Current role of injectable agents for female stress urinary incontinence

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Aim: *The current role of injectable agents in the management for female stress urinary incontinence is reviewed.*

Materials and methods: *Published manuscripts for collagen, silicone microparticles, carbon beads, hyaluronic acid dextranomer and two investigational agents were evaluated.*

Results: *While injectable agents were used in the past for pure intrinsic sphincter deficiency there is good evidence that patients with hypermobility respond similarly. Collagen has been the most widely reported agent to date. Comparative studies with surgery have demonstrated inferior efficacy but a recent study showed a similar quality of life outcome. Newer agents have been designed for superior efficacy and durability. However, of the new agents carbon beads was not shown to be superior and the results of randomized trials of silicone microparticles and hyaluronic acid dextranomer compared to collagen have not yet been reported. All currently used agents appear to be very safe.*

Conclusions: *Injectable agents have been shown to have efficacy in the management of stress incontinence in women and should be readily available as a treatment option. The definite superiority of one agent over another has not yet been established.*

Key Words: stress urinary incontinence, injectable agents, female urology

Introduction

Injectable agents were first described in 1938 by Murless who reported injection of sodium morrhuate around the urethra.[1] Quackels[2] reported paraffin wax in 1955 and Sachse[3] used sclerosing agents in 1963. The initial results were poor and pulmonary emboli and urethral sloughing were not uncommon. Polytetrafluoroethylene (Teflon) paste, was first introduced by Berg[4] and then popularized by Politano[5] in the 1970s. Shortliffe and colleagues[6] published the first report on glutaraldehyde cross-linked collagen and autologous fat injection[7] was described subsequently. Since then newer agents with attributes to improve tolerability and durability have been introduced.

This article will summarize the techniques of administration, properties, published results, and complications of the agents used and review their current status and some of the controversies.

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Patient selection

Patients with intrinsic sphincter deficiency (ISD) and normal detrusor function are candidates for injectable agents.[8] McGuire et al[9] identified these patients with the use of abdominal leak pressures to measure the strength of the intrinsic sphincter. Low leak pressures (<65 cm water) correlated well with type 3 videourodynamic findings, i.e. a poorly functioning bladder neck and proximal urethra (ISD), and higher leak pressures correlated with types 1 or 2 hypermobility.

The presence of ISD is the primary indication for the use of injectable agents in patients with stress incontinence.[10] Since ISD can co-exist with hypermobility,[11,12] injectables have been administered to patients with hypermobility, to improve the ISD

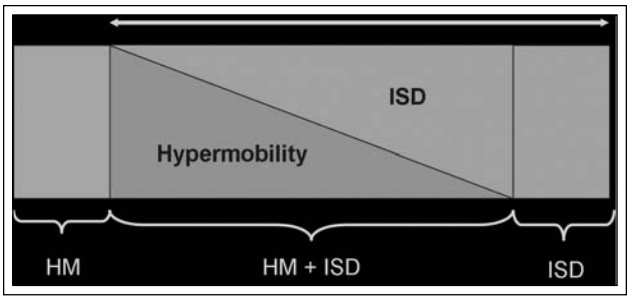

Figure 1. This schematic design depicts the different groups of women and with and without stress incontinence (SUI). The arrow across the top shows that the two right sided groups have SUI.
The box on the left is the Hypermobile (HM) group with no SUI. The large box in the middle is the group with Hypermobility and Intrinsic Sphincter Deficiency (HM + ISD). These women with hypermobility leak because they have ISD. (The ISD component in their SUI differentiates this group from the HM group that has no SUI.) The last group on the right are women with no hypermobility but have weak urethras or pure ISD. They also have SUI.

component of their incontinence.[13] Currently it is thought that all patients with stress incontinence have some degree of ISD, even those with hypermobility. A schematic way of depicting this is shown in Figure 1.

Mechanism of action of injectables

It is generally agreed that bulking agents improve intrinsic sphincter function. Collagen injections have been reported[10,14] to augment urethral mucosa, improve coaptation and intrinsic sphincter function as evidenced by an increase in post-treatment abdominal leak pressure.[15-17] Initial investigators with collagen[8,18] postulated obstruction as a mechanism of action, but Monga et al[14] showed that successfully treated patients have an increased area and pressure transmission ratio in the first quarter of the urethra. They suggested that placement of the injectable at the bladder neck or proximal urethra prevents bladder neck opening under stress. Proper placement of the injectable, possibly just below the bladder neck, rather than actual quantity[19] of the agent improves intrinsic sphincter deficiency (ISD).

The ideal injectable agent[20] should be easily injectable and conserve its volume over time. If unsuccessful it should not interfere with subsequent surgical intervention. It should also be biocompatible, nonantigenic, noncarcinogenic and nonmigratory. To date, no substance has met all of these requirements.

Injection techniques

The materials can be administered under local anesthesia with cystoscopic control as an outpatient procedure. Both the **periurethral** and **transurethral** methods are done to implant the agent within the urethral wall, preferably into the submucosa or lamina propria. It is thought that the implant should be positioned at the bladder neck or proximal urethra. Different sites can be chosen such as 3 and 9 o'clock or 4 and 8 o'clock positions. Although Defreitas and colleagues[21] demonstrated that patients with circumferentially distributed implants had better results than those with random deposits. The actual needle size required depends on the viscosity of the injectable. Pre- and postoperative antibiotics are usually administered.

The implant can also be injected transurethrally through the cystoscope with flexible needle-tipped catheters or with injection scopes and rigid needles. Silicone microparticles, due to their high viscosity, require the use of an injection gun. Devices for injection without cystoscopy have been designed. Taminini and co-workers[22] used a device that fits into the urethra and though needle guiding channels Macroplastique was injected into the 2, 6, and 10 o'clock positions. Similarly the Zuidex system involves injection of hyaluronic acid dextranomer into four quadrants of the urethra through an Implacer system.[23]

Collagen

Glutaraldehyde cross-linked collagen or Gax-collagen is a highly purified suspension of bovine collagen in normal saline containing at least 95% type I collagen and 1% to 5% type III collagen.[24] This cross-linking makes the Gax-collagen resistant to the fibroblast-secreted collagenase. As a result of this, the Gax-collagen is only very slightly resorbed. The implant causes no inflammatory reaction or granuloma formation and is colonized by host fibroblasts and blood vessels. It is not known to migrate. However, it does degrade over time and theoretically is replaced by host collagen, to explain its persistence.[24]

Since 2% to 5% of patients[25] are sensitized to collagen through dietary exposure, all patients must undergo a skin test 30 days prior to treatment. Positive responders should be excluded.

Collagen results

Many reports of its efficacy, safety, ease of administration, and relative lack of morbidity have

appeared since the first description for urinary incontinence. Table 1 lists various reported series.

Persistence of the implant itself has been demonstrated with magnetic resonance imaging of the urethra at intervals of up to 22 months after injection although the measured volume was less than that

TABLE 1. **Comparison of collagen parameters and results**

Study	No. pts.	Type of incontinence	Follow-up (mo)	No. pts. dry (%)	No. pts. improved (%)	No. pts. failed (%)
Stricker and Haylen[57]	50	ISD	Mean: 11 Range: 1-21	21 (42)	20 (40)	7 (14)
Kieswetter et al[58]	16	Not specified	9	7 (44)	7 (44)	2 (12)
Eckford and Abrams[18]	25	Not specified	3	16 (64)	4 (16)	5 (20)
O'Connell et al[59]	44	42 with ISD 2 hypermobile	1-2 (longest 7)	20 (45)	8 (18)	16 (37)
Moore et al[31]	11	Types 1 and 3	2	1 (9)	7 (63)	2 (18)
Winters and Appell[16]	50	ISD	>12	48 (96) dry or socially continent		2 (4)
McGuire and Appell[10]	17 137	Mobile ISD	>12 >12	8 (47) 63 (46)	3 (17) 47 (34)	6 (35) 29 (19)
Faerber[13]	12	Type 1	10.3 (Range 3-24)	10 (83)	2 (17)	0
Monga et al[14]	60	some hypermobile	3 (N=59) 12 (N=54) 24 (N=29)	27 (46) 22 (40) 14 (48)	24 (40) 20 (37) 6 (20)	
Richardson et al[17]	42	ISD	46 (10-66 after 1st injection)	17 (40)	18 (43)	7 (17)
Herschorn et al[12]	181	Type 1: 54 Type 2: 67 Type 3: 60	Mean: 22 (Range 4-69)	42 (23)	94 (52)	45 (25)
			>=24 (N=62) >=36 (N=25)	27 (43.5) 13 (52)	29 (46.8) 8 (32)	6 (9.7) 4 (16)
Smith et al[60]	94	Type 3	Median: 14	36 (38.3)	27 (28.7)	31 (33)
Khullar et al[19]	21	Not specified	24 (minimum)	10 (48)	2 (9)	9 (43)
Swami et al[61]	107	some hypermobile	24 (minimum)	27 (25)	43 (40)	37 (35)
Cross et al[28]	103	Type 3	Median: 18 (Range 6-36)	Substantially improved 103 (74)	29 (20)	7 (6)
Groutz et al[62]	63	Type 3	6	8 (13)		44 (70)
Bent et al[32]	90	Types 1 and 2	12	19 (21)	19 (21)	11 (17)
Corcos and Fournier[63]	40	Type 1 (8) Type2 (20) Type3 (12)	52	12 (30%)	16 (40%)	62 (58)

injected.[26] Ultrasound has also been used.[21,27]

Early results are generally good with success rates of 72% to 100%,Table 1. Maintenance of good results in the long-term may be from durability of the initial procedure itself or from reinjections with additional collagen. It is important for authors to differentiate the durability of the original procedure(s) from reinjections or top-ups by reporting the follow-up period starting from after the last injection.

Longer-term results of more than 1 to 2 years, vary from 57%, cure and improved,[19] to 94%.[28] Most patients need 1-2 treatment sessions with means of 5.6 cc to 15 cc of collagen. Since patients are treated at different times and durations of follow-up vary the Kaplan-Meier curve can be useful to display the persistence of a good result. In our series,[12] the probability of remaining dry was 72% at 1 year, 57% at 2 years, and 45% at 3 years, Figure 2. Winters and Appell[16] also reported a similar 50% rate of complete continence in the multicentre trial after 2 years. Additional administration of collagen usually resulted in restoration of continence and this has to be factored into the reporting.

Berman and Kreder[29] analyzed the cost effectiveness of collagen versus sling cystourethropexy for type 3 incontinence. They concluded that surgery was more cost effective than collagen. Corcos and colleagues[30] reported the results from a multicentre prospective randomized trial of collagen versus surgery. Although the success rate of the surgery was significantly higher than that of collagen after 1 year (72.2% versus 53.1%), the general and disease-specific quality of life scores were similar in both groups. Furthermore, the satisfaction with treatment rate was not different and there were fewer and less serious complications in the collagen group.

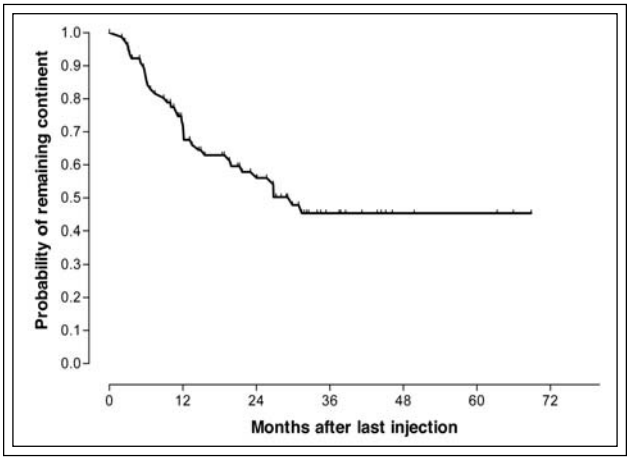

Figure 2. Durability: Kaplan-Meier curve showing durability of cure of incontinence after the last collagen injection in 78 patients .[12]

The use of collagen for patients with hypermobility has also been reported. Moore et al[31] included patients with mild hypermobility as did Faerber and colleagues.[13] In the report by McGuire and Appell,[10] the results at more than 1 year in women with ISD were similar to those in women with hypermobility, although there were far more women with ISD. However, Appell[8] subsequently reported that these patients with hypermobility all required bladder neck surgery within 2 years. Monga et al[14] included patients with hypermobility and found that cure rates were not reduced for women with up to 2.5 cm of movement. In our series of 181 patients there was no significant difference in outcome with or without hypermobility.[12] Additionally, Bent and colleagues reported a good outcome after 1 year in a prospective trial of patients with hypermobility.[32]

Collagen complications

Treatment related morbidity has been minimal. Urinary retention ranges from 1%-21%[8,15,16] and can be managed with intermittent catheterization or short-term foley. Urinary tract infection occurs in 1%-25%.[8,15,16] Extravasation resolves quickly with flushing away of the dilute collagen suspension and sealing over of the small needle site. Hematuria can occur in 2% of patients.[8] Other rare complications include periurethral abscess formation.[33]

Other complications include de novo detrusor overactivity, seen in 11 of 28 elderly women (39%) treated by Khullar et al.[19] Stothers et al reported de novo urgency with urgency incontinence in 43 of 337 patients (12.9%), 21% of whom did not respond to anticholinergics.[34]

Another rare complication is a reaction in the previously negative skin test site following a urethral collagen injection.[25] This occurred in three patients (1.9%) and was associated with arthralgias in two. This reaction has been reported before in the dermatologic literature[35] and two negative pretreatment skin test have been suggested to prevent it. The potential for hypersensitivity reactions is present since antibody production is stimulated by collagen injection.[36]

Silicone microparticles

Silicone microparticles[37] are solid polydimethylsiloxane (silicone rubber) particles suspended in a non-silicone carrier gel that is absorbed by the reticuloendothelial

system and excreted unchanged in the urine. Since 99% of the particles are between 100 mm and 450 mm in diameter, the likelihood of migration is low. Henly et al[38] demonstrated distant migration of small particles, less than 70 mm, but no migration of particles greater than 100 mm in diameter. Although there was a typical histiocytic and giant cell reaction within the injection site, there was no granuloma formation in response to the larger particles. Since the substance is quite viscous it must be injected with an injection gun and a 16-gauge tip transurethral needle.

Silicone microparticles results

The results from reported series using this injectable are shown in Table 2. Hariss et al[37] reported on 40 patients followed for a minimum of 3 years at which time 16 (40%) were dry, 7 (18%) were improved, and 17 (42%) failed. Twelve of the 16 required one injection and four needed two injections to become dry. Sheriff et al[39] reported an overall success of 48% in 34 patients after unsuccessful stress incontinence surgery and Koelbl et al[40] reported a 60% success rate in 32 women after 12 months but noted a time-dependent decrease in success. Radley et al reported a success rate of 61% (19.6% cured and 41.1% improved) in 60 women after a mean of 19 months.[41] Barranger et al in a group of 21 patients reported a dry rate of 19%, improved rate of 38% and failure rate of 52% at a median follow-up of 31 months. Interestingly, they did not observe a time dependent decrease in results.[42]

Similar success was shown by Tamanini and co-workers[22] using an implant system that allows a transurethral injection without cystoscopy.

Ter Meulen and colleagues[43] did a systematic review of silicone microparticle reports. Accessible literature consisted of 13 published manuscripts and 37 abstracts. They reviewed two randomized control trials published as abstracts and 11 pre-experimental or observational studies. The methodologic weakness that they found were a lack of random allocation procedure and pre-stratification on prognostic determinants, no blinding, small sample sizes, and a lack of proper analysis and presentation of the results. Other weaknesses were the variability in the indications for the procedure, the implantation procedure itself, and the rate and volume of silicone microparticle injections. Different outcome measures also made the studies difficult to compare. Overall they found the studies to be of low methodologic quality and could come to no firm conclusion about efficacy. This presents a challenge to investigators to improve the quality of studies for all injectables.

A North American randomized control trial (RCT) of silicone microparticles versus collagen has been completed and the results are pending.

Silicone microparticles complications

Self-limited side effects of hematuria, dysuria, frequency, and retention have been reported in a minority of patients. The lack of a granulomatous reaction and migration of the large silicone particles may provide some benefit over older agents like teflon although long-term data are not yet available. Despite the laboratory and clinical evidence of safety with the large particles, concerns still exist about the small silicone particle migration and long-term tissue response to the injection.[44]

Carbon beads (Durasphere)

Another bulking agent designed to be biocompatible and composed of nonmigratory and nonabsorbable pyrolytic carbon-coated zirconium oxide beads suspended in a carrier gel was reported by Lightner and colleagues.[45] The bead size ranges from 251 mm to 300 mm, more than three times larger than the 80

TABLE 2. **Results of Macroplastique injections**

Study	No. pts.	Follow-up (y)	No. pts. dry (%)	No. pts. improved (%)	No. pts. failed (%)
Hariss et al[37]	40	3	16 (40)	7 (18)	17 (42)
Sheriff et al[39]	34	2	16 (48)		18 (52)
Koelbl et al[40]	32	1	19 (60)		13 (40)
Radley et al[41]	60	1.5	12 (20)	25 (41)	23 (39)
Barranger et al[42]	21	2.5	4 (19)	8 (38)	9 (43)
Tamanini et al[22]	21	1	12 (57)	4 (19)	5 (24)

mm threshold for particle size associated with migration in tissue.[46] The absorbable carrier gel is 2.8% glucan – a polysaccharide used in wound healing. The agent is pre-packaged in 1.0 ml syringes and administered transurethrally through an 18-gauge needle.

In a multicentre prospective randomized double-blind trial,[45] with collagen as control, at 1 year after the last treatment 49 of 61 women (80.3%) treated with Durasphere showed improvement of one continence grade or more compared with 47 of 68 women (69.1%) treated with collagen (P=0.162). The difference was not statistically significant. There was also no difference in number of injections or pad weight test. However, the injected initial and repeat injection volumes of Durasphere were significantly lower than those of collagen. The adverse events were similar in both groups but the Durasphere group had an increased short-term risk of urgency and urinary retention. Pelvic x-rays taken at 1 and 2 years after injection showed stability of the bulking agents at the injection site. This suggests potential durability.

In another small series of 13 women and 7 men treated with Durasphere injections, Pannek and co-workers[47] reported an overall 12-month success rate of only 33%. Furthermore they demonstrated bead migration on plain x-rays in two asymptomatic patients. Their report has generated considerable controversy.

Chrouser and colleagues[48] reported a longer term follow-up of patients in the original RCT from a single institution. Forty-three of the original 56 were available. Treatment was initially successful in 63%. At 24 and 36 months Durasphere remained effective in 33% and 21% respectively. At an extended follow-up of 51 months 9 (21%) patients reported that their treatment was still effective. They matched these patients to a cohort treated with collagen and showed similar results.

Durasphere is not available in Canada.

Hyaluronic acid dextranomer (Deflux, Zuidex)

Non-animal-stabilized hyaluronic acid dextranomer (NASHA/Dx) copolymer comprises dextranomer (Dx) microspheres (80 to 250 mm) in a carrier gel of non-animal-stabilized hyaluronic acid (NASHA). The gel is a biocompatible, biodegradable material free of animal products, has no immunogenic properties, and has been shown not to migrate to different organs after submucosal injection.[49] Stenberg and colleagues first reported the use of this substance in 20 women. They injected it transurethrally through a cystoscope. After 6 months nine were cured, seven improved, and three failed. Between 6 and 7 years later five remained dry and four were still improved. Overall nine of the original 20 had a long-term response.

Subsequently the procedure was modified by injecting the NASHA/Dx copolymer through a system consisting of a handle (Implacer) through which four needles with attached syringes are mounted. A plastic protector is pushed forward to sheathe the needles. It is inserted into the urethra and positioned below the bladder neck, by measuring the distance from the meatus. The barrel is slid backwards to unsheathe the four needles and a total of 2.8 cc of NASHA/Dx is injected blindly into the urethra, 0.7 cc into each quadrant. Van Kerrebroeck and colleagues[23] reported early results in 42 women. Thirty-two (76%) had improvement in leakage at 3 and 12 months. Chapple and colleagues[50] recently reported the results of 142 patients treated in a European multicentre trial. The protocol consisted of an initial injection followed by another at 8 weeks if required. A total of 61 patients (43%) underwent the second injection. At month 12, 77% of the patients demonstrated a positive response which was ≥50% decrease in leakage on provocative testing. The side effects were similar to other injectables apart from an injection site pseudocyst in six patients. Four of these were drained and all six resolved. There were also three injection site infections.

A North American multicentre RCT with collagen is currently ongoing.

Autologous chondrocytes

A bulking agent composed of autologous chondrocytes has been used to treat children with vesicoureteral reflux.[51] Animal studies of the implant demonstrated stability and lack of migration over time.[52,53] The injectable material consists of autologous chondrocytes in a calcium alginate gel administered endoscopically through a 22-gauge needle. The chondrocytes obtained from biopsy of the external pinna of the patient's ear are expanded in tissue culture and combined with a carrier gel that degrades after injection.

Bent and co-workers[54] reported 12-month results in 32 women after a single outpatient injection in a multicentre trial. Incontinence grading indicated 16 patients dry and 10 improved for a total of 26 (81.3%). Side effects were minimal.

Calcium hydroxyl apatite

This normal constituent of bone can be synthesized and formulated in a size to resist migration. It can be

used for soft tissue augmentation and does not form heterotopic bone.[55]

Mayer and colleagues[56] reported results in ten women at 1 year. The substance used had a mean particle size of 100 mm and was injected transurethrally through a 7F catheter with a 21-gauge needle tip. Seven women were substantially improved, two used fewer pads and one had no change. No significant complications were seen.

Comment

Most of the literature reported to date consists of case series and collagen is the most widely reported injectable agent. Collagen has been compared to surgery in a randomized trial design and, as expected, did not perform as well but the patients were as satisfied and had suffered less than the group that had undergone surgery; albeit surgery that was more invasive than the new mid-urethral synthetic slings. The Durasphere randomized trial versus collagen is the only RCT that has been reported. There was no significant difference in the outcome. Although newer injectable agents like Zuidex and Macroplastique have theoretically superior characteristics to collagen, the RCT results have not yet been reported. We look forward to these reports.

Although we do not know which agent will prove to be superior, we do know that this is a truly minimally invasive treatment with an excellent safety profile. It can be administered to women of all ages who have urethral hypermobility or pure ISD. It will probably never be as effective as surgery but it has efficacy and can improve continence and quality of life. As such, it should be available to patients as a treatment alternative for stress incontinence. □

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