

# Urethral bulking agents for SUI: Rethinking their indications

Rising interest in alternatives to sling procedures and increasing evidence of successful outcomes for urethral bulking agents make them a potential primary treatment option for patients with SUI

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**S**tress urinary incontinence (SUI) is the involuntary loss of urine with increased intra-abdominal pressure, such as with physical exertion, sneezing, or coughing.<sup>1</sup> Currently, the gold standard treatment for SUI is surgical repair with the use of a synthetic midurethral sling (MUS), based on long-term data that support its excellent efficacy and durability. The risk-benefit balance of MUS continues to be scrutinized, however, with erosions and pain poorly studied and apparently underreported.

The medical-legal risks associated with the MUS are a significant concern and have led many patients to reconsider this option for their condition. Many other countries (United Kingdom, Australia, New Zealand,

and European Union) are now re-evaluating the use of the MUS.<sup>2</sup> In the United Kingdom, for example, the National Institute for Health and Care Excellence (NICE) Guideline advises considering the MUS only when another surgical intervention is not suitable for the patient.<sup>3</sup>

In light of the heightened skepticism surrounding the MUS, interest has increased in the use of urethral bulking agents. These agents consist of a material injected into the wall of the urethra to improve urethral coaptation in women with SUI.<sup>4</sup>

## A brief history of bulking agents

In 1938, Murless first reported the injection of sodium morrhuate for the management of urinary incontinence.<sup>4</sup> Other early bulking agents introduced in the 1950s and 1960s included paraffin wax and sclerosing agents. Subsequently, Teflon, collagen, and autologous fat, among other agents, were found to be efficacious for augmenting urethral coaptation; however, only collagen initially demonstrated acceptable safety.<sup>5</sup>

Contigen (bovine dermal collagen cross-linked with glutaraldehyde) was approved as a bulking agent by the US Food and Drug Administration (FDA) in 1993; however, the manufacturing of bovine collagen was halted in 2011. Contigen was the only *nonpermanent* biodegradable urethral bulking agent, and its use required skin testing prior to use, as 2% to 5% of women experienced allergic reaction.<sup>4</sup>



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Presently, 3 particle-based urethral bulking agents are FDA approved for marketing in the United States: Macropastique (Laborie Medical Technologies), Coaptite (Boston Scientific), and Durasphere (Coloplast). In addition, Bulkamid (Contura), which was approved earlier this year, is a nonparticulate agent composed of a nonresorbable polyacrylamide hydrogel.<sup>5</sup>

### Indications for use

According to the FDA premarket approvals (PMAs) for the particle-based urethral bulking agents, their use is indicated for adult women with SUI primarily due to intrinsic sphincter deficiency (ISD).<sup>6</sup> The PMA indication for the nonparticulate agent, however, allows it to be used for SUI as well as SUI-predominant mixed urinary incontinence (MUI) due to ISD.<sup>7</sup> Traditionally, ISD is defined by urodynamic criteria that includes a maximal urethral closure pressure less than 20 to 25 cm of water and/or a Valsalva leak point pressure of less than 60 cm of water.<sup>4</sup>

The American Urological Association (AUA) guideline lists bulking agents as an option for women who do not wish to pursue invasive surgical intervention for SUI, are concerned about lengthier recovery after surgery, or have previously undergone anti-incontinence procedures with suboptimal results.<sup>8</sup> In general, most urologists and urogynecologists who perform urethral bulking agree with the AUA guideline.

### Perceptions of bulking agents have shifted

Urethral bulking agents traditionally have been thought of as a “salvage therapy.” Perceived indications for these agents include use in women with persistent SUI after more invasive treatment options or in women who were medically fragile and thus could not undergo a more invasive procedure.<sup>9</sup> As mentioned, however, circumstances related to mesh use have shifted the current perception of indications for urethral bulking agents from salvage therapy only to use as a possible first-line treatment in the appropriately selected patient.<sup>9</sup>

Recent data that note improved durability and patient satisfaction, as well as better appreciation of the fact that, if the bulking agent fails, a synthetic sling procedure still can be performed without significant concerns, have contributed to this shift in intervention strategy.<sup>10,11</sup> There also has been the perception that urethral bulking agents should not be considered in women who have urethral mobility. However, studies have shown that outcomes are not significantly different in patients with urethral mobility compared with those with a fixed urethra.<sup>11</sup>

### Types of bulking agents

The ideal bulking agent should be made of a material that is biocompatible—with low host reactivity, low carcinogenic potential, low risk of migration—and easy to administer.<sup>5</sup> Currently available bulking agents are classified as particulate and nonparticulate agents. The **TABLE** on page 28 provides summary details of the available agents FDA approved for use.

#### Particulate bulking agents

**Durasphere**, approved by the FDA in 1999, is composed of carbon-coated zirconium oxide in a water-based and beta-glucan carrier. The first generation of this agent had particles that ranged in size from 212 to 500  $\mu\text{m}$  and required an 18-gauge needle for injection.<sup>4</sup> The second-generation preparation has a smaller particle size, ranging from 90 to 212  $\mu\text{m}$ , which permits injection with a smaller needle, typically 20 gauge.<sup>4</sup> Theoretically, the larger bead size reduces the risk of migration as particles larger than 80  $\mu\text{m}$  cannot be engulfed by macrophages.<sup>4</sup>

**Coaptite** is a calcium hydroxylapatite-based product approved by the FDA in 2005. The carrier media is composed of sodium carboxymethylcellulose, sterile water, and glycerin. The particle size ranges from 75 to 125  $\mu\text{m}$ , with an average of 100  $\mu\text{m}$ .<sup>5</sup> This synthetic material historically has been used in orthopedics and dental applications. The aqueous gel carrier dissipates over months,

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**TABLE** Injectable urethral bulking agents available in North America

Agent	Material	FDA approval date	Needle gauge	Cystoscope
Durasphere	Pyrolytic carbon-coated graphite beads	1999	18, 20 gauge	Standard cystoscope
Coaptite	Calcium hydroxylapatite	2005	21 gauge	Standard cystoscope
Macroplastique	Polydimethylsiloxane macroparticle	2006	18, 20 gauge	Proprietary delivery system
Bulkamid	Polyacrylamide hydrogel	2020	23 gauge	Proprietary delivery system

resulting in tissue growth; thereafter, the particulate beads slowly degrade.<sup>12</sup>

**Macroplastique**, a polydimethylsiloxane compound, was approved by the FDA in 2006. It has a long history of use primarily in Europe where it has been used since 1991. It is composed of a nonbiodegradable silicone (polydimethylsiloxane) elastomer suspended in a water-soluble gel. The initial composition was of particles that ranged in size from 5 to 400 µm, with 25% of the particles smaller than 50 µm. Because of the large number of particles smaller than 50 µm, there were concerns for migration.<sup>5</sup> The agent’s current composition contains particles that range from 120 to 600 µm, with an average particle size of 140 µm.<sup>4</sup>

**Nonparticulate bulking agent**

**Bulkamid** has been available in Europe since 2003 and was FDA approved in January 2020. It is the only available nonparticulate urethral bulking agent; it is composed uniquely of a nonresorbable polyacrylamide hydrogel made of cross-linked 2.5% polyacrylamide and water. Its bulking effect is achieved through the actual volume of hydrogel injected, which integrates with host tissue by vessel ingrowth, suggestive of a persistent durable effect. Because Bulkamid contains no particles or crystals, the theoretical risk of migration is mitigated.<sup>4</sup>

**The urethral bulking technique**

The basic technique for urethral bulking is similar for all agents, with nuances in technique for each agent.

The procedure typically begins with placement of 2% lidocaine gel in the urethra

for 5 to 10 minutes. The disposable needle is primed with the agent.<sup>4</sup> For Durasphere, an 18- or 21-gauge rigid needle is used; for Coaptite, a 21-gauge rigid side injecting needle called the SideKick is used; and for Macroplastique, an 18- or 20-gauge rigid needle is used.<sup>4</sup> Bulkamid administration requires the use of a special 23-gauge needle. Durasphere and Coaptite are delivered via a standard cystoscope.<sup>4</sup> Macroplastique requires a proprietary delivery system<sup>4</sup> (FIGURE 1, page 30). Bulkamid has a proprietary urethroscope and rotatable sheath to guide accuracy of injection (FIGURE 2, page 30).<sup>4</sup>

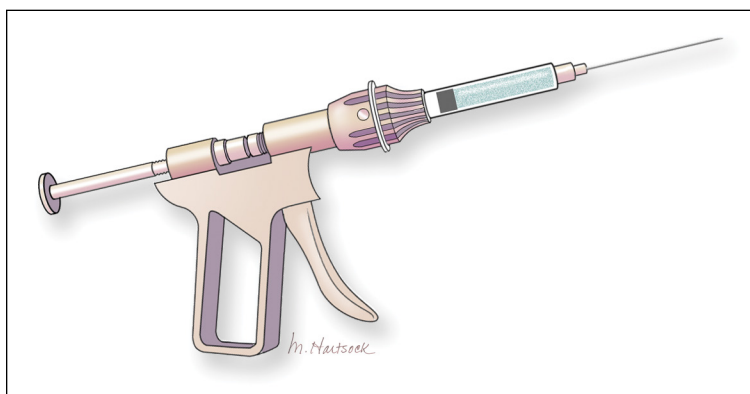
After the needle is primed and the delivery device placed into the urethra, the injection site is selected, approximately 1.5 to 2 cm from the bladder neck. The needle is introduced into the suburethral tissue at a 30- to 45-degree angle.

The injection site varies by agent. The 4 and 8 o’clock positions are recommended for Coaptite and Durasphere, while the 2, 6, and 10 o’clock positions are recommended for Macroplastique. For Bulkamid, the recommendation is to create 3 cushions at the 2, 6, and 10 o’clock positions.<sup>13</sup> Regardless of the agent used, the bulking is easily visualized and should result in the various sites meeting in the midline (FIGURE 3, page 32).

**Evidence-based outcomes**

The published data on outcomes of urethral bulking treatments have used inconsistent measures of efficacy. Most of the FDA trials used subjective success calculated with use of the Stamey Urinary Incontinence Scale (Stamey Grade) and validated questionnaires

**FIGURE 1** Proprietary injection system for Macroplastique urethral bulking agent



**FIGURE 2** Proprietary injection system for Bulkamid urethral bulking agent



Image courtesy of Contura. Used with permission.

as well as objective data collected via voiding diaries and pad tests.<sup>4</sup>

In 2007, a multicenter prospective randomized controlled trial (RCT) compared Coaptite with Contigen treatment and found that 63.4% versus 57.0% of patients, respectively, experienced an improvement on the Stamey Urinary Incontinence Scale at 12-month follow-up.<sup>14</sup>

A prospective multicenter RCT in 2009 was conducted to test the durability and efficacy of Macroplastique treatment at 12-month follow-up.<sup>15</sup> The authors noted that

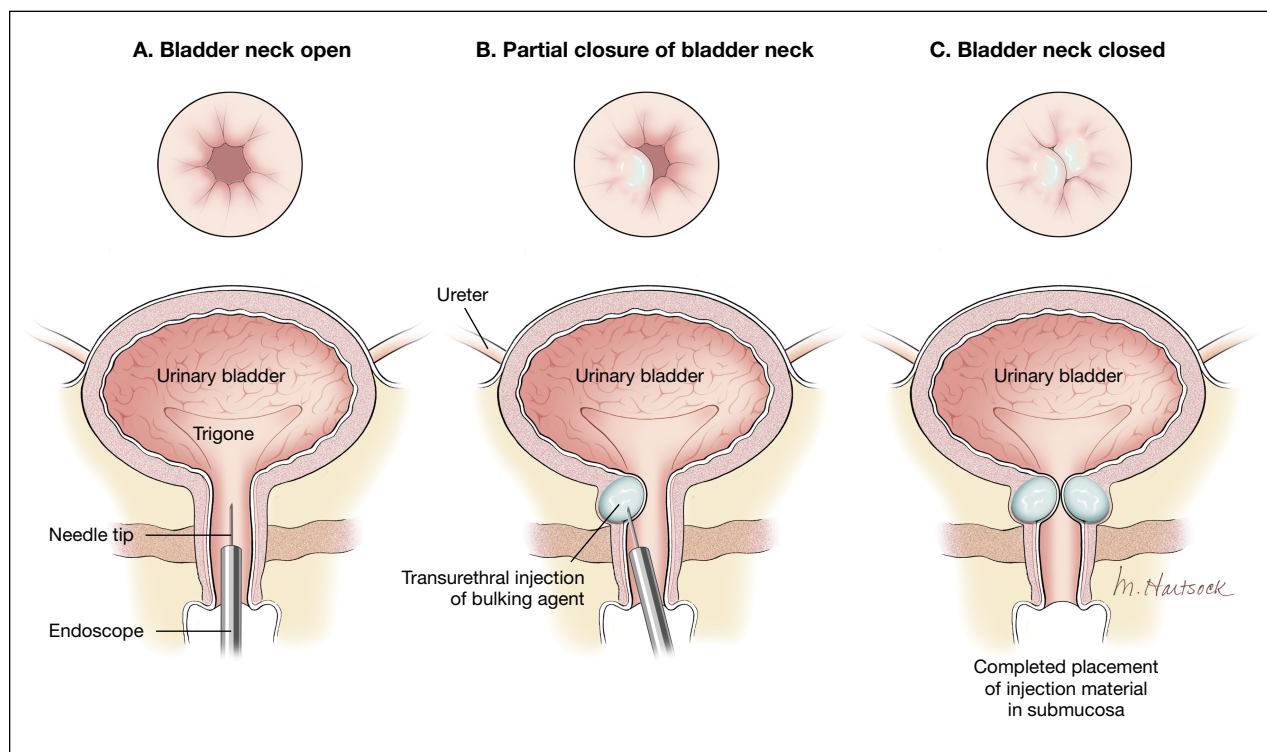
at 12 months, 62% of treated women reported significant improvement.<sup>15</sup> Further, a systematic review and meta-analysis of the literature (1990–2010) on Macroplastique use was published in 2013.<sup>16</sup> Data from 958 patients from 23 cohorts were analyzed in a random-effects model for 3 time periods: short term (less than 6 months), mid term (6–12 months), and long term (>18 months). Cure/dry rates were reported for short, mid, and long-term follow-up as 43% (95% confidence interval [CI], 33%–54%), 37% (95% CI, 28%–46%), and 36% (95% CI, 27%–46%), respectively.<sup>16</sup>

The newest bulking product in the United States, Bulkamid, has been available for use in Europe since 2003.<sup>17</sup> In a 3-year follow-up of a prospective nonrandomized single-site study, 212 of 256 (82.8%) participants were subjectively cured or had significant improvement in SUI or MUI, and this result was maintained until the end of the study period (a median of 38 months).<sup>10</sup> In 2014, an 8-year follow-up of 24 women was published.<sup>18</sup> Subjectively, 44% of the women reported cure or significant improvement, and 11 women who presented for objective evaluation all had polyacrylamide hydrogel visible on vaginal ultrasound.<sup>18</sup>

In addition, an RCT published in 2020 compared surgery with tension-free vaginal tape (TVT) and Bulkamid use in 224 women with SUI. At the 12-month follow-up, TVT was found to be more effective than Bulkamid; the median visual analog scale score for satisfaction was 99 for the TVT-treated group and 85 for the Bulkamid-treated patients.<sup>11</sup> Additionally, a cough stress test was negative in 95.0% and 66.4% of participants, respectively, but reoperations occurred only in patients who received the TVT procedure (n = 6). The authors concluded that while TVT treatment provided higher satisfaction rates than did Bulkamid, all major perioperative and follow-up complications were associated with TVT use. The study is ongoing and will eventually report 3-year outcomes.<sup>11</sup>

According to a 2017 Cochrane Review on urethral bulking, treatments with all 3 of the particulate bulking agents resulted in improvements that were no more or less effective

**FIGURE 3** Urethral bulking agent injection results in closure of the bladder neck



than Contigen treatment. The review failed to include publications on Bulkamid treatment.<sup>19</sup>

### Complications and safety issues

**Adverse events.** Reported adverse effects associated with urethral bulking include mild pain, transient urinary retention (typically resolving within 1-2 days after injection), dysuria, hematuria, and urinary tract infection (UTI).<sup>4,12</sup>

In a 12-month RCT involving 355 women treated with Durasphere or bovine collagen, adverse events were reported in 178 Durasphere-treated women; dysuria (24.7%) and temporary urinary retention (16.9%) were the most commonly reported adverse events.<sup>20</sup>

An RCT of Coaptite injection (n = 296) found that temporary urinary retention (41%) was the most common adverse event.<sup>14</sup>

In a 12-month comparative study of Macroplastique versus Contigen (n = 122), UTI was reported as the most common adverse

event (23.8%), followed by dysuria (9%) and urgency (9%).<sup>15</sup> In addition, in a meta-analysis involving 958 patients in 23 cohorts, Ghoniem and Miller reported that the median rates for adverse events were temporary dysuria, 50%; hematuria, 45%; urge incontinence, 7%; temporary urinary retention, 7%; and UTI, 3%.<sup>16</sup>

A 3-year summary outcome of 256 patients who received Bulkamid injection reported that only 1 patient developed infection, abscess, or allergic reaction at the injection site and 1 patient had a UTI.<sup>10</sup> In an 8-year follow-up of patients who received Bulkamid injection, 1 patient experienced stranguria and 7 patients had recurrent cystitis.<sup>18</sup>

It appears that transient dysuria, urgency, and urinary retention occur more frequently after urethral bulking with particulate agents.<sup>12</sup>

**Complications.** Few delayed but serious complications after urethral bulking have been reported, including suburethral abscess, urethral prolapse, and particle migration.<sup>4</sup> Cases of urethral prolapse have been reported with both Coaptite and Durasphere.

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ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

Notably, all cases of urethral prolapse occurred in patients with a history of pelvic surgery and/or previous urethral bulking.<sup>21,22</sup> Cases also have been reported of Durasphere carbon bead particles migrating to regional and distant lymph nodes, and pseudoabscess also has been reported.<sup>12,23</sup> A single case of periurethral abscess was reported after Bulkamid injection in a patient who had prior vaginal hysterectomy and a transobturator tape procedure after a total vaginal mesh repair.<sup>24</sup>

### Bulking agent use: Time to go mainstream?

Historically, urethral bulking agents have had limited utility, largely due to the inaccurate and unsubstantiated perceptions of them being indicated only in women with ISD and a well-supported urethra. More recently, ure-

thral bulking agents are commonly being used in patients who: have recurrent SUI after a surgical intervention, have infrequent but bothersome SUI symptoms, are not ideal candidates to undergo anesthesia, or wish to avoid mesh.

Some data suggest that objective and subjective success rates are lower with bulking agent treatment compared with the gold standard MUS procedure. However, in the appropriately selected patient, urethral bulking agents may be considered primary treatment due to their associated low morbidity and, as recently reported with newer nonparticulate agents, high subjective success rates. If the patient is not satisfied with the results of bulking treatment, surgical repair with any type of sling remains a subsequent option. This feature adds to the potential viability and appropriateness of considering a bulking agent as a primary treatment. ●

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#### FAST TRACK

In the appropriately selected patient, urethral bulking agents may be considered primary treatment due to their associated low morbidity and, as recently reported with newer nonparticulate agents, high subjective success rates