Injectable Bulking Agents for the Treatment of Stress Urinary Incontinence

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Abstract

Urethral Bulking Agents (UBAs) are injected locally as a minimally invasive procedure for Stress Urinary Incontinence (SUI) and are beneficial for properly selected patients. Many different materials have been developed and are available, although none so far meet all the requirements of an ideal agent. The first UBA was cross-linked bovine collagen (Contigen®), followed by autologous fat injections, solid silicone particles (Macroplastique®), microspheres covered with pyrolytic carbon (Durasphere®), calcium hydroxyapatite (Coaptite®), polyacrylamide hydrogel (Bulkamid®), and dextran/HA copolymer (Zuidex®). The latest product development is PDMS-U, a silicone gel bulking agent that polymerizes in situ (Urolastic®).

The ideal urinary bulking agent could consist of permanent microspheres, which immediately elicit a modest foreign body reaction along with the production of fibro-vascular tissue, which encapsulate every single microsphere individually and prevent their migration from the injection site. Polymethylmethacrylate microspheres have a successful history as dermal fillers used world-wide and can be safely injected submucosally at the urinary sphincter under direct vision, rather than peri-urethrally into the muscle like most of the present agents.

Overall, short-term clinical results with most of the currently used urinary bulking agents are encouraging; however, longer follow-up results are often disappointing and retreatment is required. Proper patient selection and a safe, biocompatible and non-migrating bulking agent that elicits permanent fibro-vascular tissue formation at the injection site are paramount to successful treatment of stress urinary incontinence.

Introduction

Stress Urinary Incontinence (SUI) is a major ubiquitous health problem and the most common form of urinary incontinence (75%) is often associated with childbearing and weakening of the pelvic muscles that support the bladder. SUI can be defined as a brief involuntary loss of urine due to increase of abdominal pressure in the absence of detrusor activity (Figure 1). The primary symptom of SUI is urine leakage during physical activities such as coughing, laughing, sneezing, lifting, or exercise. An estimated 85% of all patients with SUI are women and the prevalence of SUI in the U.S. ranges from 26% to 31% for all women (1:3 women), with the highest incidence in women aged 40 to 60 years, representing 30 million and 13 million women, respectively [1].

More specifically, the prevalence of severe SUI, defined as large amounts of urine leakage weekly, affects approximately 29% of women aged 25 to 44 years, 33% of women 45 to 60 years, and 86% of women over age 60 years [2].

SUI is a common problem in women with a complicated and multifactorial cause. The importance of vaginal childbirth injury in the predisposition to SUI is well known, and likely involves neurologic, muscular, and supportive tissue damage (Figure 2). Animal models of SUI replicate pudendal nerve injury as observed in women and the neurologic effects of indirect pelvic floor injuries. Animal model investigations are beginning to elucidate the neurologic and molecular mechanisms of the recovery of continence. Further research into the pathophysiology of childbirth injury and the promotion of continence preserving trainings and techniques is indispensable [3].

Treatment Options

Current treatment options for SUI beyond the use of absorbent products include behavioral or muscle therapy, medication, non-surgical medical devices including Urinary Bulking Agents (UBAs) and more invasive procedures such as slings and vaginal tapes and surgical procedures such as the Burch retropubic suspension. First line treatment is usually pelvic floor muscle exercise (Kegel). Medication and electrostimulation is usually reserved for an overactive bladder and urge incontinence [3].

Because SUI is largely a structural and sphincter-related problem, 'tissue bulking' can provide significant relief by restoring the 'mucosal seal mechanism'. The initial introduction of injectable bulking agents has provided physicians with an additional option to treat SUI. The advent of

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Figure 1: Human urethra and its muscular sphincter.

newer agents with unique individualized merits and newer injection techniques promises to dramatically alter the role of injectable bulking agents in the overall management of SUI (Figure 3).

The main advantage of injectables is their easy out-patient procedure and their safety profile, even in very ill patients. The most common complaint is pain during injection and the most common complications in the immediate post-procedure period are urinary retention and voiding dysfunction, both of which are easily treatable with intermittent self-catheterization using a 12-French catheter.

Intrinsic Sphincter Deficiency (ISD) and hypermobility

Bulking agents were originally considered to have greatest utility in patients with ISD, before patients with hypermobility were studied in the U.S. in any detail to derive benefits from this therapy [4]. In fact, no significant difference in outcomes was seen in patients with or without hypermobility in their studies. Interestingly, patients with hypermobility required less bulking agent for a successful outcome. Monga et al. [5] reported on 60 women with genuine stress incontinence and urethral excursion ("mobility") up to 25 mm. Objective cure rates (according to urodynamic assessment) were 61% at 3 months and 48% at 24 months. Subjective success rates were 86% and 68% at 3 months and 24 months, respectively.

Figure 2: Bulking agents are injected in form of blebs into or around the urethral sphincter muscle (credit: EAU Patient Information).

Figure 3: The supporting tissues of the urethra (credit: Netter Anatomy).

Sling/tape procedures

The gold-standard in the treatment of SUI today is still the upward suspension of the descended urethra with the help of a 1 cm wide plastic band, the Tension-Free Vaginal Tape (TVT) in the retropubic tissue [6] (Figure 4). An estimated 260,000 sling procedures are performed annually in the U.S. [7]. Long-term results show an improvement of SUI in about 60-80 % and a full success with dryness in around 20% of the treated patients [8]. The latest study on trans-obturator TO-TVT operations is associated with patient-reported success rates of 62% in women with previous failed continence surgery in up to 9-years follow-up [9].

There is robust evidence to support the use of Mid-Urethral Sling (MUS) from over 2,000 publications, making this treatment the most extensively reviewed and evaluated procedure for female SUI now in use [6]. It is, however, acknowledged that any operation can cause complications. For MUS (Figure 5), these include bleeding, damage to the bladder and bowel, voiding difficulty, tape exposure, and pelvic pain; all of these may require repeat surgery, but this is uncommon.

Mid-urethral sling failures

Mid-urethral sling operations have been the most extensively researched surgical treatment for Stress Urinary Incontinence (SUI)

Figure 4: A TVT-band consists of a mesh.

in women [8]. Ford et al. [10] reviewed 81 trials with 12,113 women and concluded that MUS operations have a good safety profile. Despite all positive reports on mid-urethral sling procedures, a certain number of extrusion, dislocation and loosening is a fact in all statistics [11]. It is therefore logical to try a bulking agent in these patients and satisfying results have been achieved after mid-urethral sling failure [12,13]. Surgical failure rates after MUS procedures are variable and range from approximately 8 to 57% at five years of follow-up [11,12,14].

Comparison of sling and bulking agents

According to current evidence, bulking agents should not be proposed as first-line treatment in those women seeking permanent cure for both primary and recurrent SUI [15]. A recent Cochrane review illustrates that no high-quality data exists to recommend or refute any of the different management strategies for recurrent or persistent Stress Urinary Incontinence (SUI) after failed MUS surgery [1,16]. Similar rather low success rates are also reported after the injection of the presently approved bulking agents [17] and this fact presents an opportunity for an improved UBA as an alternative treatment option [18].

Urinary Bulking Agents (UBAs)

The use of injectable agents for the treatment of SUI has first been described in 1938 by Murless and later popularized by Quackles and Sachse in the 1950s and 1960s. Their application has been limited by placement, durability, antigenicity or tissue compatibility issues (Figure 6). The “ideal” bulking agent should possess all of the following properties [19]: ♣ Non-immunogenic, ♣ Permanent, ♣ Non-migratory, ♣ Non-erosive, ♣ Non-inflammatory, ♣ Easily stored and handled, ♣ Easily injected, ♣ Painless, ♣ No long-term side effects, ♣ High safety profile, ♣ Persistent pliability.

UBAs reported in the literature include FDA-approved bovine collagen (Contigen[®], C.R.Bard), which was discontinued in 2011 in favor of their Adjust-Sling[®], carbon-coated zirconium oxide beads (Durasphere[®], Coloplast[®]), polydimethylsiloxane (silicone) particles (Macroplastique[®], Cogentix Medical) and calcium-hydroxylapatite (Coaptite[®], Boston-Scientific). Furthermore, autologous fat is harvested from the lower abdomen and injected around the urethra.

Peri-urethral bulking agents are substances that are injected peri-

urethrally to increase tissue bulk as a treatment of stress incontinence [20] (Figure 4). Patients receive one or several treatment sessions. A number of products have been developed and are commercially available; key factors in determining the optimal product are biocompatibility, durability and absence of migration. After FDA approval in 1995, Contigen[®] has been discontinued in 2011, carbon-coated beads (Durasphere[®]) received FDA approval in 1999 for use as peri-urethral bulking agent, being more durable than collagen. In 2005, a bulking agent composed of spherical particles of Calcium Hydroxylapatite (CaHA) in a gel carrier (Coaptite[®]) received FDA approval for use in women. Polydimethylsiloxane (silicone particles, Macroplastique[®]) received FDA approval in 2006 for transurethral injection. The FDA approvals are conditional on the enrollment of a minimum of 200-250 patients into a 5-year registry to further evaluate safety and efficacy.

Description of UBAs

UBAs approved by the FDA: As a second bulking agent, *Durasphere[®]* received FDA approval in 1999 [21]. The study found no difference in efficacy or in the number of treatments between the groups, although the trial length of 12 months may not have been long enough to assess comparative durability [22]. A major concern with Durasphere has been difficulty associated with the injection process, as carbon beads can become clogged in the syringe with loss of the carrier gel (Figure 6). *Durasphere[®]* has been associated with repeated local lymphatic and peri-urethral dislocation of carbon beads [23,24] and urethral prolapse due to the relatively high weight of the carbon coated zirconium beads and lack of tissue in growth [25].

Coaptite[®] (calcium hydroxylapatite, CaHA) received FDA approval in 2005 based partly on results from 231 (78%) of 296 enrolled women [26]. *Coaptite[®]* has been reported to be associated with urethral prolapse [27-30] owing to the lack of fibro-vascular tissue ingrowth and encapsulation [25]. As with bovine collagen (Contigen[®]), most patients who receive *Coaptite[®]* required additional injections after one year because the bulking effects tend to fade over time due to product absorption [27] (Figure 7).

FDA approval of *Macroplastique* (polydimethylsiloxane) in 2006 was also partly based on a randomized non-inferiority comparison with collagen in women with SUI [31]. At 12 months, 45 of the 67 (67%) patients evaluated at 24 months were dry (Stamey grade 0).

Figure 5: The TVT sling is loosely anchored in the tissue of the abdominal wall (credit: EAU Patient Information).

Figure 6: Durasphere[®] consists of comparatively heavy microspheres, which may be dislocated caudally due to gravitational forces.

Figure 7: The microspheres of calcium-hydroxyl apatite (Coaptite®) are shown during the process of absorption at 9 months.

Macroplastique remains relatively stable at the injection site, but has shown to cause excessive foreign body granulomas [32-34] most likely due to its irregular particles with sharp corners and edges [35] (Figure 8). Due to the relatively large size of those particles (10 µm-600 µm; average 140 µm) and a larger bore needle requirement (18 G), the product is also associated with the risk of peri-urethral injections.

Furthermore, because about 25% of the silicone particles are smaller than 50µm in size, they can be susceptible to migration [35]. Histologically, after injection, silicone particles are invaded by macrophages and fibroblasts, resulting in firm nodules 6 weeks after implantation [36] (Figure 9). A recent report [33] includes the cases of two women whose initial success was followed by rapid return of stress urinary incontinence several weeks later associated with growth and extrusion of the Macroplastique material. It could also be called a typical foreign body granuloma, as it occurred often after subdermal injection of Macroplastique [35]. In 2017, another similar case was published from the same Institute in San Diego [34].

Figure 8: Macroplastique® contains silicone flakes between 10- 600 µm in diameter.

Figure 9: Macroplastique histology shows strong foreign body reaction at 9 months

Deflux®: Q-Med (now Galderma) has been collecting data in Europe for a dextranomer/hyaluronic acid copolymer (Zuidex®) together with an injection system (Implacer®) for treatment of incontinence. A Dx/HA formulation (Deflux) from the same company has been commercially available for a number of years for the treatment of vesicoureteral reflux in children and has been tried as UBA as well [20].

Since the U.S. Food and Drug Administration approved dextranomer/hyaluronic acid copolymer (Deflux) for the treatment of vesicoureteral reflux in 2001, endoscopic injection therapy using Deflux has become a popular alternative to open surgery and continuous antibiotic prophylaxis. However, in recent years a less stringent approach to evaluating Urinary Tract Infections (UTIs) and concerns about long-term efficacy and complications associated with endoscopic injection have limited the use of this therapy [20]. Additional studies reported that Deflux was associated with more frequent pseudo-abscess and *de novo* urge incontinence [23,37].

Figure 10: PAAG gel (Bulkamid®) is rather inert but can be slowly phagocytosed by foreign body giant cells.

Bulking Agents in Europe: *Polyacrylamide hydrogel* (Bulkamid[®] (Contura Inc., Denmark) is a gel containing 2.5% cross-linked polyacrylamide (PAAg) and 97.5% water [13] (Figure 10). Findings from a multicenter European case series were published in 2010 [39]. A total of 135 adult women with symptomatic stress (n=67) or mixed (n=68) incontinence for at least 12 months and at least one episode of incontinence per day were included. The response rate at 6 and 12 months was 71% and 66%, respectively. Corresponding cure rates were 16% and 24%.

There were 32 treatment-related adverse effects including two cases of urinary retention requiring hospitalization and 10 cases of Urinary Tract Infection (UTI). A recent study by Mohr, including 154 women, achieved similar results after three months with an overall complication rate of 13% [40] and longer-term follow-up is required. In a European study in 60 women with failed slings the volume of Bulkamid[®] injected in the current study ranged from 1-3 ml [12], cured/improved rates were 83.6% at 12 months. Patients with MUI had a cured urgency urinary incontinence rate of 38.9%.

Urolastic[®] (Urogyn BV, Nijmegen) is a non-deformable, non-resorbable silicone elastomer that cures after injection (Figure 11). In a clinical trial in The Netherlands 88% of the patients showed subjective improvement at 25 months follow-up [41]. The rate of objective improvement experienced was 50-70%. The rate of complications classified as Clavien-Dindo>II was 24-33%. Another study from Holland reports subjective improvement by 18 of the 20 included patients [42]. The subjective cure rate was 56% and the objective cure rate was 65% at 6 month.

In a recent study from Poland, the objective success rate at 24 months was found in 32.7% patients; including 22.4% patients who were completely dry [43]. Overall, complications were observed in 17 (25.8%) patients. Although only about 30% of patients will benefit from Urolastic injection on the long-term basis, it seems to be a safe procedure in the treatment of recurrent stress urinary incontinence.

Figure 11: Urolastic[®] behaves like fully cured solid silicone in the body and is encapsulated like all solid silicone implants (shown: excised Urolastic).

Autologous cell therapy

A cell-based therapeutic approach to regenerate the sphincter muscle offers the advantage of treating the cause rather than the symptoms. Currently, clinically relevant cell therapy approaches are discussed for regeneration of the external urethral sphincter (striated muscle), internal urethral sphincter (smooth muscle), the neuromuscular synapse, and blood supply. The use of mesenchymal stromal/stem cells is a major step in the right direction, but they may not be enough for regeneration of all components of the urethral sphincter. Inclusion of other cell types or biomaterials may also be necessary to enhance integration and survival of the transplanted cells [44].

Some recent studies have focused on the use of stem cells for treatment of SUI, both for female SUI and for post-prostatectomy incontinence in men [45]. Current research has focused on autologous cells, derived either from muscle or from adipose tissue. These stem-cell therapies for urinary incontinence may have the ability to regenerate a damaged or weakened rhabdosphincter, however because their effect is improved sphincter function rather than coaptation from a bulking effect, they are not discussed further in this article.

Contraindications for UBAs

Peri-urethral bulking agents should not be used in the setting of pure urge incontinence or bladder outlet obstruction. A patient with mixed incontinence (e.g. SUI and urge incontinence) in whom the urge component is the predominant problem, may elect to address the symptoms of bladder over-activity before bulking up the urethra, but may find that treatment of the SUI also improves the urge incontinence.

Combination therapy

It is generally agreed that certain patients respond better to peri-urethral bulking than sling or tape procedures. If injection bulking does not provide sufficient relief after two injections, a suburethral sling can be performed without concern for residual material. If an anti-incontinence procedure or other pelvic floor surgery has been performed first and SUI persists or occurs, there is no contraindication to using a bulking agent, which is often highly effective in these cases [11-13].

Figure 12: 125 µm PMMA-microspheres have a 30 x larger volume than 40 µm PMMA-microspheres.

Overview of UBAs

In 2016, Matsuoka et al. [17] reviewed 28 articles with 1814 patients in fourteen trials of seven different types of urethral injection bulking: glutaraldehyde cross-linked collagen (Contigen), solid silicone elastomer (Macroplastique), autologous fat, carbon covered zirconium beads (Durasphere), calcium hydroxylapatite (Coaptite), polyacrylamide hydrogel (Bulkamid) and dextran/HA copolymer (Zuidex) [17]. There was a common tendency for the improvement in urinary incontinence to decrease over time in these studies, but no consensus as to the best agent and injection technique could be reached. According to Rovner and Goudelocke [46], “the ideal periurethral injectable agent has not yet been identified although many of the currently used agents have acceptable efficacy in selected populations” [47].

U125: Proven Safety of Injectable Polymethylmethacrylate (PMMA) Microspheres

PMMA was first synthesized in 1902 and has since been widely used in the human body as bone cement, artificial dentures, intraocular lenses, cardiac pacemaker covers, and in various other medical device implants for over 50 years [18]. Due to its excellent tissue biocompatibility, PMMA is today considered one of the safest biomaterials for human use. Its outstanding biocompatibility and lack of toxicity have been documented in many studies since 1930 [48-51].

When used in microsphere powder form, PMMA spheres are completely round with an extremely smooth surface to avoid foreign body reactions (Figure 12). When injected into soft tissue they cannot be broken down by enzymes, and if larger than 20 µm, they cannot be phagocytized [52]. The safety profile of PMMA microspheres was submitted to the FDA for review and was accepted in 2004 [18,53].

Injectable bovine collagen, until most recently, had been considered the gold-standard UBA and used for the treatment of SUI for almost two decades (Contigen®). U125 contains bovine collagen extracted from calf hides that are obtained from a controlled U.S. herd to eliminate the risk of Bovine Spongiform Encephalopathy (BSE) [18]. Soft tissue augmentation with PMMA microspheres is achieved through the stimulation of natural human collagen encapsulation and fibro-vascular issue in growth. After this remodeling process is complete, 80% of the final tissue bulk consists of the patient's own

Figure 13: PMMA microspheres become part of “living fibro-vascular tissue” after injection into host soft tissue (10-year human histology of dermis).

collagen and only 20% of PMMA microspheres by volume (Figure 13).

Submucosal placement of U125

The 125 µm microspheres are injected submucosally around the female bladder neck through a 23G needle at the 6 o'clock, 10 o'clock and 2 o'clock position (1 to 2 mL per bleb) and act as a scaffold for the patient's own collagen deposition (“Soft Tissue Engineering”). Within 3 months, the bovine collagen is completely absorbed and replaced with the patient's own collagen (autogenous collagen deposition). Each individual microsphere is encapsulated and permanently ‘anchored’ in the patient's urethra, preventing migration and dislocation (Figure 14).

A superior adaptation and mucosal plug of the urethra can be achieved with three injected sub mucosal blebs that are placed circumferentially in a pattern resembling an aortic valve or a Mercedes Benz star - or with one larger bleb resulting in a horse-shoe opening (Figure 15). The sub mucosal space is only about 500 µm wide and it requires a needle diameter of 23G with a stopper to place a bulking agent precisely within this space. U125 was specifically designed to meet this requirement in contrast to other UBAs, which need 18G-needles for injection. For human application, a special Injection-Uroscope had been developed (Figure 16).

Proof of correct placement

With endovaginal 3-D-ultrasound, we have a tool in our hands to follow the correct placement of a urinary bulking agent directly after the injection, or its possible dislocation months or years later. Yune et al. [54] reported that a bulking material does not form the characteristic round bulks in 41% of cases and tracks toward the bladder neck or the distal urethra.

Figure 14: The two different sizes of PMMA-microspheres (40 µm and 125 µm) injected into the sub-urethral space are individually encapsulated at 3 months.

Figure 15: A small submucosal deposit of U40-PMMA microspheres in a pig's urethra at day 10.

Pre-clinical safety study with U125

In order to examine the safety of both 40 μ m and 125 μ m PMMA microspheres in urethral applications, a total of 22 female mini pigs received 4 sub mucosal implantations of PMMA microspheres using a standard cystoscope. Post mortem histology showed that smaller 40 μ m microspheres were transported in some pigs to lungs, lymph nodes, and liver & spleen by veins and lymph vessels whereas no 125 μ m microspheres could be detected in any of the pigs' organs of this internally controlled study [18,53]. The apparent absence of U125 microspheres in distant organs strongly suggests a low risk of dislocation or transportation of U125 PMMA microspheres through the peri-urethral venous plexus with venous diameters up to 80 μ m.

Risk assessment of particle migration

A literature search confirmed the size of blood and lymphatic vessels in the urethral sub mucosal space in humans [55,56] and the ideal and safest implantation site for UBAs [57]. Augsburger et al. [56] performed impressive studies of the vascularity of the urethral venous plexus in female dogs, which showed to have diameters ranging from 35-60 μ m [55]. Considering histologic sections of human urethras, their venous plexus appear of similar size [55]. Malizia et al. [36] reported on a single 80 μ m particle found in the lung after peri-urethral injection of Teflon particles in a canine study.

Possible complications

Injectable gels (Bulkamid[®]), calcium beads (Coaptite[®]) and very heavy carbon coated zirconium beads (Durasphere[®]), are all extremely inert and stimulate little foreign body reaction. However,

Figure 16: The Uroscope[®] was especially developed for the submucosal intraurethral injection of U125-PMMA.

all three materials have shown to dislocate due to gravitational forces and eventually may extrude from the urethral opening [27-30]. In contrary, U125 causes immediately a controlled foreign body reaction with fixation of each microsphere in the sub mucosal tissue

A more serious potential side effect experienced with all dermal fillers and bulking agents is the development of foreign body granulomas [35] months and years after the injection. The cause of granuloma formation is not well understood, but many cases have been published where a prior systemic bacterial infection approximately three months earlier was followed by granuloma growth of the Implant [35,38].

Skin is the most immune-competent organ in the human body and therefore utilized for allergy testing and immunization. The example in Europe and China, where Artecoll was injected directly subdermally beneath wrinkles and depressions between 1994 and 2006, caused >20 granulomas in Europe and 7 in China. Since 2006, when Artecoll was injected deep, i.e. epiperiosteally right onto facial bones and fascia, no more patients with granulomas were reported in Europe and China [51]. However, 17 granulomas were reported in the U.S., where Bellafill[®] is still injected subdermally beneath wrinkles [50]. Peri-urethral tissue is like all internal organs immunologically less-reactive, and granulomas are therefore not or rarely expected to occur. If a granuloma should develop, it can be easily treated with one or more intralesional steroid injections (prednisolone or triamcinolone) [58].

Final Considerations

Stress urinary incontinence will scourge more and more women in an increasing older population worldwide. The simplest treatment is the intra- or peri-urethral injection of a bulking agent to diminish the loose opening of the urethra. All presently available bulking agents, however, have certain disadvantages due to their chemical structure, their tissue compatibility, their longevity, or their anchorage in the urethral tissue.

All present bulking agents have to be injected peri-urethrally. Collagen and crosslinked hyaluronic acid injections are absorbed within a few months and have to be repeated for a lifetime. Longer-

lasting gels like fluid silicone and polyacrylamide gel are biologically inert i.e. stimulate little connective tissue but may migrate due to gravity. Particulate injectables containing calcium hydroxyapatite or carbon-coated zirconium oxide particles are also inert and not fixed sufficiently, i.e. not encapsulated by fibroblasts and can dislocate due to gravity, therefore. Silicone particles or dextranomer beads can cause foreign body granulomas and extrude from the urethra, or inhibit urinary flow due to excessive tissue build up. Autologous fat injections, appealing at the first view as ideal, are causing certain complications [59] like absorption or oily cysts, and are abandoned by most injectors, today.

Therefore, most gynecologists and urologists prefer at present the mid-urethral sling procedure with a TVT-band, which is inserted from the vagina around the urethra and anchored in the pre-vesical tissue. In search for the ideal tissue bulking agent, microspheres from polymethyl methacrylate have proven optimal fixation also in loose tissues and appear as an effective and safe development for the treatment of SUL. First injections with U125 in the urethra of mini pigs [18] were successful and will lead to promising results in humans, as injections of PMMA-microspheres (Artefill) beneath facial folds [48] and in patients with gastric reflux [53] have demonstrated.

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