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PERIURETHRAL BULKING AGENTS IN THE TREATMENT OF FEMALE STRESS URINARY INCONTINENCE

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Review article

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SUMMARY. Stress urinary incontinence (SUI) is a common type of urinary incontinence in women, affecting large proportion of women. Surgical methods, especially suburethral sling operations are the most important modes of the treatment of SUI. Bulking agents were created as an alternative to conventional surgical methods and may be the first line of therapy in certain patients. Periurethral bulking implies implantation of various biocompatible agents around the urethra in order to improve coaptation of the urethral walls during intra-abdominal pressure elevation. The rates of cure are lower with bulking methods as compared with surgical techniques but are associated with a lower prevalence of postoperative complications. Bovine collagen remains the most frequently injected agent worldwide, with cure rates of 53% at 12 months after procedure. Polyacrylamide hydrogel and silicone micro implants have showed promising results, with about 64% improvement rate at 18 to 24 months after procedure. Application of urethral bulking agents is minimally invasive procedure and is mostly applied outpatiently in local anesthesia. Urethral bulking agents are safe for clinical usage. Bulking agents should not be recommended as a method of final cure because they only lead to short-term improvement.

Introduction

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women, affecting a large proportion of middle-aged and elderly women. Surgical treatment generally includes placement of vaginal suburethral polypropylene suspension tapes (sling procedures). Sling methods are minimally invasive surgical techniques that require short hospital stay. Sling methods are the gold standard in the management of SUI in women (1,2). Bulking procedures have emerged as an alternative option to the standard surgical techniques in the treatment of urinary incontinence in women and can be first-line therapy in some patients (3). Bulking procedures simply implantation of agents around the urethra. Bulking agents can be synthetic or biologic, and they compensate for the inadequate periurethral tissue. The agent is applied into the urethral submucosa in order to improve coaptation of the urethral walls during intra-abdominal pressure elevation. There are several types of bulking agents, as follows: collagen, polydimethylsiloxane, silicone, carbon coated zirconium beads, polyacrylamide hydrogel, and hyaluronic acid/dextranomer (4,5). In 1938, Murless described the use of sodium tetradecyl sulfate around the urethra in the treatment of urinary incontinence (6). Many bulking agents of various chemical compositions have been introduced in clinical practice since 1990. Some agents

have been withdrawn from the market due to side effects. An ideal periurethral agent for the treatment of SUI should be biocompatible, not inducing immune reaction, should maintain bulking characteristics over long period, should not undergo degeneration and migration, must be safe and efficient, and cause minimal tissue reaction. These agents can be applied in two ways, transurethral and periurethral. Bulking agent is applied by a needle, mostly under cystoscope guidance (7). Bulking agents should not be recommended as a method of definitive cure because they only lead to short-term improvement (8).

Urinary incontinence is involuntary loss of urine, thus posing a social and hygienic problem. Moderate to severe urinary incontinence involves 7% of women aged 20–39, 17% of women aged 40–59, 23% of women aged 60–79, and 32% of women aged >80 (9). It is classified into three main types: stress incontinence, urge incontinence, and mixed incontinence. According to the International Continence Society (ICS), SUI is defined as urine leakage during physical activity, cough, and any activity associated with intra-abdominal pressure elevation (10). Stress incontinence is caused by weakening of pelvic musculature and lesions of endopelvic fascia. The risk factors for developing SUI include delivery, drugs for urethral sphincter relaxation, obesity, pulmonary diseases with chronic cough, and previous pelvic surgery (11). Urinary incontinence is

caused by the loss of anatomic support to the vesicourethral junction, i.e. due to urethral hypermobility and internal urethral sphincter deficiency. In terms of urodynamics, SUI occurs when intravesical pressure exceeds maximal urethral closure pressure (12). According to McGuire classification, SUI types I and II occur due to urethral hypermobility, whereas type III develops due to intrinsic urethral sphincter deficiency (ISD) (13).

The Mechanism of Internal Sphincter Deficiency and Action of Paraurethral Biomaterials

Two mechanisms have been proposed for the occurrence of stress incontinence, i.e. weakness of the urethral supporting tissues resulting in urethral hypermobility, and a deficient mechanism of the urethral sphincter closure (ISD). It should be noted that these two mechanisms are not dichotomous but represent a continuum, thus many patients may show characteristics of both mechanisms (14). ISD is caused by damage to the system of sphincter innervation or to structures of the urethral sphincter mechanism, which consists of the striated muscle, smooth muscle, mucosa and submucosa (14). The causes of the internal urethral sphincter deficiency include lesions associated with delivery, ischemic lesions, previous operations, and neurogenic causes. ISD is a condition where the urethral sphincter cannot achieve adequate tone to overcome the intravesical pressure, in particular during the phase of bladder filling. In these patients, urine is frequently leaking continuously or at minimal exertion. Mechanical properties and structural integrity of the pelvic musculature, connective tissue and ligaments are responsible for maintaining continence in women (15,16). Damage and loss of mechanical properties of the endopelvic fascia is believed to be a major factor in the development of SUI in women. Partial or complete denervation can lead to ISD (17).

Biomaterials injected periurethrally act by increasing coaptation of the urethral walls during the phase of bladder filling and in the period of elevated intra-abdominal pressure (18). This mechanism restores continence by increasing urethral resistance. Bulking agents increase the volume of periurethral tissues (*Fig 1*), thus supporting the urethra and its angulation, which in turn facilitates closure of the urethra by increasing the ure-



Figure 1. Cystoscopic view of proximal urethra and internal urethral orifice before and after periurethral agent injection.

thral closure pressure. Bulking agents have been traditionally used in patients with ISD, with poorly compliant bladder and normal anatomic support. Urethral bulking injections can be used in all types of stress incontinence (19). Bulking agent injection should not result in fibrosis. Injectable agents should be non-antigenic, acellular and sterile to minimize the rate of rejection and postoperative inflammation. The micro-polymer particles of non-biologic agents should exceed 110 μm size to prevent their dislocation and migration (20).

Indications for Use of Bulking Agents

The use bulking agents is indicated as follows: women with ISD; women with contraindication for the use of sling techniques due to comorbidity; women of generative age planning childbirth, thus refusing sling methods; women in whom the treatment of SUI by the sling method failed; and women preferring bulking method as the first treatment modality (21). Each patient should be approached individually, respecting her preferences and expectations in the management of stress urinary incontinence. Urethral injections should not be used in case of urge incontinence and in patients with obstructive urinary disorders. In case of lower urinary tract infection, insertion of periurethral implants should also be avoided due to the high risk of abscess formation.

The workup preceding the treatment with bulking agents consists of thorough history taking, urogynecological examination, measuring post-void residual urine and urine culture. In addition, voiding diary and urodynamic testing are performed frequently to set the diagnosis of ISD. Voiding diary and measurement of urine output provide data on the bladder capacity, while uroflowmetry indicates maximum urine flow rate. Cystometry provides data on the bladder capacity and possible overactivity. Cystoscopy is another method that is helpful in diagnosing ISD by determination of bladder neck closure (22).

Types of Bulking Agents

Durasphere® consists of carbon coated zirconium beads dispersed in polysaccharide gel. At one year of application, the efficacy of Durasphere® in the treatment of ISD was superior to that of bovine collagen, with 80.3% versus 69.1% incontinence reduction. Durasphere® was associated with a higher rate of urinary retention (23). Another study revealed that the durability of this agent did not surpass that of bovine collagen; the more so, periurethral application of bovine collagen proved more successful in hysterectomized women (24). Durasphere® is injected *via* 18-gauge needle, usually transurethrally at the level of the bladder neck, guided by a cystoscope at 4.00 or 8.00 o'clock position; it can also be injected by the periurethral technique (25). The occurrence of periurethral masses has been

recorded, with the incidence of 2.9% more than 12 months of the application, as well as *de novo* symptoms of urinary retention and bladder irritation (26).

Coaptite® is a synthetic biomaterial that consists of calcium hydroxylapatite microspheres suspended in carboxymethylcellulose gel. The efficacy of Coaptite® is comparable to bovine collagen in terms of incontinence symptom reduction. At 12 months of Coaptite® injection, significant improvement of urinary continence was recorded in 64.3% of patients versus 57% for bovine collagen. The procedure of Coaptite® injection was only indicated for ISD treatment (27). There are several literature reports on the occurrence of granulomatous reaction with urethral prolapse following Coaptite® injection (28–30). Coaptite® is injected similar to Durasphere®, transurethrally under cystoscope guidance.

Macroplastique® is made up of silicone polymers, polydimethylsiloxane, that are immersed in polyvinylpyrrolidone gel (31). Its large particle diameter (>100 µm) decreases the likelihood of particle migration. Polydimethylsiloxane elastomer and polyvinylpyrrolidone are characterized by very good biocompatible properties (32). In comparison with collagen agents, Macroplastique® is superior in improving urinary continence. At 12 months of implantation, the rate of continence improvement was 61.5% and 48% for Macroplastique® and Contigen®, respectively. The rate of cure for Macroplastique® in the same period was 36.9% (31). A systematic review of the relevant literature found the rate of cure and improvement for Macroplastique® to range from 14% to 66.7% and from 46% to 80%, respectively, whereas the rate of urinary retention was 5.9%–17.5% (32). Zullo *et al.* report on the 18% rate of cure and 39% rate of improvement, whereas the rate of failure at 60 months of the procedure was 43% (33). Macroplastique® is generally implanted in local anesthesia, transurethrally under cystoscope guidance. The agent is injected into the submucosa of proximal urethra at the 6.00, 10.00 and 2.00 o'clock positions. The procedure can also be performed by periurethral technique. Besides conventional access under cystoscope guidance, a commercial system for implantation of this agent that does not require cystourethroscopy has been developed.

Periurethral collagen injection for the treatment of stress incontinence has been used since 1993 (34). Collagen injection requires immune testing due to its antigenic properties. Collagen used as a bulking agent has been demonstrated to provide good results in the management of SUI caused by ISD (35). Collagen injected in the groups of patients with ISD and with hypermobile urethra resulted in comparable rates of improvement and cure in both groups. Urodynamic parameters indicated improvement and cure in 46% of patients with ISD and 40.7% of patients with hypermobile urethra, demonstrating that hypermobile urethra is no a contraindication for use of bulking agents (36). Although col-

lagen is a safe agent, it cannot ensure long-term symptom improvement and the majority of patients need additional agent injections (36,37). Ultrasound studies revealed that most patients requiring additional collagen applications had asymmetric collagen configuration or small volume of the agent injected (38). Anti-incontinence surgery prior to collagen application contributes to prolonged success of this biomaterial (39). Collagen can be injected transurethrally under cystoscope guidance or by periurethral technique. It can be injected at multiple sites until the desired effect is achieved (40).

Bulkamid® is a synthetic hydrogel consisting of 2.5% polyacrylamide. This agent is biocompatible, durable, nontoxic, and has appropriate viscosity. At 24 months of Bulkamid® injection, 94% rate of patient satisfaction, 54% rate of improvement and 14% rate of cure were recorded (41). A favorable effect of Bulkamid® has been reported in women having previously undergone anti-incontinence surgery (42). A comprehensive literature review revealed that 24.3% of women required repeat Bulkamid® implantation to maintain its efficacy. The most common side effects were pain and urinary tract infections (43). In comparison with collagen, Bulkamid® maintained high rates of symptom improvement and cure (44). This agent has a favorable and longer effect on the symptoms of SUI with a low risk of serious side effects.

NASHA/Dx (non-animal stabilized hyaluronic acid/dextranomer) is a copolymer containing dextranomer

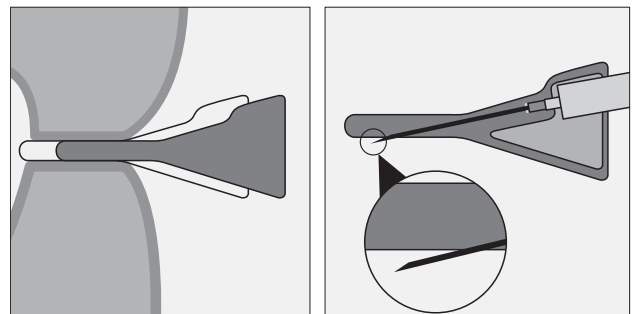


Figure 2. Urodex® injection system (with permission)



Figure 3. Urodex® Treatment kit (with permission)

microspheres in non-animal hyaluronic acid gel. The agent is biocompatible, biodegradable, free from immunogenic properties, and demonstrated not to migrate to other organs. Dextranomer consists of hydrophilic dextran polymer particles (80–120 µm). Hyaluronic acid is 1% solution of high viscosity and high molecular weight polysaccharides (40). A number of studies have shown it to be efficacious and well tolerated in the treatment of SUI (45–47). The following complications associated with the use of NASHA/Dx have been reported to date: periurethral masses, urethral granulomata, urethral abscesses, and pseudocysts (48–51). A special commercial NASHA/DxImplacer™ device has been designed, thus no cystoscope guidance being required on its implantation (52). Magnetic resonance imaging (MRI) studies have demonstrated that the agent is injected at appropriate sites of the urethral wall without the need of endoscopic guidance (53). The Implacer™ is a plastic guide with 4 holes through which the syringe needles are passed. Similar NASHA/Dx application device (Urodex®) is available on Croatian market (Fig. 2,3). The procedure is usually performed outpatiently in local anesthesia.

Ethylene vinyl alcohol was approved for use as a bulking agent in 2004, and its efficacy was demonstrated in 45% of patients at 51 months of injection (54). However, the associated side effects such as urethral erosions were a matter of concern, thus this agent was withdrawn from the market (55).

Comparison of the efficacy of porcine dermal implant and Macroplastique® yielded higher cure rates with the former at 6 months of implantation (56). Autologous myoblast implants have been studied as an agent for periurethral application in the treatment of stress urinary incontinence. Myoblasts can differentiate periurethrally into muscle fiber. Studies failed to demonstrate the efficacy of this material in increasing the volume of urethral walls as the substantial determinant of bulking agents (57).

Techniques of Bulking Agents Implantation

Transurethral approach enables direct visualization of the urinary canal and facilitates accurate agent application (58). This technique requires use of a lower agent volume (59). In transurethral technique, the cystoscope is inserted centrally in the urethra and the needle penetrates the urethral mucosa at about 1.5 cm distally from the bladder neck (60). Periurethral approach has been ever more widely adopted for avoiding trauma to the urethra and leak of the agent (59). The needle is inserted laterally along the external orifice of urethra on vaginal introitus under cystoscope guidance; then the needle is moved along the urethra to the bladder neck. There were no major differences in the efficiency of these two techniques but patients having undergone transurethral approach had less urinary retention (59).

The implantation devices that do not require cystoscope guidance have been designed for a number of

agents, e.g., Macroplastique®, Zuidex® and Urolastic® (45,61,62). These devices are based on previous urethra measurement by a catheter and device adjustment for the needle to reach a length slightly shorter than the urethra, i.e. to reach the bladder neck and proximal urethra. The devices are intended for both transurethral and periurethral approaches. Efficiency rates similar to those of cystoscopic guided procedures have been reported (63).

Preprocedural Preparation and Postoperative Course

Patients are instructed to discontinue anticoagulant drugs for 7 days before the application of bulking materials. A broad-spectrum antibiotic as prophylaxis is administered for 3 days of biomaterial injection. In case of post-procedural urinary retention, urinary bladder self-catheterization is performed. Periurethral biomaterial injection is performed in local anesthesia with 1% lidocaine solution (58). Upon agent injection, the patient's urinary continence at exertion is reassessed. Adequate patient hydration and avoiding sexual activity for at least one week is recommended. Follow up of the mechanism of micturition is scheduled in one month (60). The most common complications of these agents are urinary tract infections. Temporary urinary retention, urgency incontinence and transient hematuria may also occur (23,27). Pain and discomfort may persist for 24 hours postoperatively (58). The biomaterials intended for periurethral implantation should be safe for use, not associated with any major side effects such as granuloma, abscess or urethral mucosa erosion, and not prone to migration. The use of autologous fat has been discontinued due to particle migration and report on patient death from pulmonary embolism (64). Teflon has not been approved for use as a bulking agent by the US Food and Drug Administration due to proven particle migration to lymph nodes and distant organs, and carcinogenic effects (65,66). Zuidex® has been withdrawn from market in the USA because it caused development of sterile abscesses and infections (67). Urethral prolapse is a complication associated with several bulking agents (68,69).

Efficacy of Bulking Agents

Generally, bulking agents lead to improvement in patient condition. Improvement in the quality of life after implantation of these agents is comparable to surgical methods (70). Surgical methods used in the management of SUI were found to have longer effects and higher rates of cure at 12 months (71). Injection of silicone agents, calcium hydroxyapatite, carbon particles and hyaluronic acid dextranomer resulted in improvements comparable to collagen injection (71). Studies have shown the Macroplastique® agent to be characterized by longest durability at 2 years. Significant improvement on Stamey grading scale was recorded in 84% of patients at 12 months of the procedure, whereas two-

Table 1. Outcomes of treatment with conventional surgical techniques and bulking methods. According to: Leone Roberti Maggiore *et al.* (7). With permission of author.

Author	Objective success definition	Objective recurrence (n, %)		Subjective success definition	Subjective recurrence (n, %)	
		Surgery	Bulking		Surgery	Bulking
Maher <i>et al.</i> (75)	No urinary leakage due to SUI on urodynamic studies	4/21 (19.0)	20/22 (90.9)	Women with no or occasional (less than once a week) SUI	2/21 (9.5)	5/22 (22.7)
Corcos <i>et al.</i> (76)	Having dry 24-h pad test and no additional interventions	30/67 (44.8)	32/66 (48.5)	Answers “Somewhat satisfied” or “Satisfied” at the question “How satisfied are you with your treatment?”	14/67 (20.4)	22/66 (32.8)
Gaddi <i>et al.</i> (77)	Negative stress test no urodynamic stress incontinence and no retreatment for SUI	11/98 (11.2)	26/65 (40.0)	No symptoms of SUI (involuntary leakage on effort or exertion or on sneezing or coughing)	–	–

SUI = stress urinary incontinence

thirds were free from incontinence discomforts at 24 months (72). A meta-analysis of the efficacy of Macroplastique® showed a 73% rate of incontinence improvement in 6–18 months and 64% rate of symptom improvement at 18 months of the procedure (21). The efficacy of Durasphere® is variable. A large randomized study reports on 80.3% improvement at 12 months (23). Improvement of grade 1 incontinence according to Stamey was recorded in 80% of patients, while 40% of patients were completely free from urinary incontinence (73). A similar study found 33% efficacy of Durasphere® at 2 years (24). Coaptite® resulted in 63.4% improvement of urinary incontinence at 12 months of implantation, while cure was recorded in 39% of patients (27).

Bulking Methods and Surgical Techniques in the Treatment of Stress Urinary Incontinence

Kirchin *et al.* report on significantly better rates of objective improvement after treatment with conventional surgical methods than with the application of bulking agents (71). The rate of cure is lower with the latter, but the use of bulking agents is associated with less postoperative complications (74). A comprehensive meta-analysis compared surgical methods and bulking agents in the management of urinary incontinence and found the difference in efficacy between the two approaches to be lesser than previously believed, yet pointing to the advantages of surgical methods (7). The outcomes of SUI treatment by bulking agents and conventional surgical techniques are illustrated in Table 1.

Maher *et al.* investigated the efficacy of Macroplastique® and sling methods in the treatment of ISD. The objective efficacy of sling methods was significantly higher as compared with this bulking material (81% vs. 9%) at 12–15 months of the procedure. Morbidity was significantly lower with Macroplastique®. At 62 months, the rates of urinary continence and patient satisfaction were considerably higher in the sling group (69% vs. 21% and 69% vs. 29%, respectively) (75).

Corcos *et al.* compared the efficacy of paraurethral collagen (n=66) and surgical methods (n=67) in the management of stress urinary incontinence. At 12 months of the procedure, the rate of successful outcome was 53.1% in the collagen group and 72.2% in the surgical treatment group. The rate of patient satisfaction was higher in the group having undergone conventional surgical methods than in those treated by paraurethral collagen injections (79.6% vs. 67.2%), with statistically nonsignificant between-group difference (p=0.228). The rate of complications was lower in the collagen group (76).

After failure of treatment with sling methods, Gaddi *et al.* compared the efficacy of repeated sling methods with bulking procedures in a retrospective cohort study. In a total of 165 patients, 11 (11.2%) failures were recorded in the group with sling methods and 26 (38%) failures in the group with bulking technique. There was no between-group difference in the rate of perioperative complications. Multivariate logistic regression showed the risk of failure to be significantly higher in the bulking group as compared with the sling group (OR 3.49; CI 1.34–9.09; p=0.01) (77).

Conclusion

Bulking agents provide a minimally invasive approach in the treatment of SUI, which greatly reduces quality of life in affected women. In properly selected patients, the urethral bulking injection is an appropriate alternative to surgical methods of SUI treatment. These periurethral agents have shown acceptable rates of cure and improvement in the management of SUI. ISD is the main indication for the use of bulking agents. On choosing the method of treatment of SUI, patient goals and outcome expectations should be taken in consideration. According to meta-analyses and large studies, periurethral biomaterials should not be recommended as first-line therapy in women seeking permanent cure because the improvement thus achieved is short-lived with most bulking agents (7). The cure rates are lower with bulking procedures as compared with surgical techniques,

however, the former are associated with a considerably lower prevalence of postoperative complications. Bovine collagen (Contigen®) remains the most frequently injected agent worldwide, with up to 53% cure rates at 12 months, but its disadvantage is shorter durability. Polyacrylamide hydrogel (Bulkamid®) showed promising medium-term results, with 64% improvement rate at 24 months. All the biomaterials described have better durability than collagen, but have some other drawbacks. Duraphere® has a more demanding mode of application, whereas Coaptite® and Zuidex® more frequently cause development of urethral granulomas and abscesses (78). Macroplastique® has been shown to be an efficacious and durable material with a low rate of complications (32). Based on the literature review, it is concluded that the majority of urethral bulking agents are safe for implantation. Their advantage is that they can be injected in local anesthesia, which is in particular favorable in patients with various comorbidities (7). Bulking agents should be offered as an alternative to patients that do not want to undergo conventional surgical treatment of SUI(7). Currently, there is no consensus about the best biomaterial and the best technique of their application.

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PRIMJENA PERIURETRALNIH BIOSREDSTVA U LIJEČENJU STATIČKE INKONTINENCIJE MOKRAĆE U ŽENA

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Pregledni članak

Ključne riječi: statička inkontinencija mokraće, žene, uretralna *bulking* sredstva, suburetralni slingovi

SAŽETAK. Statička inkontinencija mokraće česta je vrsta inkontinencije mokraće u žena. Kirurške metode, a pogotovo suburetralne *sling* operacije najvažniji su modaliteti liječenja statičke inkontinencije mokraće. Periuretralna *bulking* sredstva stvorena su kao alternativa konvencionalnim kirurškim metodama i mogu biti prvi izbor terapije kod nekih pacijentica. Periuretralni *bulking* označava implantaciju različitih biokompatibilnih sredstava oko uretre kako bi se poboljšala koaptacija stijenki uretre tijekom povećanja intraabdominalnog tlaka. Stope izlječenja *bulking* sredstvima su niže u usporedbi s kirurškim tehnikama, ali zato imaju nižu pojavnost poslijepercijskih komplikacija. Govedi kolagen najčešće je aplicirani periuretralni biomaterijal u svijetu, stope izlječenja su do 53% u roku od 12 mjeseci nakon zahvata. Poliakrilamidhidrogel i silikonski mikroimplantati pokazali su obećavajuće rezultate od 18 do 24 mjeseca nakon postupka sa stopom poboljšanja od oko 64%. Postavljanje periuretralnih sredstava spada u minimalno invazivne metode i uglavnom se primjenjuje ambulantno u lokalnoj anesteziji. Periuretralni biomaterijali sigurni su za kliničku upotrebu. *Bulking* sredstva ne bi trebala biti razmatrana kao trajno rješenje s obzirom na to da dovode samo do kratkotrajnog poboljšanja.