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Treatment of stress urinary incontinence: recent developments in the role of urethral injection

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Abstract Stress urinary incontinence is prevalent in adult women and has a considerable impact on quality of life. However, it often remains undiagnosed and therefore untreated. Non-invasive treatment is likely to be offered in mild cases and may entail physiotherapy, minimally invasive devices or pharmacotherapy. Surgical intervention is widely considered as the only effective option for more severe cases. These strategies are not suitable for all patients, and urethral injection represents an alternative, minimally invasive procedure. The choice of the bulking agent is the key to the success of this treatment: the most extensively studied are silicone, polytetrafluoroethylene and bovine collagen. However, doubts regarding the safety and efficacy of these materials has led to the development of carbon-coated zirconium beads, calcium hydroxylapatite and dextranomer/hyaluronic acid (Dx/HA) copolymer. Of these, the most clinical experience has been gained with Dx/HA copolymer. Until 2 years ago, urethral injection could only be administered endoscopically. The recent development of devices for 'blind' injection has increased the speed and convenience of urethral injection, removing the need for surgical facilities. Although few data are yet available, it is conceivable that urethral injection administered 'blind' may in future be considered as an option for all patients failing non-invasive treatment.

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Introduction

Stress urinary incontinence (SUI) is a major clinical problem in adult women and the incidence of the condition increases with age [10]. It is characterised by the involuntary leakage of urine, when abdominal pressure is greater than that within the urethra. The pathophysiology of SUI involves either hypermobility (loss of support of the bladder neck and urethra leading to incontinence due to bladder neck displacement) or weakness of the intrinsic urethral sphincter (intrinsic sphincter deficiency; ISD). Patients with hypermobile SUI tend to leak urine during coughing, sneezing, laughing or any physical exercise, whereas patients with ISD tend to be incontinent with postural changes and minimal stress activity. The prevalence of ISD among women with SUI is unknown but some authors have suggested that it may contribute to the majority of cases (hypermobile SUI and ISD are often co-existent) [25].

The age-specific incidence rates of SUI increase with age [10]. The prevalence of SUI in post-menopausal women is reported to be at least 40% [31], and in this group the majority of patients with incontinence are likely to have SUI. However, it must also be borne in mind that detrusor overactivity incontinence (urge incontinence) becomes more common with increasing age. The prevalence of SUI in adult women is liable to be under-estimated due to under-reporting and consequent under-diagnosis as urinary incontinence is often considered to be an inevitable part of ageing; an embarrassing and untreatable condition [12]. Age and childbirth are the principal causes of SUI while other pre-disposing factors include obesity, smoking, previous urogenital surgery and restricted mobility [21].

SUI affects the physical, psychological and social well-being of a patient thus having a considerable impact

on quality of life. Therefore, the long-term success of treatment should be measured principally in terms of reduced incontinence [6, 22]. The patient and physician should discuss all of the available options when choosing treatment for SUI, and patients should be fully informed of the relative benefits and risks for each option.

The treatment options for SUI are physiotherapy, minimally invasive devices, pharmacotherapy, urethral injection and surgery. We intend to give an appraisal of all of these strategies, paying particular attention to the more promising developments that are emerging. It should be noted that there are problems in comparing the efficacy of the various treatments for SUI due to a lack of randomised controlled trials, a lack of standardised diagnostic criteria, a lack of standardised outcomes and a non-standardised time interval for treatments [25].

Clinical presentation of SUI

SUI is differentiated from other types of incontinence by the nature of the episodes, with leakage resulting from activities that increase abdominal pressure being exclusive to SUI. The condition may present together with detrusor overactivity incontinence (i.e. mixed incontinence). Detailed diagnosis of SUI requires careful consideration of the patient's history and a physical examination. Questionnaires, micturition charts and pad-weighing tests may be employed to ascertain the frequency and extent of incontinence episodes [25, 45]. SUI may also be classified into three specific types (Table 1), although classification according to this system requires video-urodynamics or cystoscopy and not all cases require such thorough investigation. The severity of incontinence influences the type of treatment offered to all patients. For example, physiotherapy should be considered as the first-line therapy for mild SUI, while urethral injection or surgery are the likely candidates for patients with severe SUI [22]. The extent to which hypermobility and ISD contribute to the condition is another consideration in the treatment decision, and has been identified as a key influence on the choice of surgical intervention [25]. However, the diagnosis of ISD requires urodynamic evaluations in addition to clinical assessment [2].

Table 1 Classification of SUI [45]

Classification of SUI	Description of symptoms
Type I	Bladder neck and urethra open and descend during stress. Descent <2 cm, no evidence of cystocele.
Type IIA	Bladder neck and urethra open and descend during stress. Descent >2 cm, evidence of cystocele.
Type IIB	Bladder neck and urethra closed and below the symphysis pubis at rest. Possible descent during stress, urethra open.
Type III	Bladder neck and urethra open at rest, absence of detrusor contraction.

Current treatment options

Physiotherapy

SUI in female patients is usually caused, at least in part, by a decrease in support provided by the pelvic floor muscles and connective tissue [21]. Physiotherapy aims to strengthen the pelvic floor muscles, and may take the form of Kegel exercises, weighted cones and pelvic floor biofeedback.

The main advantages of physiotherapy are that it can be performed anywhere, does not require any invasive procedure and does not entail pharmacological treatment. For these reasons, it is viewed favourably by many SUI patients. Physiotherapy is most likely to be beneficial for patients with mild SUI, although poor compliance typically limits efficacy [11, 22]. In one study, pelvic floor exercises were performed in conjunction with biofeedback to treat SUI in 31 women. After 3 months, the cure rate was 39% but this reduced to 27% at long-term follow-up (mean of 2 years) [11].

Pharmacotherapy

Drug therapy is well established in the treatment of detrusor overactivity incontinence. Agents with antimuscarinic activity are the most commonly employed. For SUI, the current aim of pharmacotherapy is to increase the urethral smooth muscle tone, thereby increasing the urethral pressure that can be generated. Although pharmacological studies have indicated that smooth muscle plays a role in urethral closure, it is considered unlikely that smooth muscle plays a major role in the pathophysiology of incontinence [21]. Several groups of drugs have been considered for use in treating SUI, the main candidates being adrenergic agonists either alone or in combination with oestrogen replacement therapy [35, 41].

Pharmacotherapy has had mixed clinical success in the treatment of SUI but may help to relieve symptoms [41, 46]. However, it is unlikely to be effective in treating severe SUI, and is associated with poor long-term compliance [41]. In addition, α-adrenergic agonists are associated with significant adverse effects including raised systolic blood pressure and increased heart rate [35, 41]. New α-adrenergic agonists with fewer side effects are currently under investigation.

Minimally invasive devices

Minimally invasive devices, such as self-adhesive patches [26], intravaginal tampons [44], dome-shaped silicone devices that are worn over the external meatus [34],

vaginal pessaries and external urethral barriers reduce the impact of SUI but do not cure the condition [4]. The disadvantages of these devices include infection, irritation, erosion of vaginal wall and a high level of non-compliance [22]. Nevertheless, minimally invasive devices may be suitable for patients in whom behavioural therapy and/or pharmacotherapy have failed and who do not wish to undergo surgery.

Surgical intervention

A large variety of surgical procedures have been reported for the treatment of SUI. The techniques can be grouped into four main categories: anterior repairs (e.g. colporrhapy) [20], retropubic suspensions (e.g. Burch technique) [2], transvaginal suspensions (Pereyra, Stamey and Raz procedures) [22] and pubovaginal sling procedures [25]. In all cases, the aim is to stabilise the urethra and maximise the urethral closure pressure during physical stress.

Surgery can be recommended both as a first-line therapy or as secondary therapy if other treatments fail [25]. It is most likely to be recommended as a first-line therapy only in severe cases, for most patients with mild to moderate SUI, surgery is only performed in the event of poor results with physiotherapy and/or pharmacotherapy. Notably, a substantial proportion of SUI cases present after childbirth. The intention to conceive again in the future is generally considered as a contra-indication to surgical intervention, as few surgical procedures are likely to remain undamaged by subsequent parturition. Therefore, this group of patients is left with few treatment options.

Cure of SUI can be expected in the majority of women treated by surgical intervention. Although no single procedure can be identified as first-line for all patients, it is well established that retropubic suspensions and sling procedures have more favourable long-term efficacy than anterior repair or transvaginal suspension. In particular, pubovaginal slings are often favoured due to their established efficacy, particularly in ISD (cure rate: 85–90%) [2, 22, 25].

The main disadvantages of the surgical treatment of SUI are that an anaesthetic (often general) and hospitalisation are required. Additionally, constraints on the use of theatre for non-essential surgical conditions may delay or even prevent treatment. Following surgery, complications may arise and it is important that the patient is aware of the potential risks. The most common complication following sling procedures is urinary retention which can occur in up to 5% of patients [2]. Other immediate complications include accidental bladder injury and excess bleeding. Delayed complications include wound infection, urinary tract infection, chronic pain and secondary detrusor overactivity (instability) [2, 6].

A recently developed addition to the surgical options is tension-free vaginal tape (TVT). TVT is associated with a high cure rate (86–90%), at least 3 years postoperative success, fewer complications and reduced probability of postoperative catheterisation and hospitalisation [32, 46]. However, no long-term data (≥5 years) on the efficacy and safety of TVT have yet been published. Although TVT is sometimes classed as a minimally invasive device, it actually entails a surgical procedure albeit under local anaesthesia. The first reports of severe complications are emerging at scientific meetings.

Urethral injection

Injection of a bulking agent to the bladder neck or proximal urethra is generally agreed to improve intrinsic sphincter function [16], although the precise mechanism of action remains uncertain. Emerging data suggest that this treatment may also be effective in treating hypermobile SUI [3, 17]. As with open surgery, urethral injection does not require long-term patient compliance to be successful. However, urethral injection is minimally invasive and can be performed as an outpatient procedure by which overnight hospital stays are avoided and substantial cost savings compared with more invasive surgery may be expected [1]. Another consideration is that previously undiagnosed ISD is a common cause of failure with surgical intervention but urethral injection appears to be successful in such cases [1, 2]. There is also evidence that patient satisfaction with urethral injection compares well with surgery (complete satisfaction post-procedure 66.1% with collagen injection vs 51.6% with surgery) [7].

The choice of bulking agent is crucial to the safety and efficacy of urethral injection for SUI. The ideal agent should be biodegradable, biocompatible, non-migratory (particle diameter $>80\ \mu$m), non-allergenic and non-immunogenic [8, 15]. The success rate of urethral injection is usually expressed as the number of patients whose incontinence is cured (dry) or improved following treatment (improvement is generally defined according to various measurements such as pad usage, pad-weighing tests and subjective questionnaires).

Silicone. Silicone (Macroplastique, Uroplasty, Minneapolis, USA) consists of solid silicone rubber particles suspended in a non-silicone carrier gel [36]. Although particle size generally falls within the range 100–450 μm, the gel also contains particles smaller than 70 μm in diameter [1]. As a result, animal studies have shown that silicone may migrate from the injection site to other organs [15]. As silicone is non-biodegradable, it will persist within the body and there is a risk of granuloma formation [15]. In addition, there have been concerns regarding a possible association between silicone and autoimmune reactions [43], although recent data suggest that there is no such association [19].

The use of silicone as a bulking agent in the treatment of SUI has been reported in a number of studies to have

a success rate of 48–61% in women followed for more than 12 months after treatment [16]. A recent study involving 89 patients with hypermobile SUI and ISD reported a success rate of 61% in 56 women after a mean follow-up period of 19 months [37].

Bovine collagen. Bovine collagen (Contigen, Bard, Covington, USA) is well established as a bulking agent for urethral injection. Advantageously, there is no risk of granuloma formation or migration with bovine collagen [16]. However, it is allergenic in up to 5% of women and skin testing must therefore be performed 30 days prior to treatment [1]. In addition, there is some concern regarding the potential for disease transmission from bovine products, particularly in the UK.

A recent review of the use of bovine collagen in urethral injections has shown that short-term success rates in patients with both hypermobile SUI and ISD range from 63–86% [16]. However, the proportion of patients remaining continent declines considerably over time following collagen injection: after 3 years, the success rate can be expected to be around 45%, necessitating repeat injections in the majority of patients [18]. This may be attributable to in vivo degradation of the implant, a phenomenon which has been noted in animal studies [5].

Polytetrafluoroethylene paste. Polytetrafluoroethylene (PTFE; Teflon, Dupont, Tex., USA) is administered as a particulate suspension in glycerine. It is non-biodegradable and carries a risk of granuloma formation wherever it accumulates [28, 30]. Concerns over possibly carcinogenic properties have prevented approval by the US Food and Drug Administration (FDA) [8]. Owing to the small size of the PTFE particles (90% are less than 40 μm in diameter), migration from the injection site is a problem [28]. Another potential risk with the use of PTFE paste is an inflammatory reaction which can adversely affect urethral function [8].

Short-term results (<12 months) with PTFE paste have been reasonably successful, with cure rates ranging from 57–86% [16]. However, the outcome of long-term follow-up studies (12–61 months) have been variable ranging from 33% to 76% [16]. In an attempt to minimise the risk of migration, a recent study investigated the efficacy of lower than usual injection volumes (total maximum injection volume of 6 ml per treatment) [17]. Although efficacy was maintained, this approach does not eliminate the safety concerns with PTFE.

Autologous fat. Autologous fat is taken from the abdominal wall of the patients' own body by liposuction. It is biocompatible, readily available and does not elicit an immunological response. However, adverse events associated with the use of autologous fat for urethral injection have included pulmonary embolism [42].

Studies with follow-up times of 6–12 months have reported variable success rates with autologous fat injections (42–86%) [16], and a 6-month study indicated a considerably lower cure rate than with collagen (13% vs 24%) [13]. As with most bulking agents, multiple injections appear to have the potential to improve the efficacy of autologous fat [33].

Carbon-coated zirconium beads. Carbon-coated zirconium beads in a gel containing beta-glucan (Durasphere, Advanced Uroscience, St.Paul, USA) is the most recent bulking agent to be approved by the FDA (1999). This material has previously been used in cardiac valvular indications [8]. The beads are non-migratory (particle size range: 251–300 μm) and non-antigenic [27].

A recent study conducted in 355 women compared the safety and efficacy of carbon-coated zirconium beads with bovine collagen in the treatment of ISD [27]. Twelve months after the first injection, 66.1% of the women treated with carbon-coated zirconium beads and 65.8% of those treated with collagen showed improved continence. Multiple treatments increased the success rates to 80.3% and 69.1% in the two groups, respectively. However, this is the only published study to support the use of carbon-coated zirconium beads as a bulking agent in SUI, and there is no evidence of the efficacy of this material in patients with hypermobile SUI.

Calcium hydroxylapatite. Calcium hydroxylapatite (Coaptite, Bioform, Franksville, USA) is a synthetic version of the material found naturally in bone and teeth. It is a non-antigenic bulking agent consisting of hydroxylapatite spheres in an aqueous gel composed of sodium carboxylmethylcellulose. Calcium hydroxylapatite is formulated to prevent distant migration (particle size 75–125 μm) and has been used in implantable medical devices, for example, replacement heart valves [29]. Animal studies have shown this material to be biocompatible, non-encapsulating, and adhesive to in-growing collagen fibres with little inflammation [8]. One advantage of using calcium hydroxylapatite as a bulking agent is that it can be detected using plain film radiography or ultrasonography.

A pilot trial investigating the use of calcium hydroxylapatite as a bulking agent in the treatment of SUI has just been completed [29]. The study involved ten women (mean age 68 years) with a history of SUI. Three women received one injection and seven received two injections. At 12 months after the last injection, seven women reported improved continence and there were no adverse events.

Dextranomer/hyaluronic acid (Dx/HA) copolymer. Dx/HA copolymer (Zuidex, Q-Med, Uppsala, Sweden) is a copolymer of dextranomer in a gel of non-animal

stabilised hyaluronic acid. The dextranomer component comprises microspheres whose diameter is 80–250 μm. Both constituents are biocompatible, biodegradable, non-immunogenic and carry no risk of granuloma formation [39]. Dextranomer has for many years been used in topical wound treatment, and hyaluronic acid has been used in ophthalmic and orthopaedic applications [23].

Dx/HA copolymer is established as a bulking agent in the treatment of vesicoureteral reflux [24, 39]. The findings of studies undertaken to investigate the use of Dx/HA copolymer in the treatment of reflux are applicable to urethral injection for SUI. First, an animal study of ^{125}I-labelled Dx/HA copolymer demonstrated that this material does not migrate from the injection site [38]. Second, after submucosal injection dextranomer facilitates the ingrowth of fibroblasts and collagen between the microspheres as hyaluronic acid is degraded, and the volume of the implant is stabilised (a decrease of only 25% during the first year) [39]. Although dextranomer is biodegradable by hydrolysis, implanted microspheres have been shown to persist for 3 years or more [23], resulting in sustained efficacy for at least 5 years when Dx/HA copolymer is used as a bulking agent [24]. Third, a 5-year follow-up of children injected with Dx/HA copolymer for vesicoureteral reflux has provided further evidence that there are no safety concerns with this material [24].

A preliminary 3-month clinical study to examine the efficacy and safety of Dx/HA copolymer for the treatment of SUI has been conducted in 20 women with ISD and/or hypermobility [40]. After 3 months, 17 of the 20 patients were cured or showed improvement, and there was no deterioration in these 17 women when followed for a further 3 months.

Administration methods for urethral injection

Endoscopic administration. Until recently, endoscopy provided the only means of delivering bulking agents into the urethra. The chosen route of administration may be periurethral or transurethral, and outcomes with the two methods are comparable [9]. The procedure usually involves at least two injections administered around the urethra, with different surgeons preferring different sites (most commonly 3 and 9 o'clock or 4 and 8 o'clock positions). The procedure is minimally invasive, requires only local anaesthetic (1% lidocaine) and is performed as an outpatient procedure [1]. Endoscopic urethral injection is recognised as an option for women who do not wish to undergo major surgery, or for whom surgery may represent a high risk (e.g. elderly patients) [22].

An important aspect of endoscopic administration is accurate positioning of the implant [9, 16]. The inherent mobility of the urethra and folding of the inner epithelium makes this difficult to achieve. Care is required to ensure that the needle is not placed too close to the urethral lumen to avoid the risk of mucosal rupture and extravasation. Also, the second and third injections must be positioned correctly with respect to the first injection as there is a risk of puncturing the previous implant. The need for precision is complicated by impaired vision from the endoscope, owing to the need for a continual water-flush. It is likely that these factors have contributed to the variability in published outcomes with urethral injection.

'Blind' administration. Devices allowing 'blind' administration of urethral injection have recently been developed specifically for use with silicone and Dx/HA copolymer. Although local anaesthetic is required, this procedure can be performed in a consulting room without surgical facilities. This removes a potential constraint on the number of procedures that can be performed, and is likely to be favoured by patients. Provided that subsequent surgical procedures can be proven to be feasible, urethral injection could therefore be considered for all patients failing behavioural therapy and/or pharmacotherapy. Only patients failing urethral injection would then undergo surgery.

The Macroplastique implantation device was the first means of administering 'blind' urethral injection, with three deployment sites for injection of silicone at the 10, 2 and 6 o'clock positions (Fig. 1). The device is advanced into the urethra until urinary drainage occurs, withdrawn slowly until drainage ceases and then withdrawn a further 1 cm. A needle is then inserted into the first deployment site, angling the device in the direction of the site to ensure penetration of the mucosa. The injection procedure is repeated for the other two injection sites. The Macroplastique device does not address the problem of urethral mobility, and is therefore subject to some of the precision difficulties experienced with endoscopic administration. In addition, anatomical differences between patients could lead to inter-patient variability in the location of the implants.

Fig. 1 Macroplastique implantation device for delivering silicone. One needle is transferred between each of the three deployment sites to complete the urethral injection

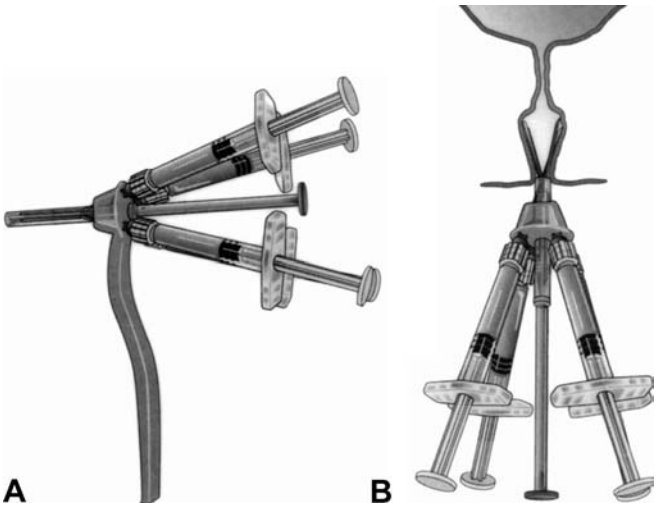

Fig. 2 The Implacer device for delivering Dx/HA copolymer, **A** ready for insertion into the urethra, **B** positioned within the urethra prior to injection from each of the four syringes

A 3-month study of the safety and efficacy of the Macroplastique device in 40 women with SUI also included assessment of patient and physician acceptability of the procedure [14]. At 3 months after the first treatment, an overall success rate of 53% was reported, increasing to 74% after re-treatment (three of these patients underwent open surgery as their second treatment).

The Implacer device has been developed for the 'blind' administration of Dx/HA copolymer, using four syringes and needles (Fig. 2). This device is inserted to a depth that is predetermined according to urethral length, while the four needles are held parallel to the urethral channel. The needles are then released outwards, stretching the urethra and holding the mucosa in a fixed position. One by one, the syringes are retracted by 5–10 mm then advanced fully for submucosal injection of Dx/HA copolymer. The principal advantages of this device are improved positioning of the implants and convenient administration, increasing consistency while reducing the level of equipment required for optimal results.

A 12-month pilot study of Dx/HA copolymer administered using the Implacer device is currently underway and 3-month data are newly available. Thirty-two women (mean age 52.9 years) were included in the study on the basis of SUI (hypermobile or ISD) for at least the previous 12 months. After 3 months, 20 women (62.5%) considered their incontinence to be improved (14 had received two injections). The mean number of incontinence episodes per day decreased from a baseline value of 4 to 1.9.

Conclusion

SUI is a common condition among women following childbirth and post-menopause. The range of treatment options, their outcomes and possible complications must be discussed in detail with the patient before treatment commences. Surgery is often considered as the only effective option for women with SUI who do not respond to physiotherapy or pharmacotherapy. However, there are several drawbacks with surgery including the risk of complications and the lack of suitability for women likely to conceive in the future. Urethral injection is a minor procedure for which future childbirth is unlikely to be considered as a contra-indication.

The safety and efficacy of urethral injection is dependent on the choice of bulking agent. Safety concerns have been raised with PTFE paste and silicone, whereas bovine collagen and autologous fat have questionable efficacy, at least in the long term. Three other candidate materials (carbon-coated zirconium beads, calcium hydroxylapatite and Dx/HA copolymer) appear more promising in this respect. Of these, the most clinical experience has been gained with Dx/HA copolymer as its long-term safety and efficacy as a bulking agent have already been established for the treatment of vesicoureteral reflux.

The development of new devices to allow 'blind' administration of bulking agents is an important enhancement of this treatment for SUI. By eliminating the need for surgical facilities, the speed and convenience of urethral injection is greatly increased while the consistency and accuracy of implantation is maintained. Preliminary data indicate the short-term efficacy of this method using the Implacer device to inject Dx/HA copolymer. It therefore appears that urethral injection administered 'blind' could be considered for first-line active treatment for patients with SUI, although further data are first required to prove the efficacy and safety of this approach, as well as the feasibility of subsequent surgical procedures.

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