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ORIGINAL ARTICLE

Bulking agents: an analysis of 500 cases and review of the literature

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Abstract
Introduction and hypothesis Stress urinary incontinence (SUI) is common, impacts women's quality of life, and generates high costs. Physiotherapy is the first-line therapy, and if it fails, suburethral slings are the gold standard in SUI surgery. Bulking agents injected periurethrally might be a beneficial alternative, but there is a paucity of data on bulking therapy. The aim of this study was to prospectively analyze the efficacy and safety of bulking agents in the setting of a tertiary referral center.
Methods In the last 13 years, 514 elderly women with SUI were treated by injection therapy with either collagen (Contigen®), hyaluronic acid (Zuidex®), ethylene vinyl alcohol (Tegress®), or polyacrylamide hydrogel (Bulkamid®). Subjective and objective outcome was recorded at the 12-month postoperative appointment using the King's Health Questionnaire, visual analogue scale (VAS) describing their incontinence severity, standardized pad test, and urethral pressure profile.
Results Demographic data were equally distributed in all four groups of agents used. Sixty-one patients were lost to follow-up (10.6 %). Statistically significant changes were found for maximum urethral closure pressure (MUCP), pad weight, and VAS before and after bulking for the four agents used. Pad test was negative in 73.2 % of patients after bulking therapy. Subjective assessment showed improvements in general health and role limitations. The overall complication rate was low for all agents.
Conclusions This study shows improvement in incontinence after bulking therapy according to subjective and objective outcomes in an elderly population. In contrast to earlier reports, side effects due to injections were few and mild. We can advocate bulking therapy for treating SUI, as it is simple, safe, and shows both objective and subjective improvement and relief.

Keywords Bulking agent · Bulking therapy · Geriatric patients · Stress urinary incontinence

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Introduction

Involuntary urine loss during coughing, sneezing, physical exertion, or sudden changes of position characterize stress urinary incontinence (SUI) caused by either sphincter abnormalities and/or urethral hypermobility [1, 2]. SUI, with its high socioeconomic burden and negative influence on women's quality of life (QoL), is a common problem, with approximately 35 % of women >18 years suffering from involuntary loss of urine; at the age of 60 years, the rate rises to 45 % in Europe [3]. Annual costs related to urinary incontinence (UI) are estimated to be $27.8 billion in the USA [4], and 359–655 Euros per patient treated in European countries [5]. Treating incontinence might improve QoL and cut these costs significantly.

The first treatment step is pelvic floor rehabilitation [6], followed by surgery if physiotherapy fails. As for surgery, suburethral slings are as effective as colposuspension, with lower perioperative morbidity, and are the gold standard in patients with SUI, displaying high and long-term cure rates [7, 8]. However, there is a need for alternative therapeutic approaches in patients with significant comorbidities; in women who are unwilling to undergo surgery because of its associated risks, pain, and recovery; in patients with recurrent SUI; and in women in whom surgical options are limited (e.g., postoperatively or after irradiation) [9–14]. The study reported here focuses on injection therapy with bulking agents, as this technique may be considered as a first-line treatment option in selected patients [11].

There is a paucity of data comparing bulking agents, results of studies describing the efficacy of bulking agents are inconsistent [10, 15]. Hence, the choice of substance still depends on safety considerations, ease of use, availability, and physician preference, as there is no strong evidence that one agent is superior to the other [11]. Despite the theoretical advantages of injection therapy, the latest Cochrane review from 2007 concluded that a lack of sufficient data on bulking agents impeded creation of a meta-analysis [10]. The paucity of long-term follow-up and health economic data, as well as the finding of a possible placebo effect (improvement in pad weight after saline injections), were further points of criticism in the review [10]. However, another aspect was the lack of a comparison between treatment with bulking agents and physiotherapy [10], which was made redundant recently, as bulking seems to be more effective than pelvic floor training [16]. The Cochrane review concludes that limited data suggest surgery to be objectively superior to bulking; however, as patients are equally satisfied with either option, and regarding the few side-effects of bulking therapy, the latter is considered to be a reasonable first-line option [10].

Aim of this study was to analyze the efficacy and safety of bulking agents in the setting of a tertiary-referral-center prospectively.

Materials and methods

Between December 1999 and January 2012, 514 elderly women with SUI or mixed urinary incontinence (MUI) were treated by injection therapy with either glutaraldehyde cross-linked bovine collagen (Contigen®), hyaluronic acid/dextranomer copolymer (Zuidex®), ethylene vinyl alcohol (Tegress®), or polyacrylamide hydrogel (Bulkamid®) in the University Women's Hospital, Department of Urogynecology, Bern, Switzerland. Choice of bulking agent was dependent upon substance availability and patient allergy to collagen. Demographic data, including age, body mass index (BMI), previous incontinence operations, number of injections and perioperative data were noted. The study was approved by the local ethical committee, and all patients gave informed consent to participate.

The King's Health Questionnaire (KHQ) assesses QoL and is widely used in patients with incontinence [17]. It is validated in several languages, including German [18]. The questionnaire deals with the domains general health perception, role limitation (e.g., household, cleaning, shopping), physical and personal limitation (walking, sports, travel, social life, relationship, sex, family life), emotions (depressed, anxious, nervous, feeling bad about oneself), sleep (feeling worn out, tired), and incontinence impact (pad usage, need to change underwear, restrict drinking, fear bad smells). Moreover, bladder problems are specified in the KHQ as questions for frequency symptoms, nocturia, urgency, stress incontinence episodes, coital incontinence, urinary tract infections, and bladder pain exist. The scores for each domain range from 0 to 5 and 1 to 5, respectively, are added up, and a change of at least five points is considered significant [18]. Subjective outcome was further assessed by patients judging their incontinence severity on a visual analogue scale (VAS). The VAS is a validated tool for assessing health and satisfaction in patients, for investigating pain, and for measuring attitudinal attributes and QoL [19]. Additionally, as objective measurements, a standardized 2-h in-office pad test according to International Continence Society (ICS) recommendations [20] was performed, and residual urine was measured using transabdominal ultrasound. Additionally, urethral pressure profile was measured using microtip catheters. Microtip measurements were taken in the 45° upright position with the patient at rest and at bladder capacity using an 8-F double microtip transducer (Gaeltec®) withdrawn at 1 mm/s and the transducer orientated in the 3 o'clock position, with one transducer inside the bladder and the second distally positioned in the urethra. Three consecutive measurements were taken for each patient and the average calculated.

Before and following intervention, the presence of urinary tract infections was excluded using dipstick screening, and infections or bacteriuria was treated. For the injection procedure, women were placed in the lithotomy position, 10–20 ml of 1 % lidocaine was injected in the periurethral tissue at 4 and 8 o'clock, and the bulking agent was injected transurethrally into the submucosa under cystoscopic control. Two to three deposits were placed in the midurethra, and quantity was decided by the surgeon's judgement of coaptation. Needle position was corrected if it was suspected to not be in the mucosa or if there was bulking agent extravasion. If coaptation was considered appropriate, the bladder was emptied. Patients received a single-shot antibiotic prophylaxis with trimethoprim-sulfamethoxazole and were discharged if postmicturition residual volume was <100 ml. Evaluation was performed 12 months postoperatively and a clinical control without validated patient-orientated outcome measurements

was conducted 6 weeks post-operatively. All adverse events were monitored and registered. If the operation was not successful, the women were offered a further injection after 6 weeks.

For statistical analysis, Graph Pad Prism version 5.0 for Windows was used (Graph Pad, La Jolla, CA, USA) to calculate Student's *t* test and Mann–Whitney rank sum test.

Results

The four types of bulking agents used in this study were collagen (n=312), ethylene vinyl alcohol (n=104), hyaluronic acid (n=54), and polyacrylamide hydrogel (n=44), resulting in a total number of 514 patients. Demographic data were equally distributed in all four groups: age (median 79 years, range 41–91), BMI (median 29 kg/m^2, range 21–41 for polyacrylamide hydrogel and 19–41 for the other agents, respectively), previous incontinence operations (median 1, range 0–4), number of injections (median 1, range 1–3), hospital stay (median 2 days, range 1–3 except for one maximum stay of 34 days in a patient in whom complications occurred after a collagen injection), and operation time (median 10 min, range 10–25). Eighty percent of patients answered the questionnaire in German, 18 % in French, and 2 % in English; 67 % had SUI and 33 % MUI. Despite one third of patients having MUI, the complaint of SUI was predominant. Sixty-one patients were lost to follow-up. For the agents used, the median changes in maximum urethral closure pressure (MUCP) and the pad test are shown in Fig. 1. VAS score as a measurement of self-reported disturbance is illustrated in Fig. 2.

Analysis with the Mann–Whitney rank sum test for non-normally distributed groups showed statistically significant changes for MUCP, pad weight, and VAS before and after bulking for all four agents used [all p<0.001, except for

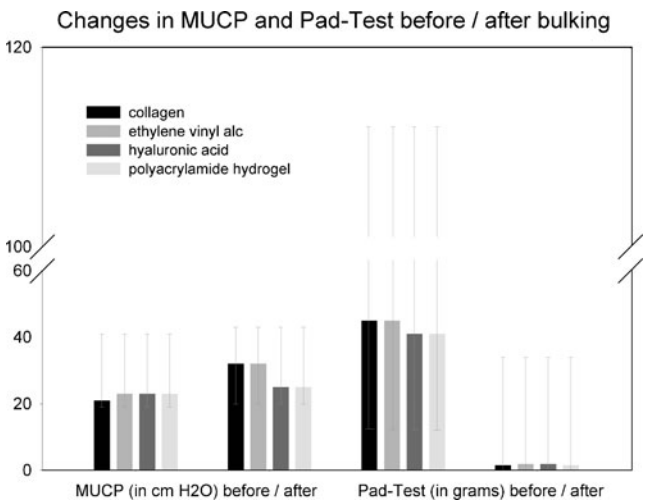

Fig. 1 Objective outcome: maximum urethral closure pressure (MUCP) and pad test measurements before and after bulking therapy

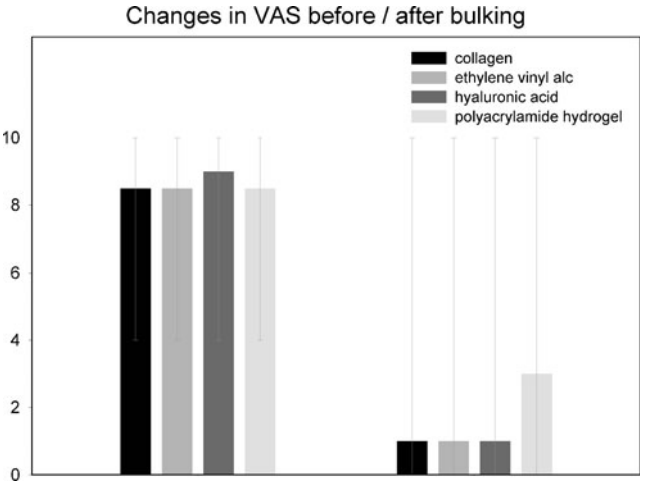

Fig. 2 Subjective outcome: changes in visual analogue scale (VAS) results of incontinence severity before and after bulking therapy

MUCP with hyaluronic acid (p=0.004) and for polyacrylamide hydrogel (p=0.011))] Estimating that a pad test is negative if ≤2 g, the exact percentage of objective success is 73.2 % of patients. In the subjective assessment of QoL after bulking therapy, the domains general health and role limitations of the KHQ were rated significantly better (Fig. 3), whereas the other domains showed at least no deterioration of QoL aspects.

The overall complication rate was low for all agents (collagen 3.2 %, ethylene vinyl alcohol 5.7 %, hyaluronic acid 5.6 %, polyacrylamide hydrogel 0 %). The most serious side effects were found for collagen, with two women having a late-onset allergic reaction to collagen 3 and 6 weeks postoperatively, respectively, requiring analgetics and steroids. One of these women had to be hospitalized for 34 days. Another serious event (n=1) was exposure of ethylene vinyl alcohol after 2 years, requiring cystoscopic removal of the agent and resulting in incontinence relapse. Further complications comprised: urinary retention for 1–7 days, treated with intermittent catheterization using a self-lubricating catheter and ultrasound check of residual urine after next micturition (collagen, n=4); simple urinary tract infection, treated with antibiotics (collagen, n=4 and ethylene vinyl alcohol, n=3); temporary frequency requiring anticholinergics for up to 2 weeks (ethylene vinyl alcohol, n=1 and hyaluronic acid, n=1); worsening of incontinence (hyaluronic acid, n=2); tachyarrhythmia during local anesthetic injection (before ethylene vinyl alcohol procedure, n=1); blood-stained urine for 3 days (ethylene vinyl alcohol, n=1).

Discussion

This study found improvement of incontinence after bulking therapy by applying subjective and objective outcomes in an

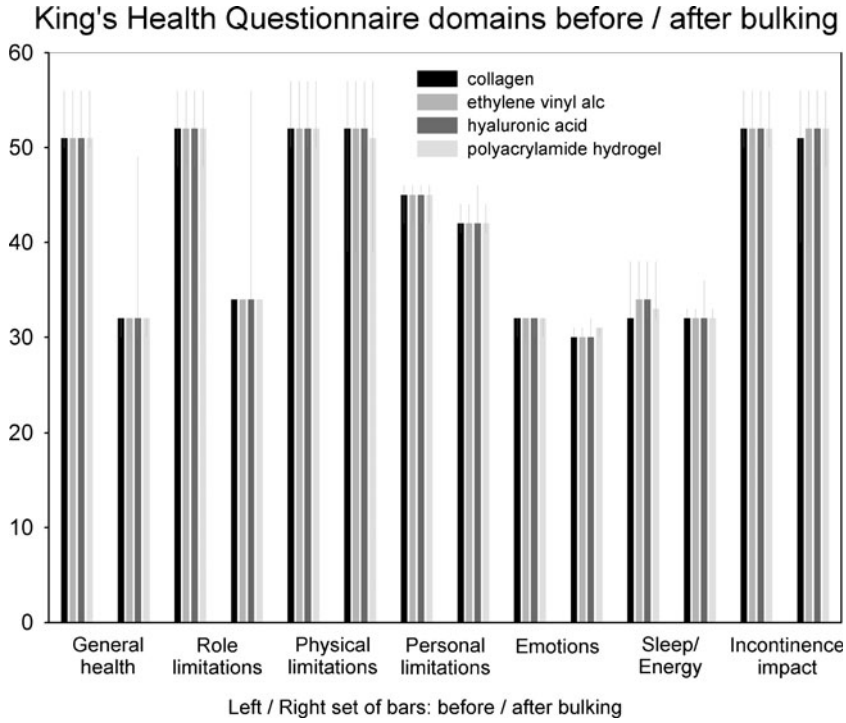

Fig. 3 Subjective outcome: King's Health Questionnaire domains before and after bulking therapy

elderly population. Side-effects due to injections were few and mild. The 514 women in this study showed a similar demographic distribution for each of the four bulking agents used. Thus, comparison of the results is not biased by different patient collectives. Outcomes after bulking therapy for four different bulking agents were studied. Although ethylene vinyl alcohol (Tegress®) and hyaluronic acid (Zuidex®) have been abandoned due to safety issues [15, 21, 22], their treatment outcomes were in line with the other agents, and data are helpful for evaluating the bulking principle.

Two types of outcomes are distinguished in this study: objective measures (MUCP, pad test) and subjective assessment (VAS, KHQ). Results for the objective measurements were clear cut and showed a significant improvement. MUCP might reflect the anatomic improvement with a better coaptation of the urethral mucosa, and the pad test indicates decreased urinary loss. The subjective assessment revealed statistically significant improvements on the VAS and several domains of the KHQ—namely, general health and role limitations. The other domains were valued equally or higher, yet not significantly, postoperatively. The KHQ especially deals with the questions of how far women still use incontinence pads and fear bad smell. Despite incontinence being improved or cured, patients might fear urinary leakage and thus use pads in everyday life. This might explain why incontinence impact in the KHQ did not improve. Patient-reported outcomes in incontinence therapy are important, because objective parameters might be necessary to verify improvement of urine leakage when comparing interventions, but the impact on QoL may differ substantially from objective measurements [14]. Achievement of what is best for our patients by investigating and discussing treatment goals [11] is possible only if we have a sound knowledge of subjective perceptions of a therapy's consequences.

The most recent Cochrane Review on bulking therapy concluded not to be very helpful for clinical practice. However, injection therapy was considered useful as an option for short-term symptomatic relief in selected patients with comorbidities [10]. The minimal invasiveness; favorable safety profile; high cure rates, at least in the short-term; and improved QoL support the application of bulking therapy [11, 14]. Moreover, prior bulking therapy seems not to negatively affect outcomes if future anti-incontinence surgery is needed [23]. Conversely, bulking can be used after failed midurethral sling placement, with a low cure rate but high patient satisfaction and no significant complications [24].

The efficacy of the bulking principle in general is not yet proven [25]. Continence, among other things, is achieved by urethral mucosal coaptation established by the mucosa itself, submucosal vascular cushions, and smooth-muscle activity [10]. Injection therapy into the urethral submucosa creates cushions and is therefore meant to improve coaptation [10]. Additionally, bulking agents are suggested to act as a central filler volume, which lengthens the muscle fibers and thus increases urethral sphincter strength [26]. However, urodynamic data are limited, and according to the Cochrane review, urodynamic measures should be included

in trials if the mechanism of any action is to be verified [10]. In this regard, our data, including MUCP measurements, follow these recommendations, and our subjective outcomes argue for efficacy of the bulking principle.

Although urethral bulking was thought to be particularly helpful in women with a low MUCP (intrinsic sphincter deficiency) [27], bulking is equally effective in both urethral hypermobility and intrinsic sphincter deficiency [11, 14]. Endoscopic delivery of bulking agents under local anesthesia is typical, yet a blind administration via special devices may be considered beneficial [28]. The appropriate site for injection is the midurethra [29], and the mode of delivery of the agent (periurethral vs. transurethral) leads to similar outcomes but increased early complications if administered periurethrally [10]. Two or three injections are likely to be required to achieve a satisfactory result [10]. A learning curve for mastering injection therapy via an endoscope seems to be present [15]. Data on cost-effectiveness of bulking are inconsistent, being cheaper than tension-free vaginal tape (TVT) at least in the short term, whereas economic modelling predicts a higher cost for injection therapy [11].

Poor long-term results and the necessity of repeat injections hamper the use of bulking agents, and factors that impact treatment success and durability are to be identified [30]. The search for the ideal bulking agent aims at improving the bulking procedure. The properties of an ideal bulking agent should be durable, biocompatible, hypoallergenic, deformable, nonimmunogenic, cause minimal inflammatory and fibrotic response, and particles—usually suspended in a biodegradable carrier gel—should be big enough to prevent migration (>110 μm) [10, 14, 27]. Wide confidence intervals and a diversion of outcome parameters complicate comparison of agents in earlier studies [31]. In our study, follow-up beyond 12 months was not feasible, as most patients were referred for the bulking procedure only and after the 1-year control patients were followed up by their referring doctors. Thirty percent of patients (only ones who were followed up by us or were re-referred) needed further injection therapy after 12–18 months. Nevertheless, due to this geriatric age group, the rate for reinjection might be even higher: Patients may become seriously ill and unable to return in the outpatient incontinence clinic for follow-up or may even decease before incontinence reoccurs.

Silicone particles (Macroplastique™), calcium hydroxylapatite (Coaptite™), ethylene vinyl alcohol (Uryx™), carbon-coated zirconium beads (Durasphere™), porcine dermal implant (Permacol™), and glutaraldehyde cross-linked bovine collagen (Contigen™) show equal effectiveness [10, 32–34], with variations in long- and short-term outcomes [34–36]. Cure or improvement rates vary between 62 % and 80 % or 20 % and 86 %, depending on the source used [9, 10, 37]. Autologous fat proved to be unsafe (one death due to fat embolism), and a favorable outcome was not found [10]. Polytetrafluoroethylene (Polytef™) made from Teflon™ has been abandoned from clinical use because of particle migration [10]. Paraffin, ethylene vinyl alcohol, and hyaluronic acid have been abandoned because of safety issues [15, 21, 22]. Polyacrylamide hydrogel (Bulkamid™) was specifically developed for urethral bulking, being biocompatible, nonbiodegradable, nonallergenic, nonmigrational, atoxic, stable, and sterile [9, 15]. Its efficacy is proven, and its properties might circumvent drawbacks of other agents mentioned [15, 38]. Further experimental agents have been evaluated [10, 14, 39–41]. However, as in our study a large number of patients showed similar outcomes for all four different agents used, we demonstrate the usefulness of bulking therapy regardless of the specific agent.

Bulking agents have become popular, with a substantial efficacy and low morbidity, but complications are not to be ignored [14]. Although urethral bulking is considered to be safe and simple [9, 14, 31], there are several reports on complications caused by the different bulking agents, such as urethral erosion [15], prolapse [42], and diverticula [43]; periurethral pseudocyst and mass formation [44]; retention; de novo frequency; sterile and nonsterile abscess formation [45]; hypersensitivity and urinary infection [15, 43]; granuloma formation and possibly carcinogenesis due to particle migration [43]; need for endoscopic evacuation due to bladder outlet obstruction [46]. Treatment-related (minor) adverse events were found to occur in a range of 22–50 %, with UTI being the most common [15, 38]. Side effects noted in our 514 patients are not in line with these data, as we had very low and primarily minor side effects related to bulking therapy.

The large number of patients is the major strength of our study. Another strength is the assessment of both subjective and objective outcomes, as subjective outcome might reflect the patient's goals more accurately than objective outcomes. The use of validated tools underlines these findings.

A weakness of this study is the use of four different types of bulking agents; however, this was entirely due to availability of substances and probably reflects the real-world practice, with bulking agents appearing on and disappearing from the market. A further weakness is patients who were lost to follow-up (10.6 %). We do not know why these patients were lost. It might be due to dissatisfaction, and if we count these patients as still incontinent, the success rate of bulking might be lower.

In conclusion, we can advocate bulking therapy for treating SUI, as it is simple, safe, and shows both objective and subjective improvement and relief in women, although it is less effective than slings [47]. Our study might help supporting the use of bulking agents because of efficacy and minimal invasiveness.

Conflict of interest None.

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