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REVIEW

Stem cell therapy for stress urinary incontinence: a systematic review in human subjects

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Abstract
Purpose To systematically evaluate the current evidence on the safety and efficacy of stem cell therapy (SCT) in stress urinary incontinence (SUI) to allow objective comparison with existing surgical techniques.
Methods Systematic literature search of Medline from years 1946–2012 using terms: "stem", "cell", "stress", "urinary", and "incontinence". Included studies presented empirical data on the treatment of SUI using SCT. Outcomes: adverse events, incontinence, quality of life, urodynamic, transurethral ultrasound and urethral EMG findings.
Results Eight studies met inclusion criteria (seven observational and one randomized). Quality score: median 10.75 of 20 (range 2–12.5). Adverse events: one patient had bladder perforation and two procedures could not be completed due to pain. Temporary urinary retention and cystitis were also reported. Incontinence score: Four studies describe significant improvement. Quality of life: significant improvement in four studies. Urodynamic outcomes: four studies show significant improvement in contractility of urethral sphincter; three studies demonstrate no change in bladder capacity and significant reduction in residual volume; significant improvement in urinary flow three studies, although two found no difference; increase in leak point pressure and detrusor pressure in three studies. Urethral ultrasound: three studies found significant increases in rhabdosphincter thickness and contractility. Urethral EMG: two studies found significant increases in the EMG at rest and at contraction.
Conclusion Data suggest that SC treatment for SUI is safe and effective in the short term. However, the quality and maturity of the data are limited. Robust data from better quality studies comparing this to current surgical techniques are needed.

Keywords Stem cell · Therapy · Stress · Urinary · Incontinence

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Introduction

Urinary incontinence is a major cause of morbidity affecting over 200 million people worldwide, and is thought to affect up to 46 % of the female population [1]. Stress urinary incontinence (SUI), the most common form of incontinence, is defined as the involuntary leakage of urine with effort or exertion, such as coughing or sneezing. SUI significantly impairs sufferers' quality of life, placing a large financial burden on health systems worldwide and in the UK alone, over £740 million annually is spent on its management [2].

Urinary continence is achieved by a functioning urethral sphincter complex, made up of the internal urethral

Table 1 Current treatments for SUI can be divided into conservative, medical and surgical options

Conservative
Pelvic floor muscle training
Medical
Duloxetine (noradrenaline and serotonin reuptake inhibitor)
Surgical
Urethral bulking agents (e.g., collagen, carbon beads, silicon)
Anterior colporrhaphy
Retropubic procedures (e.g., urethropexy—Burch procedure)
Suburethral slings (e.g., autologous, synthetic)
Tension-free vaginal tape (TVT)

sphincter (IUS) and the external urethral sphincter (EUS or rhabdosphincter). Atrophy of the rhabdosphincter and surrounding smooth muscle as well as damage to connective tissue, vascular structures and nerve supply all contribute to SUI. Risk factors for this include vaginal delivery as this often causes anatomical and neuromuscular changes, resulting in weakening of the muscles of the pelvic floor and consequent urinary incontinence. Other risk factors include multiparity, ageing, obesity, smoking, race and previous hysterectomy [3].

SUI occurs when an increase in intra-abdominal pressure causes bladder pressure to exceed urethral pressure, resulting in involuntary leakage of urine. The aim of treatments for SUI is to augment existing urethral function by restoring normal anatomy and this is achieved via behavioral, medical and surgical approaches (Table 1). Presently the gold standard for the management of SUI is the tension-free vaginal tape (TVT), which provides structural support to the female urethra through a minimally invasive surgical procedure. The treatment of more severe cases of SUI relies on other more invasive surgery to correct associated anatomical defects, such as colposuspension or abdominal sling. However, even minimally invasive surgery carries risks for the patient, and long-term complications such as voiding dysfunction and de novo detrusor overactivity are a significant cause of morbidity [1, 4].

Studies using adult stem cells (SC) to induce tissue regeneration and repair the damaged urethral sphincter have shown promising results. The aim is for implanted cells to promote muscle and nerve regeneration by fusing with existing muscle and releasing trophic factors [5]. Such treatment could have a role in patient preference, when surgical treatment has failed or if surgery poses too great a risk [6].

In the correct environment, SC have the ability to proliferate quickly and differentiate into desired tissue types [5]. SCs used in the clinical treatment of SUI can be embryonic and mesenchymal SC. Embryonic are pluripotent cells derived from cultures of inner cell mass cells, while mesenchymal SCs come from adult sources but still maintain the ability to differentiate [7]. The use of embryonic cells is limited by regulations on their usage, ethical dilemmas, and the potential for tumorigenicity. Conversely, the use of mesenchymal cells is not hindered by these considerations, as adults can consent and there is no destruction of embryos [8, 9].

Studies of bone marrow derived stem cells (BMSC) have shown significant improvement in measures of continence function in animal studies [10], but the process of harvesting BMSCs is often a clinically invasive and painful procedure, which limits its potential uptake. Mesoderm derived stem cells (MDSCs) are derived from muscle biopsies and have shown some improvements in continence measures in studies using rats [11, 12]. Adipose derived stem cells can be obtained via liposuction in large quantities with minimal morbidity. Treatments with these cells have shown promising results in urodynamic outcomes in animal models [13–15]. Umbilical cord derived stem cells (UCB) have been used for decades as a source of hematopoietic SC. These have a reduced risk of infection and chromosomal abnormalities compared to other sources of SC and have shown some improvement in continence when used in rat studies [16, 17].

Although data from animal studies is promising, most studies are small with short follow-up making long-term efficacy difficult to predict [10, 12, 15, 17]. Moreover, preclinical studies involving young animals may not reflect an older human population in whom there is a decline in molecular signaling and reduced numbers of dormant SCs [18, 19]. Furthermore, the complications in animal models have been found to include the development of bladder stones, abdominal wound abscesses and death before end of experiment [20].

This paper aims to systematically evaluate the current evidence on the safety and efficacy of SC use in the treatment of live patients with SUI. Such a review will allow a more objective comparison with existing surgical techniques.

Methods

Search strategy and selection criteria (Figs. 1, 2)

We undertook systematic literature searches of Medline (using OvidSP) between the years 1946 and June 2012. The free text and MeSH search terms used were variations of "stem", "cell", "stress", "urinary" and "incontinence". Results were limited to publications pertaining to human beings and in English language (Fig. 1). We also hand-searched studies through consultation with experts in the field, scrutiny of reference lists of retrieved papers, existing

Fig. 1 Search strategy

1	exp *Urinary Incontinence, Stress/ (6568)
2	stress.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (478624)
3	urinary.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (312186)
4	incontinence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (39828)
5	exp *Stem Cells/ (75261)
6	stem.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (251580)
7	cell*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3956767)
8	2 and 3 and 4 (10522)
9	6 and 7 (190739)
10	1 or 8 (10522)
11	5 or 9 (194673)
12	10 and 11 (89)
13	limit 12 to (english language and humans) (50)

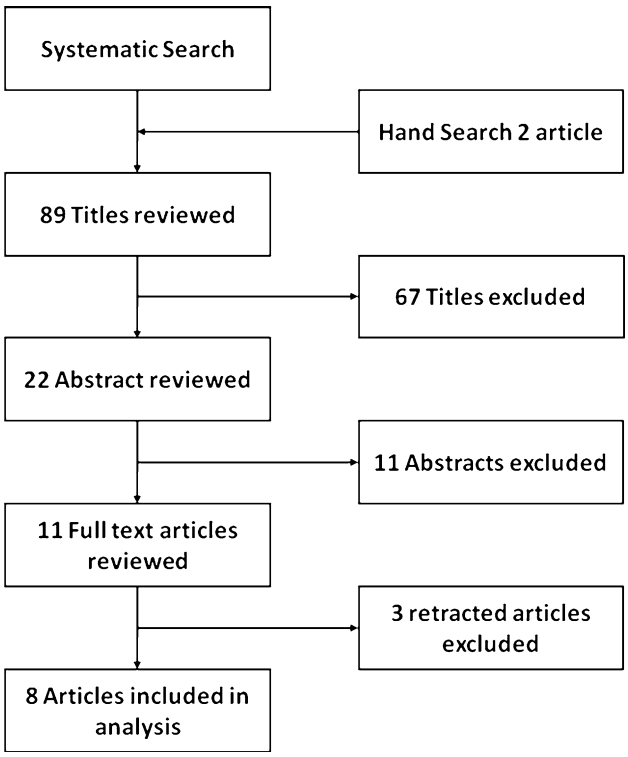

Fig. 2 Flow diagram of study selection

reviews, guidelines and Department of Health documents. Retrieved titles and abstracts had to present empirical data relating to studies of the treatment of SUI using stem cell therapy (SCT).

Quality assessment

Quality of the included papers was assessed formally with an assessment tool designed for use in systematic reviews of heterogeneous articles [21]. Papers were scored by two authors (M.A.A. and B.W.L.), blinded to each other's scores, in different domains from zero to two giving a minimum of zero and a maximum of 20 (the quality scoring data are available from the corresponding author on request). Internal validity was checked using Cohen's Kappa coefficient: a score of 0.737 indicated substantial agreement.

Data abstraction

Data were abstracted for SC source, number of participants by intention to treat, patient demographics and length of follow-up. Study findings were collated under the headings of adverse events, incontinence score, quality of life (QOL) score, urodynamic findings, transurethral ultrasound findings and urethral sphincter electromyography (EMG) findings.

Table 2 Study characteristics

References	Stem cells	Quality score (0–20)	Primary endpoint	Study design	*N*	Population	Follow-up (*M*)
Blaganje et al. [22]	Autologous MDSC	12.5	Urinary incontinence episodes, number of voids, patient satisfaction, and QoL	Prospective intervention study. Injection into urethral sphincter with electrical stimulation.	38	Women, mean age 52 years, parity 2, BMI 26.6.	1.5
Surcel et al. [23]	Autologous MDSC	2	Not stated	Prospective intervention study. Injection of stem cells into mid-urethral sphincter.	8	SUI, mean age 54.9 years	12
Sèbe et al. [27]	Autologous MDSC	11.5	Presence of dysuria. Safety at 3 months (flow rate, post-void residual and urine culture)	Randomized prospective intervention study. 3 doses MDSCs.	12	SUI due to ISD, mean age 58, mean BMI 27.6. Female. Failed surgical treatment.	3
Lee et al. [28]	UCSC	10.5	Patients' voiding diaries, and satisfaction	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	39	SUI; all failed conservative, 1 failed surgical treatment; mean age 51.5 years; para 2.3	Mean 13
Carr et al. [29]	Autologous MDSC	4.5	Voiding diary, pad test, QoL.	Prospective intervention study. Myoblast and fibroblast injection.	8	SUI, mean age 54 years, BMI <30, failed conservative treatment.	Med. 17
Mitterberger et al. [30]	Autologous MDSC	9.5	Incontinence score (voiding diary, pad test, self-report)	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	63	Men, post-prostatectomy, mean age 68 years	12
Mitterberger et al. [31]	Autologous MDSC	11.5	Incontinence score (voiding diary, pad test, self-report)	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	20	Women with intrinsic sphincter insufficiency, mean age 49.8	24
Mitterberger et al. [32]	Autologous MDSC	11	Incontinence score (voiding diary, pad test, self-report)	Prospective case series. Injection of fibroblast and myoblast into rhabdosphincter	123	All SUI, failed PFE, 68 previous surgery	12

QoL Quality of life

Outcome measures

The outcomes to be assessed in this study are safety/adverse events, measures of QOL and urinary incontinence. In addition, data will also be collected on urodynamic parameters and ultrasound and EMG findings of studies of the urethral sphincter.

Results

Study characteristics (Table 2)

Initial thorough systematic literature search revealed 87 potential articles for inclusion, while a subsequent hand search revealed two further studies for potential inclusion [22, 23]. Studies not reporting empirical data and those relating to non-human subjects were excluded (Fig. 2).

Of these 89 studies, 11 met the inclusion criteria for the review. However, three were subsequently excluded as the papers had previously been retracted (two for lack of compliance with ethical standards [24, 25] and another for undisclosed reasons [26]). Of the eight remaining studies which formed the basis of this review, one was randomized [27] and the remaining seven were observational studies [28–32]. Seven of the included studies used autologous MDSCs from skeletal muscle biopsies [22, 23, 27, 29–32] and one used umbilical cord derived stem cells (UCSC) [28]. The technique of SC injection varied, with researchers using varying compositions of injected myoblasts and fibroblasts. Although all eight studies used transurethral

injections, there was variation between using cystoscopic or transurethral ultrasound guidance, and the precise anatomical locations of the injections differed between studies. Both male post-prostatectomy ($n = 63$) [30] and female patients ($n = 248$) with SUI were studied with a cumulative number of 311 patients for this review. Duration of follow-up varied from 3 to 12 months.

Quality assessment

The results of quality assessment are detailed in Table 2. The median quality score was 10.75 of 20 (range 2–12.5). Study methodology included seven prospective uncontrolled intervention studies, and one randomized prospective intervention study. Every endpoint presented in the studies has been included in Table 3.

Outcome measures

Adverse events

No major adverse events were reported in the included studies (Table 3) apart from one inadvertent bladder perforation during administration of the SC [30]. In addition, three papers report that patients withdrew, or were lost to follow-up, but no specific data are given [28, 29, 32]. Sebe et al. [27] found no occurrence of the primary endpoint of a significant reduction in Q_{max} of >15 ml/s, an increase in post-void residual of >100 ml, or evidence of bladder outflow obstruction. However, Lee et al. [28] reported that failure of the procedure due to pain occurred in two patients, with other studies reported minor events such as pain during injection, temporary post-operative retention and cystitis [22, 27, 30–32].

Stress leak episodes and pad tests (Table 3)

All studies reported improvement in objective measures of stress incontinence such as stress leakage episodes and pad usage except for Lee who used predominantly QOL questionnaires and urodynamic parameters such as mid-urethral closure pressure (MUCP) as outcome measures. Blaganje et al. [22] reported significant improvements in incontinence episodes, stress test results and overall improvement. Sebe et al. [27] reported an improvement in leaks and pad test, but no statistical test of significance was performed. Lee et al. [28] reported that over two-thirds of patients reported improvement, and about a quarter reporting failure. Carr et al. [29] showed improvement in voiding diary and pad tests, but again no test of significance was performed. In his three studies, Mitterberger et al. reported significant improvements in incontinence scores (combination of stress leakage episodes and 24-h pad tests) with cure rates of in 18/20 women in one study, 41/63 men with post-prostatectomy stress incontinence and 94/119 women in the third study [30–32]. Surcel et al. [23] reported a reduction in the number of pads required and an improvement in visual analogue scale rating of QOL at 12 months.

Quality of life score (Table 3)

Five of eight studies assessed QOL using various scores including validated (Incontinence Impact Questionnaire) and unvalidated (Patient Satisfaction Score) questionnaires. All five reported improved QOL scores following treatment [22, 27, 30–32].

Urodynamic outcomes (Table 3)

Six studies assessed urodynamic outcomes, of which five looked at the contractility of the urethral sphincter pre- and post-operatively. All found some improvement and Metteberger et al. and Lee et al. reported this change as significant [27, 28, 30–32]. Metteberger et al. found no change in bladder capacity, but a significant reduction in residual volume and increase in leak point pressure and detrusor pressures [30–32]. The same authors also found significant improvement in urinary flow [30–32], although the two other studies to assess this found no significant difference between the pre- and post-operative measurements [23, 27].

Urethral ultrasound (Table 3)

Three studies by Mitterberger et al. presented data on ultrasound measurements of the urethral rhabdosphincter and found significant increases both in the thickness and contractility [30–32].

Urethral EMG (Table 3)

Two studies by Mitterberger et al. found significant increases in the EMG at rest and at contraction [31, 32].

Comparison with other treatment modalities

In an observational study, Surcel et al. [23] compared patients with stem cell injection ($n = 4$) to Burch colposuspension ($n = 11$), TVT ($n = 26$) and TOT ($n = 41$). The presented data show that surgical techniques are associated with a decrease in maximum flow and an increase in detrusor pressure, whereas no such association was found in the stem cell group, although data on statistical analysis were not presented.

Table 3 Study outcomes

References	Adverse events	Incontinence score	QoL score	Urodynamic studies (pre-op vs. post-op)							TUUS (pre-op vs. post-op)		EMG (pre-op vs. post-op)	
		(pre-op vs. post-op)	(pre-op vs. post-op)	Max residual vol. (mls)	Qmax (ml/s)	Max capacity (ml)	Max Pdet (cm H20)	MUCP at rest(cm H20)	MUCP at contraction (cmH20)	VLPP (cm H20)	Thickness (mm)	Contrac.	At rest (μV)	At contract. (μV)
Blaganje et al. [22]	2 cystitis, 1 pain at donor site	UIEs: 13 vs. 5[a]; negative stress test result: 0 vs. 29[a]; cured: 5, improved: 29, no change: 3[a]	56.5 vs. 78[a]											
Surcel et al. [23]	–	Pad test: 6 vs. 1	Improvement on VAS rating		20.3 vs. 18.2		18.7 vs. 19.3							
Sèbe et al. [27]	UTI, pain	Leaks: 6/12 improved; Pad test: 10/12 improved	9/12 improved	No increase	No reduction			1/3 groups improved						
Lee et al. [28]	3 lost to follow-up, 2 procedure failure due to pain.	Patient satisfaction: Cure = 13, improved = 13, failure = 10.	–					20.3 vs. 45.0[a] ($N = 10$)						
Carr et al. [29]	3 withdrew	5/8 improved diary and pad weight.	–											
Mitterberger et al. [30]	1 bladder perforation, 1 UTI, 3 temporary post-op catheters.	Authors own continence score range 0(continent) to 6 (incontinent) Median 6 pre-op, 1 post-op[a]	52 vs. 101[a]	49.5 vs. 12.5[a]	16.6 vs. 18.3[a]	420 vs. 446	64.42 vs. 56[a]	42.9 vs. 62.8[a]	95.6 vs. 112.7[a]	46.3 vs. 68.2[a]	2.2 vs. 3.3[a]	0.7 vs. 1.2[a]		
Mitterberger et al. [31]	1 temporary post-op catheter	Authors own continence score range 0(continent) to 6 (incontinent) Median 6 pre-op, 0 post-op [a]	53 vs. 104[a]	49.2 vs. 8.5[a]	21.6 vs. 23.2[a]	420 vs. 455	35.4 vs. 32.2[a]	27.0 vs. 42.2[a]	95.6 vs. 112.7[a]	37.4 vs. 55.3[a]	2.0 vs. 3.4[a]	0.58 vs. 1.75[a]	32.0 vs. 47[a]	42.1 vs. 65.3[a]
Mitterberger et al. [32]	10 temporary catheter post-op. 4 lost to follow-up	Authors own continence score range 0 (continent) to 6 (incontinent) Median 6 pre-op, 1 post-op[a]	51 vs. 108[a]	49.2 vs. 12.5[a]	21.6 vs. 25.2[a]	425.9 vs. 450.5	36.6 vs. 31.2[a]	28.8 vs. 40.5[a]	51.8 vs. 78.1[a]		2.1 vs. 3.4[a]	0.65 vs. 1.39[a]	34.0 vs. 45.1[a]	43.1 vs. 55.4[a]

UIE urinary incontinence episodes, *QoL* quality of life, *VAS* visual analogue scale, *TUUS* transurethral ultrasound scan, *EMG* electromyogram of rhabdosphincter

[a] Statistically significant finding

Discussion

The results from the studies published to date are promising. Data from included studies suggest that techniques for treatment of SUI with SC may improve patients' QOL as well as objective measures of urinary incontinence. Furthermore, the use of SCs for SUI is safe with reports only of minor adverse events, but this must be viewed with caution as from a cumulative total of 311 male and female patients, several of whom withdrew from studies and others were lost to follow-up without explanation.

The goals for treatment of SUI are efficacy in reducing or curing SI in a safe and enduring manner. Initial management involves lifestyle changes such as weight loss, exercise and stopping smoking [4]. Pelvic floor muscle training (PFMT) is widely used for first line treatment and may include additional electrical stimulation, biofeedback or other devices such as pessaries or vaginal cones [33] and medical treatment, such duloxetine (serotonin and noradrenaline reuptake inhibitor) can also be attempted although results have been controversial and the product is not currently licensed in the US [34, 35].

In the UK, recommended surgical treatments following the failure of conservative measures include retropubic and transobturator mid-urethral tape procedures, colposuspension, retropubic allograft slings, and artificial urinary sphincter. The most commonly used surgical treatment, tension-free vaginal tape (TVT), has been reviewed extensively, and 83 studies involving over 15,000 patients were reviewed by NICE [4]. Of these studies, 39 studies had followed up 4,017 women at 2 years, and were able to demonstrate a median cure rate of 87 %, although this effect appears to decrease over time with one study reporting a reduction in cure rate from 60 % at 3 years to 30 % at 6–8 years [4]. The Burch colposuspension involves elevating the bladder neck and was considered gold standard with subjective cure rates of 82–95 % at 1 year [4]. When data from 14 centers in the UK and Ireland compared TVT to colposuspension [37], cure rates at 2 years were found to be only 63 and 51 %, respectively. Robust comparison of longer term outcomes between studies of the surgical management of SUI and those in this review are difficult as studies using SC have only data from short-term follow-up. In addition, patient numbers are much smaller in stem cell studies ($n = 311$). Overall, data from stem cell studies are promising and we have found no evidence of inferiority to existing techniques in terms of short-term clinical outcome.

In the current financial climate, one has to accept that operative time for minimally invasive sling techniques is approximately 30 min with a length of stay about one and a half days [38], while it requires at least 3 weeks to simply culture and isolate the SCs at not an inconsiderable cost. However, the procedure itself takes only 15 min and requires just one trained operator in an outpatient setting [27].

Intraoperative complications for TVT include infection, hemorrhage and bladder perforation and post-operative complications such as voiding problems/urinary retention, de novo urgency and wound infection are well described [40]. Clinical trials in this review suggest that SC therapy is safe, with reports of minor complications such as pain, bruising, local reactions, mild self-limited urinary retention and urinary tract infection and no iatrogenic urethral obstruction, which can occur with conventional therapies (Table 3).

The cost of surgery for SUI in the UK, including theatre, inpatient and outpatient costs has been estimated at £1,396 for colposuspension and £1,135 for TVT [41]. It is difficult to ascertain the cost of SC therapy, due to variations in production technique: there is no large-scale commercial production at present. Expert opinion places the latter at approximately 5,000 Euros per injection which is substantially more expensive than other techniques (Blaganji M, personal communication). However, with improved SC expansion from adult sources, it is hoped that SC therapy may become more affordable. The shorter procedure and hospital stay together with the added effectiveness of a regenerative therapy may be an incentive for providers to develop SC therapies on a large scale. If healthcare providers are to continue to develop stem cell therapies for SUI, then we believe that it should be within the context of ethically approved clinical trials. Such ethical approval should take into consideration the scientific uncertainty surrounding such treatments, as well as the significant financial costs, which may have an impact on the funding of other streams of research.

Further research is needed using randomized blinded controlled trials to gain robust data on the efficacy and safety of SCT for SUI. However, these trials are difficult to undertake as stem cell use is in its infancy and patient selection is important. In addition, due to limitations of methodology, such as the need for autologous stem cell donation through a muscle biopsy, the procedure itself cannot be blinded at present. Specific issues regarding the limitations of current techniques that need to be addressed include the future of the re-implanted cells, the re-innervation process, the contribution of the bulking effect at short-term follow-up and the vitality of the cells once implanted. In particular, long-term data are absent at the present time. By demonstrating EMG activity in patients who have received SCT, Mitterberger and colleagues are seeking to demonstrate the neuromuscular activity of implanted SC, and that they are not just acting as a bulking agent [30–32]. However, there is as yet no data in human patients pertaining to the muscular activity of implanted SC

in the urethral sphincter, and as such there is not yet evidence that SC actually have their effect through muscular activity. Larger clinical trials with long-term follow-up are also needed to demonstrate the optimal technique, in particular the optimal injection site, cell processing and concentration of cells per injection. Moreover, research using UCSC may be limited by ethical and practical issues such as consent, collection and storage [8, 9]. Future research with MDSCs, which are autologous, should find it easier to comply with ethical issues than has been the case for embryological SC therapies.

Conclusion

At present there are a variety of treatments available for SUI with good outcomes. SC therapy is an exciting new approach to the treatment of SUI and data from the studies included in this review suggest that the techniques used are safe and effective in the short term. Robust long-term data are needed with comparison to existing surgical techniques before firm conclusions can be drawn. Although SC therapy is very expensive, it is hoped that the shorter procedure and hospital stay could make this a cheaper alternative and that with further development SC therapy may become a successful option in the future.

Conflict of interest None.

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