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A systematic review of autologous stem cell therapy in female stress urinary incontinence

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Background : *Stress urinary incontinence (SUI) is uncontrolable leakage of urine, induced by physical activities such as coughing and laughing. The prevalence of SUI is going to increase. In addition, the quality of life in those patients is much lower than that of normal people.*

Objectives : *To determine the effect of autologous stem cell therapy in female SUI. This review assesses clinical outcome of autologous stem cell therapy compared with other techniques.*

Design : *Retrospective study.*

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Materials and Methods : *Selection criteria: all randomized controlled trials and clinical controlled-trials that compared effectiveness between injections of autologous stem cells and conventional treatments in women with SUI. The outcomes were clinical improvement of urinary incontinence and complications after intervention.*

Search strategy : *MEDLINE, Cochrane Library, and Scopus were searched monthly from June to September 2008.*

Methods of the review : *All review authors assessed the trials for methodological quality.*

Results : *There was only one randomized control trial with data available for 63 women with SUI. After 1-year follow up, the median incontinence score of patients treated with autologous cells significantly decreased compared with patients treated with collagen (p value <0.0001, RRR = 0.895, NNT = 1.235). The rhabdosphincter in patients treated with autologous cells was thicker and more improved in contractility than patients treated with the standard treatment (p value <0.0001). The thickness of urethra was not significantly different between the two groups (p value = 0.366). The quality of life score and electromyography activity, both at rest and during voluntary contraction of the rhabdosphincter muscles, significantly changed in patients treated with autologous cells than those given collagen therapy (p value <0.0001). The treatment with transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts in women with SUI is significantly more effective than treatment with standard endoscopic injections of collagen. All patients did not have any complication.*

Conclusion : *The evidence from this review suggested that at present stem cell therapy for SUI should not be applied as a standard treatment. Further randomized controlled trials are needed to be done before make definite conclusion.*

Keywords : Stem cell, Stress urinary incontinence.

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เหตุผลของการทำวิจัย : *โรคไอจามปัสสาวะเล็ด (SUI) เป็นภาระที่มีปัสสาวะเล็ดราดเวลาไอจามหรือการเคลื่อนไหวร่างกายมีแนวโน้มที่ความชุกของโรคกำลังเพิ่มขึ้น. ผู้ป่วยที่เป็นโรคนี้มีคุณภาพชีวิตที่เลวลงกว่าคนทั่วไป*

วัตถุประสงค์ : *เพื่อประเมินผลของการใช้เซลล์ตัวอ่อนของตนเองในการรักษาโรคไอจามปัสสาวะเล็ดในสตรี บทความนี้จะทบทวนประสิทธิภาพในการรักษาทางคลินิกโดยวิธีนี้เปรียบเทียบกับวิธีอื่น ๆ*

วิธีการศึกษา : *ทบทวนบทความย้อนหลัง*

วัสดุและวิธีการ : *เกณฑ์การคัดเลือก : เลือกเฉพาะงานวิจัยเชิงทดลองชนิดสุ่ม ที่มีการเปรียบเทียบประสิทธิผล ระหว่างการฉีดเซลล์ตัวอ่อนของตนเอง เปรียบกับวิธีดั้งเดิมในการรักษา โรค SUI. พิจารณาผลของการรักษาจากอาการปัสสาวะเล็ดที่ดีขึ้น และภาวะแทรกซ้อนของการรักษา*

แนวทางการค้นคว้า : *ค้นคว้าใน MEDLINE, Cochrane library, and Scopus ทุกเดือนระหว่าง มิถุนายน กับ กันยายน 2008.*

วิธีการทบทวน : *ผู้วิจัยทุกคนจะประเมินคุณภาพของทุกบทความ*

ผลการศึกษา : *มีเพียงการศึกษาเชิงทดลองชนิดสุ่มเพียงการศึกษาเดียวที่มีการทดลองในสตรี 63 ราย ที่เป็นโรค SUI หลังการตรวจติดตามระยะเวลา 1 ปี ทายว่าค่าส่วนเบี่ยงเบนมาตราฐานของคะแนนปัสสาวะเล็ดของผู้ป่วยที่ได้รับการรักษาโดยการฉีดเซลล์ตัวอ่อน มีค่าคะแนนลดลงเปรียบเทียบกับผู้ที่ได้รับการฉีดสารคอลลาเจน (p value <0.0001, RRR = 0.895, NNT = 1.235). กล้ามเนื้อสายหูรูดของผู้ที่ได้รับการฉีดเซลล์ตัวอ่อนมีความหนาและการบีบรัดตัวเพิ่มมากขึ้น (p value <0.0001). ค่าความหนาของท่อปัสสาวะไม่ต่างกันระหว่างกลุ่ม(p value=0.366). คุณภาพชีวิตและค่าการนำไฟฟ้าของกล้ามเนื้อในเวลาพักและบีบตัวของกล้ามเนื้อสายหูรูดเปลี่ยนแปลงมากกว่ากลุ่มที่ได้รับการฉีดคอลลาเจน (p value <0.0001). การรักษาโดยการฉีดเซลล์ตัวอ่อนทางท่อปัสสาวะร่วมกับ fibroblastsในสตรีที่มีโรค SUI มีประสิทธิภาพดีกว่าการฉีดสารคอลลาเจน. ไม่มีรายงานถึงภาวะแทรกซ้อนในผู้ป่วย*

สรุป : *ปัจจุบันจากหลักฐานทบทวนข้อมูลพบว่าการฉีดเซลล์ตัวอ่อนในการรักษาโรค SUI ยังไม่มีข้อมูลเพียงพอที่จะใช้เป็นการรักษาแบบมาตรฐาน จำเป็นต้องรอการศึกษาเชิงทดลองชนิดสุ่มเพิ่มเติมก่อนที่จะสรุปผลถึงประสิทธิภาพของการรักษาโดยวิธีนี้*

คำสำคัญ : *โรคไอจามปัสสาวะเล็ด, เซลล์ตัวอ่อน.*

Urinary incontinence is uncontrollable leakage of urine that occurs with physical activity such as coughing and laughing; it is called stress urinary incontinence (SUI).

Epidemiology

Several studies have been constructed to measure out the prevalence of SUI. The prevalence reported from each study was found to be in discordance due to differences in sample sizes.

In 1980, prevalence of urinary incontinence was 8.5% in women aged 15 - 64 and 11.6% in women aged 65 and over. [1]

In later studies, the prevalence has been shown to be increasing with time. In 2005 - 2006, 15.7% of women were experiencing urinary incontinence. [2]

In Thailand, the prevalence of SUI in menopausal women was the second common type of urinary incontinence. [3,4] The risk factors of urinary incontinence are namely: vaginal delivery, menopause before 50-year-old, postmenopausal women who had never used hormone therapy [4] advancing age, obesity, high parity, weight lifting work and post-hysterectomy. [3] The patient who has SUI was discovered to have a statistical significant impairment in quality of life. Some studies were constructed to advocate this statement. [5]

In spite of the differences in the characteristics of the sample in each study, they all represent a significant proportion of people affected from SUI. Due to ineffectiveness of the current treatments, the number of patient is going to increase. In addition, the quality of life in those patients is much lower than the normal people. The high impact of SUI was proven by these previous studies. And this finding is now a new challenge to the specialists in the field to find new strategies for this condition.

Pathophysiology of SUI

SUI refers to increased pressure on the bladder from ordinary physical activities. The two main mechanisms of SUI are, namely: “urethral hypermobility” and “intrinsic sphincteric deficiency”.

1. Urethral hypermobility:

After pregnancy, childbirth and pelvic surgery, the possibly weakened pelvic muscles may cause the downward position of the urethra which results in urine leakage during normal physiological pelvic pressure on the bladder.

2. Intrinsic sphincteric deficiency:

Despite of abnormal urethral positioning, the weakening urethral sphincter muscles that cannot seal off the flow of urine can also cause urinary leakage especially during physical activities. [6]

Treatment modalities

So far there are several treatment modalities of approaches for the best outcome for patients with SUI; however, no treatment modality has been evidently accepted as the gold standard. Although surgical treatment (colposuspension, suburethral sling procedure which 1 year continent 85 - 90% and five year continent 70%, no significant different between both of them) is commonly used at present, it still does not provide satisfactory outcome. In addition, there are a lot of complications. Complications of colposuspension are urinary retention, detrusor

overactivity, and injury to the bladder or ureter, infection, hemorrhage and enterocele. Suburethral sling procedure also has intraoperative complications which are bladder perforation, bladder laceration, urethral transection, vascular damage, GI damage, and nerve damage and postoperative complication which is urinary retention due to sling obstruction. Bulking agent injection such as collagen is one of the non-invasive treatments which has a good outcome especially in the first year, but in five-year outcome are not quite impressive and late complications are also observed. Most complications such as urethral obstruction, erosion and abscess are due to foreign body injected. [7]

Stem cell therapy for SUI

Stem cell therapy has been used in non-urologic diseases for a while. Nowadays, it is used as a new modality of treatment in urologic diseases including SUI. Since the experiments in animal model have been successful, stem cells are applied to human in many studies. [8-11] Human myoblast and fibroblast which obtained from autologous skeletal muscles, then cultured in the specific media, are injected to rhabdosphinter and submucosa of urethra. Compared with surgical treatment, the stem cell injection has better long-term outcomes and fewer complications; however, the existing data covered only in mild-to-moderate hypermobility of the urethra and bladder. Furthermore, the data are limited by the small number of population and researcher groups.

Since the outcome of this new modality of treatment is scattered and variable in methodology and outcome measurement. A systematic review may be beneficial in providing a complete understanding in all of the crucial aspects of this modality.

Objectives

To determine the effect of autologous stem cell therapy in female SUI. This review assesses whether autologous stem cell therapy provide clinical improvement than other techniques.

Materials and Methods

Criteria for considering studies for this review

Types of studies

This systematic review consisted of all randomized controlled trials and clinical controlled-trials that compared effectiveness between injections of autologous stem cells and conventional treatments in women with SUI. Quasi-randomized trials and clinical trials were excluded.

Types of participants

We included studies whose subjects were women who had SUI with only mild hypermobility of the urethra and urinary bladder or intrinsic sphincter insufficiency, which did not improve with pelvic floor exercise. We also required good status of health and signed informed consent. Exclusion criteria were urge incontinence and pronounced hypermobility of the urethra. The patients between 45 - 59 years old are the most affected from SUI. [1, 3-5]

Types of intervention

Injections of autologous stem cells (i.e. myoblasts or fibroblasts) compared with other techniques, e.g., collagen injection, pubovaginal sling.

Types of outcome measures

Primary outcomes:

- Incontinence score
- Contractility of the rhabdosphincter and thickness of the urethra and the rhabdosphincter measured by transurethral ultrasonography
- Incontinence quality of life score
- Urodynamic test: cystoscopy, pressure-flow studies, and urethral closure pressure.

Secondary outcomes:

- Complications: stricture, voiding dysfunction, urinary tract obstruction, urinary retention measured by cystoscopy, urodynamic test and interview the effectiveness

Search methods for identification of studies

MEDLINE, Cochrane Library, and Scopus were monthly searched from June 2008 to September 2008. We also manually searched from reference lists and from the library of the Faculty of Medicine, Chulalongkorn University. No restrictions were placed on language, publication date, or publication type for the initial search within these databases. Search terms included “stem cells”, “stress urinary incontinence”, “SUI”, “myoblast”, “fibroblast” and “controlled trials”.

Methods of the review

All review authors assessed the trials for methodological quality without consideration of results. We also noted the authors’ names, institutions and the sources of publications. We excluded the trial by selection criteria (Figure 1 and Table 1). Each author has read all trial abstracts

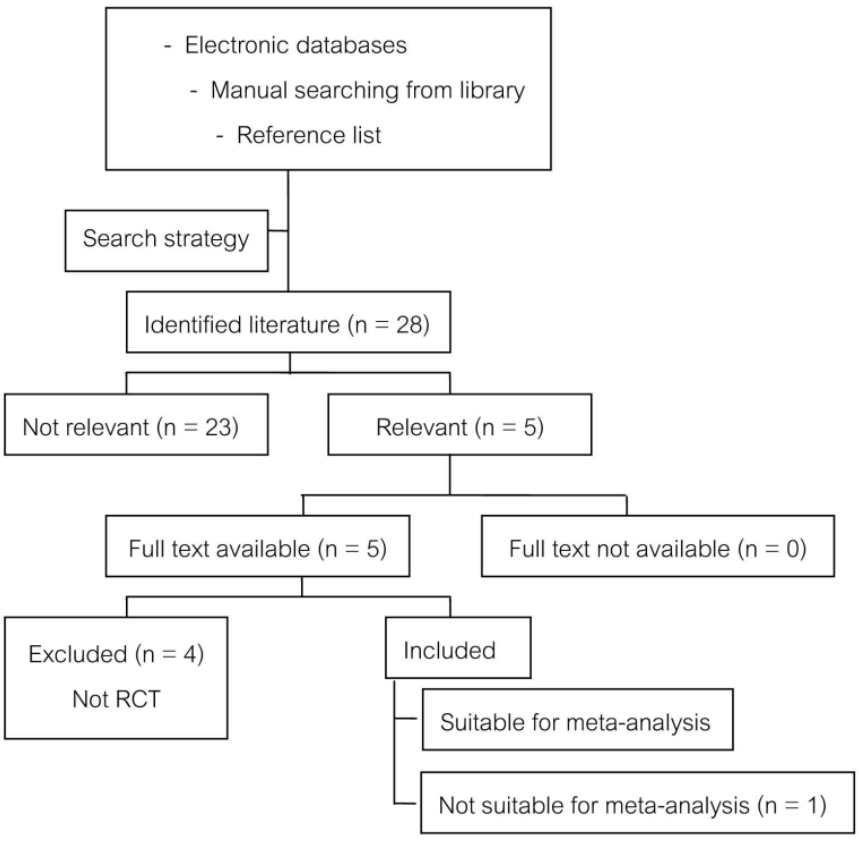

Figure 1. The inclusion and exclusion criteria of the identified trials

Table 1. Characteristics of excluded studies.

Bent 2001	The study uses chondrocyte as a bulking agent in intrinsic sphincter deficiency, no comparison groups.
Chen 2003	This study investigates the effect of increasing estrogen concentrations on metalloproteinase and tissue inhibitors of metalloproteinase protein expressions in cultured pelvic fibroblasts.
Chen 2004	This article studies about morphology of levator ani muscle of patient with stress urinary incontinence.
Chen 2005	This study uses relaxin as a therapeutic method.
Chen 2006	Define gene of vaginal tissue in SUI by microarray analysis: not a therapeutic trial.
Chen 2007	Define role of neutrophil elastase.
Falcony 1994	This article explains collagen metabolism, not a therapeutic trial.
FitzGerald 2000	This study compares histologic structure of pre- and post-implantation myofibroblasts.
Kuhn 2004	This article is a narrative review of injectable therapy in out-patient case; use of bovine origin collagen, silicone, autologous fat, chondrocytes and ethylenevinylalcohol.
Mitterberger 2007	This study uses autologous fibroblasts and myoblasts for treatment of post-prostatectomy urinary incontinence and no controlled or comparison groups.
Mitterberger 2008	This study use autologous myoblasts and fibroblasts for treatment female with stress urinary incontinence but no controlled or comparison groups.
Rechberger 1995	To locate estrogen receptors by immunohistochemistry.
Shiroki 2007	This article is a narrative review about future treatment of strees urinary incontinence.
Sokol 2008	This study combines trans- and periurethral injections of bulking agents for the treatment of intrinsic sphincter deficiency.
Strasser 2004	This study investigates about transurethal ultrasound-guided myoblasts and fibroblasts injections in both male and female patients with SUI but no comparison groups.
Strasser 2007 [1]	This trial compares autologous stem cells therapy versus collagen injection in both male and female patients and is not a randomized trial.
Tomaszewski 2003	This study compares 17 beta-estradiol and phytoestrogen daidzein on the proliferation of pubocervical fascia and skin fibroblasts.
Trabucco 2007	This trial uses proteoglycan as a therapeutic method.
Wen 2008	This study compares relaxin's effect on transforming growth factor (TGF) - beta1 and latent TGF-beta1-binding protein (LTBP-1) in vaginal fibroblasts.
Woodruff 2008	This trial uses pubovaginal sling as a therapeutic method.

received from the sources described above. If the opinions of all review authors were not in concordance, we would discuss until a conclusion was reached. Articles were excluded from further analysis when they reported no clinical outcome, i.e. a review, editorial letter, or an animal study. The trials, selected from abstract readings, were further searched for full texts. Then we appraised the full texts with Critical Appraisal Skill Program (CASP) [12] and JADAD score. [13] The trials that passed all questions in the critical skill program were included.

We analyzed outcomes on a number-needed to treat basis and have calculated relative risk and p-value for dichotomous data. As for continuous data, we have calculated an average (median or mean difference) and standard deviation of the outcomes.

Results

Description of studies

According to our criteria, there was only one randomized control trial with data available for 63 women, age 36 – 84, with SUI [14] (Table 2).

Table 2. characteristics of included studies.

Methods	*Type of study:* Randomized controlled trial
	Method of treatment allocation: Computer-generated randomization list
	Stratification: No.
	Comparison group: Yes. (Endoscopic collagen injection)
	Sample size calculation: Yes.
	Intention-to-treat analyses: No.
	Losses to follow up: No. (0 lost follow up, 0 discontinued intervention, 0 excluded from analysis)
	Funding: Innovacell Biotechnologie and Institut fuer Gewebe- und Organrekonstruktion (IGOR)
	Supported by: Fonds zur Foerderung der wissenschafthichen Forschung, Vienna; Institute for Biochemical Pharmacology, Medical University Innsbruck; Austria
Participants	*Location:* Department of Urology of the Medical University of Innsbruck, Austria
	Timeframe: September 2002 to the end of 2004
	Eligibility criteria: Female patients with age 36-84 years old who had intrinsic sphincter insufficiency or SUI with only mild hypermobility of the urthra and the urinary bladder. Good state of health. Signed inform consent.
	Exclusion criteria: Urge incontinence and pronounced hypermobility of the urethra.
	Total recruited: 63 women
Interventions	$3.8*10^7$ fibroblasts (range $5.4*10^5$ –$6.0*10^7$) and $2.8*10^7$ myoblasts ($5.1*10^5$ –$3.6*10^7$) were injected with transurethral ultrasonography-guided to patients in the cell treatment group.
	4.8 mL of collagen (2.5–7.5) were injected under endoscopic guidance in the collagen group.
Outcomes	*Primary outcomes:* Incontinence score (24 hr voiding diary, 24 hr pad test, Questionanaire) from 0(Continence) to 6(Incontinence), Contractility of rhabdospincter, Thickness of urethra and rhabdosphincter.
	Secondary outcomes: Quality of life score from 22(Severely restricted quality of life) to 110(No restrictions on quality of life), Urodynamic and clinical test (Cystoscopy, Pressure-flow studies, Measurement of urethral closure pressure, Muscle activity of rhabdospincter)
Methodological quality – CASP 9/10 AND JADAD score grade 5	

All samples have SUI or intrinsic sphincter insufficiency without urge incontinence and pronounced hypermobility of urethra. In addition, these patients had failed pelvic floor exercise.

The method of randomization used in the study is computer-generated randomization. 42 patients were assigned transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts and 21 patients were assigned to receive endoscopic inserted collagen injection. The article was single-blinded of outcome assessment and single hospital. The outcome measurement was divided into two categories; primary outcomes and secondary outcomes.

The study is conducted in Austria from 2002 to 2004 (University of Innsbruck) and sisters of Charity Hospital, Wels, Austria.

Methodological quality

All patients were appropriately allocated to the intervention and control groups. The method of randomization used in the study was computer-generated. The list consisted of seven permuted blocks, each of which contained nine randomly selected and unsorted combinations of the numbers 1, 2, and 3. Patients allocated numbers 1 and 2 were assigned to receive treatment with autologous cells, and those allocated number 3 were assigned to receive treatment with collagen (controls). Patients were sequentially allocated to these randomized numbers in the order in which they were enrolled.

The study method did not reach classic prospective double-blind trial due to autologous cells had to undergo muscle biopsy and application procedures of collagen and cells were completely different. Since the patients and operator knew each method allocation, incontinence score which is evaluated by a questionnaire may be erroneous.

Regarding endoscopic injection of collagen (control group), this might not be correctly done in the same depth as well as the transurethral ultrasonography-guided injections, i.e., whether or not they were done by the same operator, this was not stated.

The follow-up period was 12 months, however, no detail of the procedure or investigation in each visit was given. Also, no follow-up interval was stated in this study.

The factors that may influence the results are co-intervention, confounders, contamination, and compliance. We considered that there was no co-intervention and contamination. For the confounders, the study had appropriately restrictive inclusion criteria and randomization, but no matching and stratified sampling. The problematic compliances in the study were pelvic floor exercise that was individually depended, and the follow-up schedule should be more regularly attended.

The study processed data with SPSS statistical software (Version 11.5.1) and compared the treatment groups by the use of the Mann-Whitney U test. A p value of 0.05 or less was regarded as statistically significant.

Primary outcomes

After 1 year follow-up, the median incontinence score of patients treated with autologous cells decreased from baseline 6.0 to 0, compared with 6.0 to 6.0 in patients treated with collagen (p value <0.0001, RRR = 0.895, NNT = 1.235).

The difference of the mean cannot be calculated because of only one study, so the mean was used instead. The mean thickness of the rhabdosphincter in patients in patients who received autologous cells was increased (from 2.03 mm to 3.38 mm) compared with control group (from 2.32 mm to 2.32 mm) with p value <0.0001.

The mean contractility of the rhabdosphincter in patients who received autologous cells was increased (from 0.54 mm to 1.56 mm) compared with control group (from 0.66 mm to 0.67 mm) with p value <0.0001.

The mean thickness of the urethra in patients who received autologous cells was increased (from 3.73mm to 5.41mm) compared with control group (from 4.59 mm to 5.36 mm) with p value = 0.366. The median quality of life score in patients who received autologous cells was increased from 49 to 108 (possible range 22 - 110) when in control group was increased from 59 to 64 (p value <0.0001).

The results of urodynamic test were not significantly different between the two groups except for the electromyography activity at rest and during flow (p value <0.001) and maximum closure pressure during voluntary contraction of the rhabdosphincter (p value =0.029). All results are shown in Table 3.

Table 3. Primary outcomes of patients treated with autologous cells and collagen, baseline and 1 year after intervention.

	Patients assigned to receive autologous cells		Patients assigned to receive collagen		p value
Outcomes	**Baseline**	**Result**	**Baseline**	**Result**	
Incontinence score	6.0	0.0	6.0	6.0	<0.0001
Number of incontinent patients	42	4	21	19	
Thickness of rhabdosphincter (mm)	2.03	3.38	2.32	2.32	<0.0001
Contractility of rhabdosphincter (mm)	0.54	1.56	0.66	0.67	<0.0001
Thckness of urethra (mm)	3.73	5.41	4.59	5.36	0.366
Quality of life score	49	108	59	64	<0.0001
Maximum residual urine (mL)	49.29	13.83	6.43	8.81	0.651
Maximum urinary flow (mL/s)	21.62	25.29	19.7	19.63	0.052
Maximum detrusor pressure during flow (cmH_2O)	36.62	31.26	32.81	34.76	0.194
Maximum bladder capacity (mL)	441.69	469.86	399.95	404.05	0.153
Maximum closure pressure at rest (cmH_2O)	28.88	40.52	32.24	35.24	0.204
Maximum closure pressure during voluntary contraction of the rhabdosphincter (cmH_2O)	38.52	53.26	40.71	40.57	0.029
Periurethral EMG recording at rest (μV)	34.31	44.23	31.38	31.57	0.001
Periurethral EMG recording during voluntary contraction of the rhabdosphincter (μV)	45.10	56.47	41.76	41.62	<0.0001

Secondary outcomes

Muscle biopsies, endoscopic injections of collagen, and transurethral injections of autologous cells were complete without any complication in all patients. Urethroscopy and transurethral ultrasonography immediately after endoscopic injection of collagen showed good adhesion of the mucosa, and allowed the size and location of the collagen deposits to be recorded. No participant was lost after 1-year follow up. The results were recorded again three years after the intervention. The post-operative results show no change.

Discussion

Our findings from one randomized controlled trial including 63 participants followed up for 1 year demonstrate that the treatment with transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts in women with SUI is significantly more effective than treatment with the standard endoscopic injections of collagen.

The rhabdosphincter in patients treated with autologous cells was thicker and more improved in contractility than patients treated with the standard treatment. The thickness of the urethra was not significantly different between the two groups.

The quality of life score and electromyography activity both at rest and during voluntary contraction of the rhabdosphincter muscles significantly changed in patient treated with autologous cell than those who were given collagen therapy. The weakness of this study is the short follow up period. The efficacy of new treatment for stress incontinence required long term follow up for the proof of safety and success rate.

Even though one randomized controlled trial may not be enough to make a definite conclusion, the results were supported by other clinical trials that we did not include into the review. Strasser *et al*. 2004 [15] performed in 29 women and 13 men who suffered from SUI, demonstrated that 35 patients were cured and 7 patients improved after transurethral ultrasound-guided injections of autologous myoblasts and fibroblasts.

Strasser *et al*. 2007[16] studied in 63 women and 28 men with SUI; 42 women and 21 men were treated with transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts, while 21 women and 7 men received standard transurethral endoscopic injections of collagen. The postoperative results after a 12-month follow up revealed the effectiveness of injections of autologous myoblasts and fibroblasts and indicated higher benefits in women over men.

Mitterberger *et al*. 2007[17] performed a study on 123 women with SUI in the same age groups, materials and methods, evaluation and follow up. After 1-year follow up, it showed significant improvement in incontinence score, incontinence quality of life, instrument score, thickness of urethra and rhabdosphincter, contractility of rhabdosphincter and electromyographic activity (p value = 0.001). Another clinical trial of Mitterberger *et al*. published in 2008 [18] also showed significant improvement in 16 of 20 women with SUI after a 2-year follow up (p value = 0.001).

This review has, however, some limitations. Publication bias may exist by limiting some well-known databases that cannot be accessed, e.g., EMBASE, ISI. The test for heterogeneity and meta-analysis

cannot be done. Unfortunately, there has not been any previous systematic review to be compared with. Late complications cannot be currently concluded due to the lack of long-term follow up and insufficient number of randomized controlled trials. This review may be considered premature. The other limitation is that only one study can be included in our review, so the quantitative systematic review is not possible. Anyhow, the best evidence from our review articles is still beneficial for choosing the new technique.

The application of stem cell therapy in SUI is still questionable. There is no clinical trial made within the same settings in our country. Many things need to be considered including the professional surgeons and radiologists, the available stem cell center, and health economics. Due to one study can be included in our study, this technique is not recommended as the standard treatment, more studies are required for further conclusion.

Conclusion

Implications for practice

The evidence from this review suggests that stem cell therapy for SUI should not be applied as a standard treatment at present. However, there was no negative result from stem cells therapy.

Implications for research

Further randomized controlled trials are needed to be done before making any definite conclusion. Follow-up studies should be undertaken to confirm the long-term effects of this treatment. Multicenter-based and better blinding techniques should be designed.

With the assistance of the recommendations proposed, it is now a time to proceed to the next step with well-controlled clinical trials.

Potential conflict of interest

No.

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