Injectable Agents: Present and Future

Deborah J. Lightner, MD, Nancy B. Itano, MD, Susan D. Sweat, MD, Kristin L. Chrouser, MD, and Felecia Fick, PA-C

Address
Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: lightner.deborah@mayo.edu

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Stress urinary incontinence (SUI) is primarily managed by conservative strategies. When these methods fail, minimally invasive treatments, if effective, safe, and durable, can result in a considerable reduction in current medical costs for this common condition. Injection of currently available bulking agents is a safe, minimally invasive procedure and offers a degree of efficacy. The long-term durability of several of these agents is yet to be determined. The use of bulking agents for the treatment of anatomic SUI has been demonstrated to produce success rates similar to those observed when these materials are used in patients with intrinsic sphincter deficiency, opening up new therapeutic options for women with SUI. We review the current basic science and clinical research into the development of newer agents for soft-tissue bulking.

Introduction

Stress urinary incontinence (SUI) is a condition that primarily affects women. The proximate cause may be extrinsic: poor anatomic support of the urethra and bladder neck leads to an inability to resist intra-abdominal stressors. This may respond to pelvic floor retraining, and failing that, to pelvic floor resuspension procedures. SUI, likewise, may result from poor urethral function, often described as intrinsic sphincter deficiency (ISD), and may respond to sphincter augmentation in the form of artificial urinary sphincters, pubovaginal slings, and the object of this review, periurethral bulking agents. In the United States, treatment with bulking agents for SUI has largely been limited to use in patients with poor urethral function, whereas our colleagues abroad and in Canada have applied bulking agents to both broad categories of SUI. Several important trials suggest that the currently available bulking agents are equally efficacious in both groups of patients.

This review also discusses recent papers about bulking agents, with emphasis on commercially available materials, and reviews current trials and the basic science literature that suggest areas for future clinical trials.

Currently Available Agents

Worldwide, three agents are clinically available and agreed upon to be safe and efficacious: glutaraldehyde cross-linked bovine collagen (Contigen; CR Bard, Covington, GA); cross-linked polydimethylsiloxane elastomer in a hydrogel suspension (Macroplastique; Uroplasty Ltd., Reading, Berkshire, UK) currently in United States trials; and carbon-coated zirconium beads (Durasphere; Carbon Medical Technologies, St. Paul, MN). Polytetrafluoroethylene (PTFE) remains under investigation [1], but in the decades since its first clinical trials this agent has never been approved by the US Food and Drug Administration (FDA). There are several reports of adverse events with PTFE including granuloma formation and systemic embolization.

Contigen is the most widely studied bulking agent for SUI. There are several important studies analyzing the long-term success of this agent. Corcos and Fournier [2] tested Contigen in 40 women; 40% of the patients improved, and an overall 30% of those patients were dry when followed for an average of 50 months [2]. Winters *et al.* [3] reported on 89 elderly women with either anatomic or ISD-related stress incontinence. Forty-five percent of these women reported continued improvement at 24.4 months mean follow-up. Interestingly, reinjection on subsequent failure (after an average of 7.9 months) resulted in restored continence in only 42% of the initial responders. Gorton *et al.* [4] reported on 53 incontinent women treated with Contigen; only 26% reported continued improvement when questioned 5 years after initial treatment.

These disappointing long-term results attributable to Contigen also occur with purportedly more durable injectable agents. Beckingham *et al.* [5] reported reduced efficacy of PTFE over time, as evidenced by short-term success rates of 80% that fell to 27% after 3 years. On the other hand, a recent report suggest that PTFE is capable of delivering stable, but overall poor, performance: Barranger *et al.* [6] reported a failure rate of 50% (measured at 1 year) using silicone microimplants for ISD, but a stability rate of 50% at an average of 31 months after injection [6]. Unfortunately, the results reported from clinical trials remain poorly comparable, even with identical agents; differing methods of assessing success significantly affect the ability to compare studies. Strict outcome criteria may lead to a report of poorer outcomes, such as the 60% fair-to-poor results reported with Contigen by Groutz *et al.* [7]. Alternatively, results gleaned from retrospective chart reviews and telephone interviews may led to more favorable reporting;

the American Urological Association Guidelines Panel on SUI [8] has called for standard criteria to be used in the reporting of all studies, in order to reduce this difficulty in the future. Recently reported studies of bulking agents may still be faulted for failure to use a control.

One recent randomized double-blind trial includes a control report on autologous fat injections [9••]. Beyond the obvious constraints that the bulking agent must be safe, easily injected, and not incite a host reaction, the type of material injected for treatment of SUI is significant. For example, there is an intuitively obvious advantage for materials that retain their volume over time. Lee *et al.* [9••] demonstrated that autologous fat fails in this regard, and ultimately that periurethral fat injection was no more effective than a placebo saline injection. Contrariwise, long-term volume retention of the injected agent might not be universally important. Contigen has been shown to degrade over time, yet it most likely represents a scaffold durable enough for new collagen ingrowth, much like heterologous, naturally occurring materials achieve when used as a pubovaginal sling. Thus, Contigen might provide long-term results similar to less biodegradable agents such as Durasphere or Macroplastique. It is as yet unknown whether bulking agents that are impervious to degradation will achieve more durable results; this potentiality is suggested by several studies at 2-year follow-up with Macroplastique [6], but not by others using Teflon (DuPont, Wilmington, DE) at average of 5.1 years follow-up [10].

Another recently reported controlled-randomized trial includes a multicenter comparison of Durasphere and Contigen [11••] in which 355 women from 10 centers received injections of one of these agents for the treatment of ISD. Results from both of these agents were roughly comparable at 1 year of follow-up; 80.3% of the Durasphere-treated women improved by one continence grade compared with 69.1% of the women treated with Contigen ($P = 0.162$). Results of studies comparing Durasphere with Contigen in long-term follow-up are anxiously awaited.

One single-arm study treated 60 women with ISD with Macroplastique [12•]. Investigators administered a total of 89 injections, and patients were followed up after an average of 19 months. A number of patients (19.6%) reported their incontinence was cured, with an additional 41.1% noting significant improvement.

Does one commercially available product have a clear advantage over another? Apart from skin test requirements, the different refrigeration needs among products, or subjective reports of ease of injection, there does not appear to be a reliably appreciable difference in short-term results from randomized trials [11••]. The critical difference will be the long-term durability of these agents, but this remains a largely unanswered question. Longer trials of both Macroplastique and Durasphere are not yet published. If newer bulking agents, which provide a lower initial cure rate over traditional surgical procedures, prove temporary a sling is likely to prove more cost effective [13]. Alternatively, if a bulking agent could provide lasting continence in one third of the women so treated, as is suggested by the available data from short-term follow-up studies (Table 1), bulking agents will continue to play a significant role in the management of SUI [14•,15,16•,17–28].

Use of Periurethral Bulking Agents for Anatomic Stress Urinary Incontinence

Based on the historic bias that bulking agents were unlikely to be useful where poor anatomic support was putatively the cause of incontinence, United States trials have largely been limited to patients with ISD. Contigen and Durasphere, the two FDA-approved bulking agents in use in the United States, are limited for use in patients with demonstrable ISD. However, most researchers accept that there is considerable overlap between SUI related to loss of extrinsic support and SUI related to ISD; hypermobility alone is a poor discriminator of those who leak or not. Additionally, several bulking agent trials analyzed success in relation to the presence of urethral hypermobility and found no correlation [17]. A retrospective review of Contigen administered to 60 women with ISD suggested that bulking agents were effective, regardless of the presence or absence of urethral hypermobility, and that these patients required no greater volume or number of injections to achieve success [25]. Stronger evidence for the effectiveness of bulking agents for anatomic SUI is supplied by the recent prospective multicenter trial of Contigen in 90 patients [26]. Bent *et al.* [26] included only those patients who exhibited evidence of urethral hypermobility on radiographic analysis, and excluded all patients with ISD radiographically diagnosed by an open bladder neck at rest. Using standardized endpoints of the Stamey grading system and abdominal leak-point pressure, 58 patients reached 12 months of follow-up: one third of the patients were dry and one third of the patients were improved, results extremely similar to bulking agents studies limited to the treatment of pure ISD (Table 1). Furthermore, the baseline abdominal leak-point pressure was not predictive of a successful outcome in either studies conducted by Steele *et al.* [25] or Bent *et al.* [26], although the latter authors were able to correlate an improvement in incontinence grade with improvement in abdominal leak-point pressure.

In addition, Bent *et al.*'s [26] multisite study underscored differences between objective study criteria and more subjective patient satisfaction. Nineteen of 58 patient were objectively improved; contrariwise, 36 (62%) considered themselves subjectively improved. This disparity could be because patients may report that they found bulking agent injection to be extremely valuable in improving their quality of life, although not necessarily resulting in cure. Thus, 96% of the improved patients were able to

Table 1. Selected reports of bulking agent trials by stress urinary incontinence diagnosis

Study	Bulking agent	SUI classification*	Patients, *n*	Improved, %	Dry, %	Reported follow-up
Bent *et al.* [14•]	Chondrocytes	III	32	31	50	< 12 months
Beckingham *et al.* [5]	PTFE	I, II, III	26	27	7	3 years
Lopez *et al.* [15]	PTFE	III	128	19	54	31 months (m)
Mayer *et al.* [16•]	Calcium hydroxylapatite	III	10	40	30	12 months
Herschorn and Radomski [17]	Collagen	I, II, III	181	52	23	21 months (m)
Faerber [18]	Collagen	I	12	17	83	10 months
Corcos and Fournier [2]	Collagen	I, II	40	40	30	50 months
Swami *et al.* [19]	Collagen	I, II, III	111	40	25	> 2 years
Cross *et al.* [20]	Collagen	III	139	94	NR	NR
Smith *et al.* [21]	Collagen	III	96	29	38	> 1 year
Haab *et al.* [22]	Collagen	III	22	62	24	7 months (m)
Appell [23]	Collagen	III	327	34	45	> 1 year
Gorton *et al.* [4]	Collagen	I,II, III	53	26	0.5	5 years
Stanton and Monga [24]	Collagen	I, II	32	29	50	12 months
Winters *et al.* [3]	Collagen	I, II, III	58	45	NR	24.4 (m)
Steele *et al.* [25]	Collagen	I, II vs III	9 vs 31	NR	71 vs 32	6 months
Groutz *et al.* [7]	Collagen	III	63	17	10	6.4 months (m)
Bent *et al.* [26]	Collagen	I, II	90	33	33	12 months
Su *et al.* [27]	Fat	I, II, III	26	15.4	50	12 months
Lee *et al.* [9••]	Fat	I, II, III	35	20.7	22.2	3 months‡
Radley *et al.* [12•]	Silicone	III	60	41.1	19.6	19 months (m)
Koelbl *et al.* [28]	Silicone	III	32	NR	59	12 months
Barranger *et al.* [6]	Silicone	III	21	42	10	2 years
Lightner *et al.* [11••]	Durasphere†	III	176	80.3	NR	12 months

*Stress urinary incontinence (SUI) types I and II refer to the degree of urethral hypermobility, unrelated to abdominal leak-point pressure. SUI type III refers to poor urethral function and may be measured by various means, including absence of hypermobility, open bladder neck at rest, or abdominal leak-point pressure.
†Carbon Medical Technologies, St. Paul, MN.
‡Equivalent to saline controls.
m—mean; NR—not reported; PTFE—polytetrafluoroethylene.

increase their activities of daily living. If the primary indication mandating intervention for SUI is the presence of urinary incontinence that significantly affects activities of daily living, a measured improvement in a patient's ability to proceed with just this is an important, yet underutilized, marker of treatment efficacy.

Correlates of Success

Clinical success with bulking agents has recently been correlated with complete circumferential bulking, as visualized by subsequent transurethral ultrasound examination, whereas a failed procedure will show incomplete filling [12•]. Failure rates increase with an increased number of injection sites [6], with significant vaginal atrophy [29], and in heavily surgically or otherwise scarred urethras, as has been the experience in male sphincteric incompetence.

Safety Issues and Complications

Acute local complications at the time of injection are acceptably low and include transient microscopic and gross hematuria, urinary retention, uncomplicated urinary tract infection, and as reported with all invasive SUI therapies, the development of de novo urge incontinence.

The use of certain agents is strongly discouraged. Autologous fat should be avoided because of its association with systemic embolization and death [9••,30]. PTFE is to be decried because of unfavorable safety profiles.

Complication rates, however, with Contigen, Durasphere (available in the United States), and Macroplastique (available in Europe) are extremely low; these complications are largely single case reports or are associated with few numbers of patients. Contigen is associated with one unique complication attributable to the material itself, that of an acceptably low rate of delayed hypersensitivity

response [31]. Other complications are potentially possible with all approved bulking agents and include a low incidence of a pseudoabscess. These fluid-filed cavities are larger in volume than the initially injected bulking agent, and can form at variable times after injection. The presence of a pseudoabscess may be indicated by obstructive voiding symptoms or true urinary retention. These phenomena have been variously reported as periurethral pseudocysts [32], pseudoabscesses [30], or noncommunicating diverticula [33], and while these defects have been mainly reported with Contigen they have also been observed with Durasphere (Lightner, submitted). The etiology of this fluid-filled cyst is unknown. Analysis of the reported cases demonstrate an overall lack of infection with either normal Gram stains of the material or normal flora on culture, except for a single report that suggested the periurethral fluid was infected [34]. When surgical exploration was performed, a thick-walled cystic or multiloculated cavity with few or no malignant changes was found. A similar process may be responsible for incidences of urethral prolapse reported with Macroplastique [35] and with Contigen [36], because injection into the periurethral stroma may cause localized separation, predisposing the patient to the prolapse (Scotti, Personal communication) or formation of pseudoabscess. Additionally, local pressure necrosis has been described in the dermatologic literature [37] and might result in subsequent diverticulum formation [38] and/or fistulization [39]. All injected materials are capable of migration when injected under pressure. Radio-opaque materials such as Durasphere are traceable, and migration has been reported without adverse sequelae [40]. Additionally, under the category of "anything can happen" a single case of osteitis pubis has been reported after bulking agent injection [41].

New Possibilities

Another type of bulking material used in the treatment of SUI is the microballoon. Urovive (American Medical Systems, Minneapolis, MN) is a 0.9 cm^3 silicone elastomer balloon that can be implanted periurethrally. Results are promising, with 70% of 19 women dry at last follow-up (up to 4 years postimplantation). The technique is complicated because balloons placed too close to the mucosa will erode. A newer implantable microballoon, the ACT system (Uromedica, Minneapolis, MN) allows for postprocedural adjustments to the volume contained within the balloon. The ACT system is currently undergoing early trials.

Clinical trials using Deflux (Q-Med AB, Uppsala, Sweden), a copolymer of dextranomer microspheres (80 to 250 μm) and hyaluronic acid, are planned after European studies have demonstrated this bulking agent has a high safety profile [42] and good efficacy [43]. This agent is stable in situ for up to 3 months and forms a framework for fibroblasts, and subsequently, new collagen formation.

Autologous chondrocytes harvested from ear cartilage and grown in cell culture were found to have high safety profiles and early success when injected into children with vesicoureteral reflux [44]. Autologous chondrocytes have recently been used to treat 32 women with ISD, with 50% of the patients dry at 12 months using rigid subjective and objective criteria. Importantly, 31% of the patients were improved after a single injection [14•].

Calcium hydroxylapatite, a normal component of bone, has also been investigated as a bulking agent because it remains pliable when injected into soft tissues [45]. This easily injected, radio-opaque material was used in 10 women with ISD; three of the women were cured and four women reported significant improvement at 1 year of follow-up [16•]. There was a high incidence of acute but spontaneously resolving urinary retention noted with this material. The material was otherwise well tolerated.

Alginate hydrogels, naturally occurring polysaccharides, are under investigation as an extracellular matrix capable of providing a scaffold for the ingrowth of soft tissues [46]. Alginate gel demonstrated good tissue ingrowth, vascularization, and stability of injected volume over time [47••], all characteristics desirable in a bulking agent for periurethral application.

The delivery of cells acting to augment sphincteric function and generate mild fibers may be possible if preliminary reports of success with autologous primary myoblasts are proven in future trials. Chancellor *et al.* [48••] demonstrated in a rat model that a cells from a mouse myoblast line could be delivered to, survive in, and regenerate myofibrils in the both bladder and urethra.

Other potential injectable materials may include small intestinal submucosa, now commercially available as a xenograft sheet for pelvic floor reconstruction (StrataSIS; Cook Biotech, West Lafayette, IN). Results from 6-month canine trials demonstrated that this material is capable of de novo smooth muscle generation at the site of injection [49•]. We await further trials with this and other agents.

Conclusions

The use of periurethral bulking agents yields a modicum of success in the treatment of SUI, resulting in a minimally invasive procedure and a high degree of patient safety and acceptance. Bulking agents appear to be equally efficacious when applied to the hypermobile urethra or the more classically defined ISD. Patient satisfaction with bulking agents is higher than strictly defined cure rates, as many women are pleased with improvement. The currently approved agents, likewise, appear similar in safety profiles and short-term efficacy. Long-term follow-up of Macroplastique and Durasphere are awaited with interest.

Research into tissue bulking materials remains of significant clinical importance. The development of new tissue replacement materials, expanders, and injectable

soft-tissue bulking agents has wide implications for congenital, post-trauma, burn, extirpative, or benign soft tissue reconstruction, and may ultimately yield new solutions for the treatment of SUI.

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