle-derived stem cells, adipose tissue-derived stem cells, human umbilical cord stem cells, minced autologous striated muscle
Synthetic agents
No longer used:
Sodium morrhuate, paraffin wax, sclerosing materials
Polytetrafluoroethylene (Teflon), ethylene vinyl alcohol (Tegress), dextranomer/hyaluronic acid (Deflux, Zuidex)
Currently used and FDA-approved agents:
Silicone particles (Macroplastique), carbon beads (Durasphere), calcium hydroxylapatite (Coaptite)
Other currently used agents:
Polyacrylamide hydrogel (Aquamid, Bulkamid), silicone polymer (Urolastic)

midurethral sling is more common nowadays, urethral bulking agents are less invasive and can provide rapid improvement without the need for anesthesia. This article focuses on the latest advances in urethral bioinjectables within the last 5 years and their role in treatment of SUI.

Ultrasound Evaluation

The optimal site for urethral injection and the amount to be injected have been investigated to promote success rate of urethral bulking therapy. Ultrasound has been used to evaluate the location and distribution of the bulking agent as well as the degree of urethral coaptation. In 2012, the Cleveland clinic group reported the use of three-dimensional endovaginal ultrasound (3D EVUS) in 100 patients post-transurethral injection of Macroplastique [10•]. The patients were divided into two groups by patients' subjective satisfaction and self-reported number of incontinent events per day. They found that the good-clinical-outcome group (n = 72) had a greater proportion of women with Macroplastique located in the proximal urethra, while the poor-response group (n = 28) was more significantly associated with a midurethral location of Macroplastique (p = 0.036). The proportion of a circumferential periurethral distribution of Macroplastique in the good-response group was significantly higher than that in the poor-response group (79 versus 25%, $p < 0.001$). The authors concluded that the combination of circumferentially distributed and proximally located Macroplastique is associated with better short-term clinical outcomes.

Lately, Yune et al. also reported their 3D EVUS results after an uncomplicated transurethral injection of Macroplastique [11]. Macroplastique was injected at 3- and 9-o'clock position of proximal urethra in 22 patients. 3D EVUS was performed within 1 h post-procedure. The injected Macroplastique was visualized as hyperechoic densities around the urethra. In their study, 82% of patients showed two sites of bulking agent periurethrally, corresponding to the injection sites at 3- and 9-o'clock position. Sixty-eight and 84% of the right- and left-side Macroplastique was observed in the expected position of proximal urethra, respectively. Twenty-seven percent of patients had more than 10-mm difference in bulking agent to the bladder neck distance between right and left side, which suggested an asymmetric distribution of bulking agents. Nine of the 22 patients (41%) had a significant spread of bulking agent either into the bladder neck or towards distal urethra. However, the authors found no association between any sonographic finding and clinical outcome at 3 months, in contrast to the Cleveland clinic's report.

Unger et al. [12] studied the ultrasound findings in women with SUI after transurethral injection of Coaptite. Patients completed the Urinary Distress Inventory and Incontinence Severity Index pre-injection and 3 months post-injection. Translabial ultrasound was performed immediately after and 3 months post-injection. At 3 months, 90% of the 20 studied patients reported 50% or greater improvement while 45% of them had 90% or greater improvement. The mean distance of Coaptite from the bladder neck at 3 months was not statistically different from that immediately post-injection. There was a 40.9 to 45.8% mean reduction in Coaptite volume and a 39.5% reduction in urethral coaptation at 3 months. The degree of clinical improvement was associated with the mean change in bulking agent volume over time. The initial injection volume, percentage of coaptation, and number of vials used for injection were not associated with patient symptoms improvement.

Macroplastique

Macroplastique (Congentix Medical, Minnetonka, MN, USA) has a long history in the treatment of female SUI, primarily in Europe, and it is the leading bulking agent outside the USA. It is composed of highly textured polydimethylsiloxane elastomer implants suspended in a polyvinylpyrrolidone-carrier hydrogel. It consists of particulates of various shapes and sizes ranging from less than 50 to 400 μm while 99% of the particulates are greater than 100 μm [13]. However, there is still concern for particulate migration especially for those less than 70 μm. Macroplastique is fairly viscous and thus requires a high-pressure injection technique via an 18-gauge rigid endoscopic needle gun. It is supplied in pre-loaded 2.5-ml syringes. Transurethral injections are recommended at 2- and 10-o'clock position with 1.5 ml of Macroplastique and 6-o'clock position with 2.5 ml of the implant. There is also an option of

using a proprietary, non-endoscopic transurethral injection device, the Macroplastique Implantation System (MIS).

Ghoniem et al. reported a series of studies on the clinical use of Macroplastique in treatment of SUI. In 2009, the group reported a multicenter randomized controlled trial of 247 ISD patients to transurethral injection of either Macroplastique or Contigen [14]. After 12 months, there were significant better dry/cure rates in the Macroplastique group versus Contigen group (36.9 versus 24.8%, respectively, $p < 0.001$). 61.5% of patients in the Macroplastique group had improved one Stamey incontinence grade compared to 48% in the Contigen group. Other parameters including pad weights, quality of life measures, and rates of adverse events were similar between the two groups. In 2010, the same group reported the 24-month follow-up results of patients in the Macroplastique group who had cure/improvement at 12 months [15]. Eighty-four percent of women maintained the success and 67% of them were dry at 24 months. Also, 41% of patients who had improved at 12 months became completely dry at 24 months. In 2013, Ghoniem et al. performed a systemic review of the literature on the safety and effectiveness of Macroplastique for female SUI [16•]. A total of 958 patients from 23 cohorts were included and analyzed. The outcome was classified into three time periods: short-term (<6 months), mid-term (6–18 months), and long-term (>18 months). The improvement rates were 75, 73, and 64%, respectively, while the cure/dry rates were 43, 37, and 36%, respectively. The median reinjection rate among studies was 30% and higher study reinjection rates were associated with better long-term SUI outcomes.

Urolastic

Urolastic (Urogyn BV, Nijmegen, The Netherlands) is composed of vinyldimethyl-terminated polydimethylsiloxane polymer, tetrapropoxysilane cross-linking agent, platinum vinyltetramethyl siloxane complex as catalyst, and titanium dioxide as a radio-opaque agent [17]. This agent is non-biodegradable and it polymerizes and hardens in situ upon injection. It is provided in a pre-filled dual container (2 syringes × 2.5 ml) that contained a static mixer for adequate pre-mixing of the syringe content at time of injection. Urolastic can be injected under local anesthesia using an 18-gauge needle and a proprietary applicator. The applicator was introduced into the urethra to facilitate periurethral injection of Urolastic. It is injected at 2, 5, 7 and 10 o'clock with 0.6–1.2 ml per spot. Zajda and colleagues first presented the use of Urolastic for SUI and their 12- and 24-month result [17, 18]. In the 12 months' follow-up, the mean Stamey incontinence grade decreased significantly from 1.9 at baseline to 0.4 among a cohort of 19 patients. They reported 68 and 45% of the patients were dry at 12 and 24 months, respectively. The 1-h pad test showed more than 50% reduction in the average weight in 84 and 66% of patients at the 12 and 24 months' follow-up, respectively. Thirty-five percent of patients required a second injection at 6 weeks. Thirty and 32% of patients developed minor complications related to the injection at 12 and 24 months' follow-up, respectively. These included urinary urgency, transient retention, urinary tract infection (UTI), vaginal infection, and dyspareunia. There was one patient with vaginal erosion of the implant due to too superficial injection [18].

Futyma and colleagues [19, 20••] reported the use of Urolastic in the setting of recurrent SUI after surgical interventions. The objective success was measured by a negative cough test and a standard 1-h pad test. 59.3% of 91 patients with recurrent SUI achieved objective success after 12 months post-injection while 32.7% of 66 patients maintained objective success during 24 months' follow-up. They reported a complication rate of 25.8%. Most of them were minor and there was no any fistula, abscess formation, or vaginal erosion. However, there was extrusion of oval-shaped Urolastic material inside the bladder in three (4.5%) patients who presented with recurrent UTI [20••].

Polyacrylamide Hydrogel (Bulkamid)

Bulkamid (Contura International, Soeborg, Denmark) consists of 2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water. It is a biocompatible, non-resorbable, non-allergenic hydrogel which contains no solid particles. Therefore, it has the advantage of having no risk of particle migration. In the USA, Bulkamid is still investigational and under clinical trials. While in Europe, it has been widely used and the same material is used as facial filler for plastic reconstructive surgery for many years. Bulkamid requires no special handling or refrigeration. It is supplied in a 1-ml pre-loaded sterile syringe and can be injected transurethrally using a 23-gauge needle with standard cystoscopy set or using the proprietary Bulkamid Urethral Bulking System (Contura International, Soeborg, Denmark). This system includes an 11-cm female urethroscope with a rotatable sheath. The sheath consists of a working channel for the needle, a 2.7-mm lumen for an endoscope, and water flow tubings. Approximately 0.5 ml of Bulkamid is injected each at 3-, 6-, and 9-o'clock positions to achieve full urethral coaptation.

In 2015, Pai et al. reported their 3-year result of Bulkamid injection for SUI and mixed urinary incontinence [21]. Two hundred fifty-six patients underwent transurethral injection with the Bulkamid Urethral Bulking System. Patient-completed International Consultation on Incontinence Questionnaires (ICIQ) and a 10-point visual analogue scale on quality of life (VAS QoL) were used for assessment. Forty-three and 82% of patients reported complete cure and cure/significant improvement at 3 months, respectively. The authors reported

maintenance of this high satisfaction rate in both VAS QoL and ICIQ scores at the final follow-up (median follow-up time: 38 months). There were no reported significant adverse reactions except cystitis and one patient with transient urinary retention.

In 2016, Zivanovic et al. reported their use of Bulkamid in treatment of recurrent SUI in post-midurethral sling women [22]. Sixty patients with recurrent SUI or mixed urinary incontinence after a previous sling surgery were injected with Bulkamid. Patients were classified as cured based on a negative cough test and <2 g urine on 1-h pad test and a VAS score improved by 90%. Patients were considered as improved if they had only a few drops of urine loss during cough test and 2–10 g or reduction >50% of urine loss on 1-h pad test and a VAS score improved by 75%. The cured/improved rates were 93.3, 88.3, and 83.6% at 1, 6, and 12 months, respectively. At 12 months, 25.4% of patients were cured. There was no difference in treatment outcome between ISD and non-ISD patients, defined by pre-operative urethral pressure profile. Adverse events were short term and uncommon. Voiding dysfunction and UTI rates were 1.8 and 3.6%, respectively, at 12 months.

Cell Therapy

The regenerative potential of cell-based therapy for SUI has been explored in many pre-clinical and clinical studies. It aims at curing the disease by restoring the natural mechanism of continence rather than symptomatic relief by other conservative or surgical treatments. Cell therapy may improve the urethral sphincter muscle bulk and contractility, neuromuscular transmission, and blood supply. A systemic review of stem cell injection in human subjects with SUI was performed by Aref-Adib and colleagues [23]. Eight studies met their inclusion criteria and they concluded that stem cell treatment for SUI is safe and effective in the short term. However, most of them are small, non-controlled studies using different methodologies, cell types, and assessment methods. Therefore, an overall assessment of the treatment efficacy is not reliable. Studies of efficacy of cell-based therapy in humans have shown cure rates between 40 and 75% [23–26].

Different types of stem cells have been used. These cells include skeletal-muscle-derived cells: muscle-derived stem cells, myoblasts, muscle progenitor cells, and satellite cells; human umbilical mononuclear cells; bone marrow stem cells; and adipose-derived stem cells. Different methods of cell delivery have also been used including transurethral or periurethral injection under ultrasound or cystoscopic guidance. However, the optimal technique still remains unknown. Besides the variability, there are also some limitations in preclinical studies using animal models. First, small animal models such as rodents or rabbits are convenient and commonly used, but their results may not be applicable or relevant to humans. Second, common models simulating SUI, e.g., vaginal distension and pudendal nerve crush/ transaction, are acute events compared to the chronic, irreversible nature of SUI in humans. Therefore, these models are not durable and self-recovery may affect study results. Third, common methods to assess SUI in animal models include leak point pressure and electromyography (EMG) of the external urethral sphincter. Leak point pressure measurement requires a learning curve and it also varies with different bladder volume prior to measurement. Urethral sphincter EMG is invasive and traumatic requiring concentric needle placement. There is also potential bias due to noise of the raw EMG signals. Hakim et al. introduced the use of high-frequency micro-ultrasound as a reproducible method to assess urethral function in female rats following simulated birth injury [27]. They validated the ultrasound results by comparing them to the gold standard EMG. It has the advantages of less operator dependent, non-invasive, and no bias due to raw signals.

Carr et al. injected autologous muscle-derived stem cells transurethrally or periurethrally in eight women with SUI [25]. Three women withdrew from the trial 1 month after injection while in the remaining five women, one achieved total continence and the others showed improvement in bladder diary and pad test. Onset of improvement only started between 3 and 8 months after injection. At a median of 10 months, there was still sustained improvement. The group continued a dose-finding study of 38 women having intra-sphincteric injection of low (1, 2, 4, 8, or 16×10^6) or high doses (32, 64, or 128×10^6) of autologous muscle-derived stem cells [28]. Primary endpoint was the incidence and severity of adverse events. Only minor events such as pain or bruising occurred and efficacy data showed greater response towards high-doses group. In their latest report of the pooled data from two phase I/II studies in patients with SUI refractory to other treatments, there were 72 patients with 12-month follow-up data [29]. Depending on the dose of stem cells, 20 to 64% of patients had at least 50% improvement in 24-h pad test in 12-month follow-up, with better response for higher dose. There were no adverse effects related to stem cells injection reported.

Sèbe et al. performed intra-sphincteric injections of autologous muscular progenitor cells derived from deltoid muscle biopsy on 12 patients with severe SUI and fixed urethra [24]. At 1 year after treatment, three patients were dry, seven were improved on pad test, and two were worsened. Cornu et al. reported the long-term, 6-year follow-up result of 11 of these patients [30]. Two of the three cured patients at 12 months were still perfectly dry while SUI had recurred in five patients considered improved at 12 months. This study sheds insight on potential durable result for cell therapy in some carefully selected patients with ISD.

Cells other than muscle precursor cells have been used for SUI including adipose-derived stem cells, umbilical cord stem

cells, and freshly minced autologous skeletal muscle. Kuismanen et al. injected five women transurethrally with autologous adipose-derived stem cells combined with bovine collagen gel and saline [31]. The primary end point was a negative cough test. At 6 months, one patient was continent while two more were continent at 12 months. No adverse effects of treatment were reported. Lee et al. injected umbilical cord stem cells transurethrally in 39 women with SUI [26]. There were no complications reported. At 12 months, there was more than 50% subjective improvement in 72% of patients. The group also noted a progressive improvement of SUI with time after treatment. Gras et al. reported using freshly harvested, minced autologous skeletal muscle tissue with its inherent content of regenerative cells in women with SUI [32•]. Twenty and 15 women with uncomplicated and complicated SUI, respectively, were injected periurethrally under vaginal ultrasound guidance. At 1 year, there were statistically significant reductions in the mean number of leakages and ICIQ-SF score in both groups. In the uncomplicated group, the cure and improvement rates were 25 and 63%, respectively. In the complicated group, they were 7 and 57%, respectively.

Novel Agents

Mann-Gow et al. investigated and compared two novel bioceramic urethral bulking agents with three currently used injectable agents [33••]. In their pre-clinical study using a previously described rat model [34], they examined two bioceramic particles, silica-calcium phosphate and cristobalite, suspended in sodium hyaluronate. Both of the two bioactive ceramic particles have been studied extensively in bone regeneration and reconstruction. The novel agents were injected into the midurethra of the rats and 5 months later, histology and immunohistochemical analysis of the urethra were performed. The results were compared to rats injected with Coaptite, Bulkamid, and Macroplastique using the same methodology. Distant organs were also evaluated for the presence of particles and their component. They found that both silica-calcium phosphate and cristobalite induced a more robust fibroblastic reaction compared to current agents. This promoted integration and encapsulation of the particle aggregates led to a larger bulking effect. No particles were detected in distant organs (the lung, liver, kidneys, and spleen), and concentrations of ions of the particle component in the experimental groups were comparable to normal control animals. They concluded that the local host tissue response and bulking effects of bioceramic particles were superior while also possessing a comparable safety profile to other bulking agents. However, further pre-clinical studies in larger animals are needed.

Conclusion

Despite the limitations of urethral bulking agents, they complete the armamentarium for treatment of SUI. Interestingly, in a recent cost-utility study comparing bulking agents with midurethral sling in SUI patients without urethral hypermobility, Kunkle et al. showed that midurethral sling costs $436,465 more than bulking agents for every 100 women treated in 1 year [35]. Using midurethral sling compared with bulking agents leads to an incremental cost-effectiveness ratio of $70,400 per utility gained. The study suggested that bulking agents can be a more cost effective first line treatment than midurethral sling in appropriately selected patients. To conclude, urethral bulking agents are safe and minimally invasive; they represent an important option in appropriately selected and well-informed patients. They are definitely vividly alive in the management flowchart of SUI.

Compliance with Ethical Standards

Conflict of Interest Dr. Wayne Chan and Dr. Peggy Chu declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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