Autologous Muscle-derived Cell Injection for Treatment of Female Stress Urinary Incontinence: A Single-Arm Clinical Trial with 24-months Follow-Up

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Purpose: This clinical study evaluated the effect of autologous muscle-derived cell (MDC) injection for the treatment of female patients with pure stress urinary incontinence (SUI).

Materials and Methods: A total of 20 women with SUI received transurethral injections of autologous MDCs. Baseline and follow-up evaluations consisted of physical examinations (cough stress tests), one-hour pad test, Incontinence Impact Questionnaire-7 (IIQ-7), and Urogenital Distress Inventory (UDI-6) scoring. The patients were followed one week as well as 1, 3, 6, 9, 12, and 24 month(s) after the procedure. Multichannel urodynamic study were performed before and 24 months after the intervention. The incidence and severity of adverse events (AE) were also recorded at each follow-up visit.

Results: A total of 20 eligible female patients with the chief complaint of SUI that was unresponsive to conservative management, was enrolled in the trial, 17 of whom completed all follow-up visits. At 12th months, 10 (59%) patients had complete response, whereas 2 (12%) and 5 (29%) patients had partial and no response, respectively. At 24th months, relapse of SUI in 5 out of 10 complete responders (29%) and 2 out of 2 partial responders to the treatment, respectively. The intervention produced no serious AE during the trial.

Conclusion: According to our results, though obtained from a limited number of patients, MDC therapy was a minimally invasive and safe procedure for treatment of female patients with pure SUI. However, currently, the efficacy of this type of treatment for SUI is not sufficiently high and multi-center randomized clinical trials are required to be conducted before reaching a concrete conclusion.

Keywords: urinary incontinence, stress; urethra; cell- and tissue-based therapy; muscle-derived stem cell

INTRODUCTION

Stress urinary incontinence (SUI) is a common health problem in women. It has been reported that 25-35% of women over 18 years of age suffer from urinary incontinence[(1)]. The International Continence Society defined SUI as involuntary leakage of urine on exertion/effort, coughing, or sneezing. SUI is categorized into two subtypes: urethral hypermobility which is a result of weak anatomical support, and intrinsic sphincter deficiency (ISD) which occurs due to the weakness of striated external sphincters and control mechanisms within the bladder neck and urethra[(2,3)]. The initial management of SUI is comprised of a conservative approach that includes lifestyle modification, biofeedback, pelvic floor physiotherapy, electrical stimulation, and pharmacotherapy. However, surgery is the mainstay method employed for non-responsive cases [(4)].

Urethral slings are the most popular surgical options which repair the anatomical defects regardless of SUI pathophysiology. Related postoperative complications include erosions, permanent urinary retention, bladder perforation, urethral trauma, persistent suprapubic and groin pain, wound infection and dehiscence, and dyspareunia[(5,6)].

Tissue engineering and cell therapy are novel interventions developed to overcome the sphincteric deficiency. Some clinical studies evaluated the safety and efficacy of intraurethral injection of adult stem cells for treatment of SUI [(7,8)]. We previously reported the safety of muscle-derived cell (MDC) injection in female patients with ISD and urethral epispadias [(9)].

Thought many studies were conducted on the ef-

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Table 1. Patients' demographic data.

Patients	Race	Age (years)	Weight (kg)	Number of deliveries
01	Caucasian	32	78	1
02	Caucasian	48	72	2
03	Caucasian	59	69	3
04	Caucasian	44	74	2
05	Caucasian	45	76	2
06	Caucasian	54	69	3
07	Caucasian	30	66	0
08	Caucasian	53	71	3
09	Caucasian	60	74	4
10	Caucasian	60	71	5
11	Caucasian	65	79	5
12	Caucasian	46	81	2
13	Caucasian	51	84	3
14	Caucasian	60	69	5
15	Caucasian	48	86	3
16	Caucasian	51	73	3
17	Caucasian	70	73	3
18	Caucasian	46	69	2
19	Caucasian	53	83	2
20	Caucasian	44	68	3

fect of MDC injection for treatment of female SUI (9,17,19,19,23,24 , few clinical studies completed a follow up of ≥2 years[25,29].

The current clinical trial evaluated the safety and potential efficacy of adult MDC injection in 20 women suffering from pure SUI, during a 24 months follow-up period.

MATERIALS AND METHODS

From September 2013 to March 2016, this single-center prospective study enrolled 20 women with SUI unresponsive to conservative management. In this trial, SUI patients with urethral hypermobility with Valsalva leak point pressure (VLPP) of 60-90 cm H_2O, were included. Exclusion criteria consisted of the history of anti-incontinence surgery in the past 12 months, evidence of acute vulvovaginitis, grade 3 (or higher) cystoceles, active urinary tract infection, urogynecologic malignancies, coagulopathies, grade 3 (or higher) rectocele, diabetes mellitus (DM), hypertension (HTN), smoking, post–void residual volume of ≥100 ml as assessed by ultrasound scan, abnormal cystourethroscopic findings (diverticula, mass, etc.), and abnormal urodynamic study results (low capacity, low compliance, and detrusor over activity). The Ethics Committee of the Urology and Nephrology Research Center of Shahid Beheshti University of Medical Sciences (Tehran, Iran) approved this study with the registration No. NCT02156934. All patients received information about the process of the clinical study and provided written informed consent.

Table 2. Patients' parameters at baseline and one week following the cell injection.

Patient parameters	Baseline	week 1 visit
Urinary tract ultrasound		
Anatomic anomaly	Neg	Neg
PVR urine (cc)	10-20	10-20
Hydronephrosis	Neg	Neg
U/A	Neg	Neg
RBC (number)	0-2	0-2
WBC (number)	0-1	0-1
Prot	Neg	Neg
U/C	Neg	Neg

Abbreviations: PVR: Post-void residual; U/A: Urine analysis; RBC: Red blood cell; WBC: White blood cell; Prot: Protein; U/C: Urine culture.Neg: Negative.

In baseline and follow-up evaluations, medical history and results of physical examination, cough-induced stress test in lithotomy and upright position, urinalysis (U/A) and culture, urinary tract ultrasound, one-hour pad test, multichannel urodynamic study, and cystourethroscopy, were recorded. The patients were visited at week 1, and at the end of month(s) 1, 3, 6, 9, 12 and 24 after cell injection. Maximal urethral closure pressure (MUCP) and maximal flow rate were assessed before and 24 months after the intervention. Hypermobility during Valsalva maneuver was defined as a □45º change in the angle between the horizontal line and urethra. The degree of pelvic organ prolapse was graded according to the Pelvic Organ Prolapse Quantification System[10]. Urine analysis and culture, and urinary tract ultrasound evaluations were performed at baseline and 1 week after the cell injection.

The severity of symptoms were scored according to the Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory (UDI-6)[11]. A multichannel urodynamic study was performed by using a dual-lumen 6 Fr catheter according to the standards proposed by the International Continence Society[12].

Eligible patients underwent an open biopsy of the quadriceps femoris muscle under local anesthesia. A 5×5 mm square of the muscle was excised, collected, and transferred to the clean room in a cold box.

All procedures performed on human participants were conducted in accordance with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki, related amendments or comparable ethical standards.

Muscle-derived cell (MDC) processing

Human MDCs were isolated by the fiber enzymatic dissociation technique described in our previous phase-I study[9]. Briefly, the biopsy specimens were minced into approximately 1 mm pieces. Tissues were subjected to enzymatic dissociation using a solution of collagenase XI (Sigma, Cat. # C7657) and 1 mg/ml dispase (Gibco, Cat. # 17105-041), plated in collagen-I-coated flasks (Sigma-Aldrich, Cat. # 7624), and incubated at 37°C with 5% CO2. Quality control tests included karyotyping for the chromosomes; immunofluorescence for the expression of Desmin as a popular muscle marker; and flow cytometric evaluation of the expressions of CD34 (as a general stem cell marker), CD56 (as muscle progenitor marker), and CD45 (which was used to rule out the hematopoietic origin of these cells). Samples safety was assessed using the following assays: microbial test, mycoplasma test, and limulus amebocyte lysate (LAL) gel clot assay for endotoxin detection.

Autologous muscle-derived cell (MDC) transplantation

The final culture of MDCs was suspended in normal saline, counted, and loaded into 10-ml sterile syringes. For each patient, at least 50×106 cells were injected endoscopically and submucosal at 5 and 7 o'clock positions approximately 1-1.5 cm distal to the bladder neck, at the presumed level of external sphincter with the aid of a flexible 23-gauge needle of 5.7 French (Fr) in diameter and 8 mm in lengths (Cook Williams Medical company).

Response assessment

All patients were followed for 24 months after cell

Table 3. Mean maximum flow rate in patients at baseline and 24 months after the muscle-derived cell (MDC) injection.

	Baseline	24th months follow-up	*p*-value*
Mean Qmax All patients (ml/s)	20.5 (±4.2)	18.5 (±1.6)	0.035
Mean Qmax Complete response patients (ml/s)	19.5 (±2.2)	16.2 (±1.3)	0.002
Mean Qmax Partial response patients (ml/s)	20.1 (±2.3)	18.6 (±2.0)	0.8
Mean Qmax No response patients (ml/s)	22.8 (±7.1)	18.9 (±2.0)	0.1

Abbreviations: Qmax: Maximum flow rate; ml/s: Milliliters per second
* as evaluated by Paired *t*-test.

transplantation. Objective response was assessed by the cough stress test and one-hour pad test. Subjective response was assessed by the IIQ-7 and UDI-6 questionnaires. Complete response or cure was defined as: negative cough stress test for all positions and one-hour pad test result of below 2 g. Decrease in one-hour pad test weight and negative cough stress test in the lithotomy position (with positive cough test in the upright position) were defined as partial response. Pad test grades were defined based on their weight, as follows: 1 (< 2 g); 2 (2-10 g); 3 (10-20 g); and 4 (> 20 g).

Primary and secondary endpoints

Primary endpoint was a complete response after 12 months as assessed by subjective criteria (IIQ7-UDI6) and objective criteria (cough test and pad test). Severity and incidence of adverse events (AEs) related to cell injection were secondary endpoints.

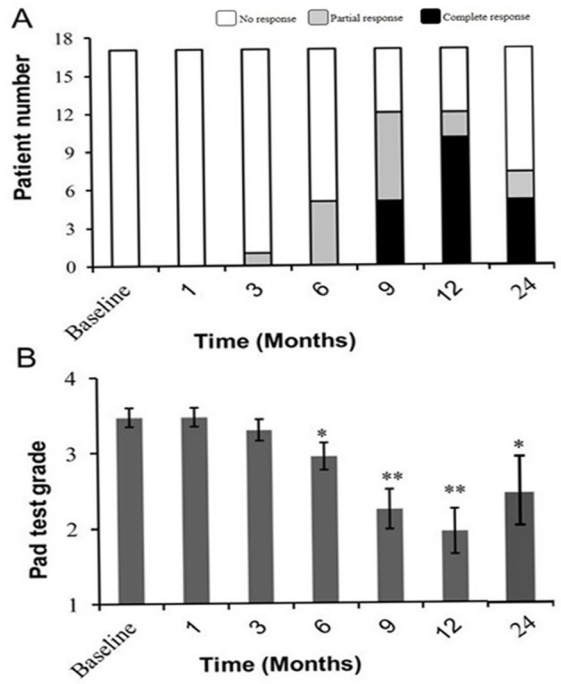

Figure 1. (A) The rates for complete, partial, and no response to the muscle-derived cell (MDC) injection at baseline and month(s) 1, 3, 6, 9, 12, and 24 after the injection. **(B)** One-hour pad test at baseline and month(s) 1, 3, 6, 9, 12, and 24 after the cell injection. * $p < 0.003$ and ** $p < 0.0001$ as compared to the baseline.

Statistical analysis

We used mean and standard deviation (SD) for data presentation. A p-value ≤ 0.05 was considered statistically significant. Paired *t*-test was used for comparison of quantitative and qualitative variables, respectively. To compare the mean age between complete, partial and non-responders, ANOVA test has been used. The non-parametric Wilcoxon test was used for data with abnormal distribution. SPSS version 19 was used statistical analyses.

RESULTS

We initially evaluated 51 females and then, recruited 20 eligible patients to participate in this trial **(Table1)** Of those, 17 were followed for 24 months. Two patients did not complete the follow-up period due to lack of attendance and no phone response within the first 3 months. Two weeks after the intervention, one patient was diagnosed with breast cancer, and received systemic chemotherapy and could not attend the follow-up visits.

The mean age of participants was 51.5 (ranging from 30 to 70) years. 12 months after injection, 10 (59%) patients had complete response, 2 (12%) patients showed partial response, and in 5 (29%) subjects, treatment failed (**Figure 1A**). At the end of 2-year follow-up, there was a recurrence of SUI in 5 out of 10 cured patients as well as 2 out of 2 partial responders. There was no statistically significant difference (P =.33) in mean age among complete (52.4 ± 9.9 years), partial (51.5 ± 10.6 years), and non-responders (49.8±13.8 years). The mean number of normal vaginal deliveries was not statistically different (P = .33) among patients who completely responded (3), partially responded[2], and had no response[2].

The mean of maximum flow rate (Qmax), measured by urodynamic tests, decreased at the final follow-up visit from 20.506 ml/s to 18.572 ml/s in all patients (**Table 3**, P = .0.35). However, statistically significant decrease in mean Qmax changes was only observed in complete responders (19.5 ml/s to 16.21 ml/s; P = .002; **Table 3**). Mean MUCP was 51.19 ± 5.1 cm H_2O (range 44-59 cm H2O) at baseline and 51.69±4.9 cm H_2O (range 47-59 cm H_2O) at the end of 24-months follow-up (P = .136). An improvement in the cough–induced stress test (only in the upright position) was observed 3 months post–injection in complete responders; however, at the end of 24-month follow-up, a negative cough stress test was recorded in these patients. There was a decrease in the one-hour pad test at third month and negative result (<2 g) at the end of 24-months follow-up in complete responders (**Figure 1B**). Improvements in UDI-6 and

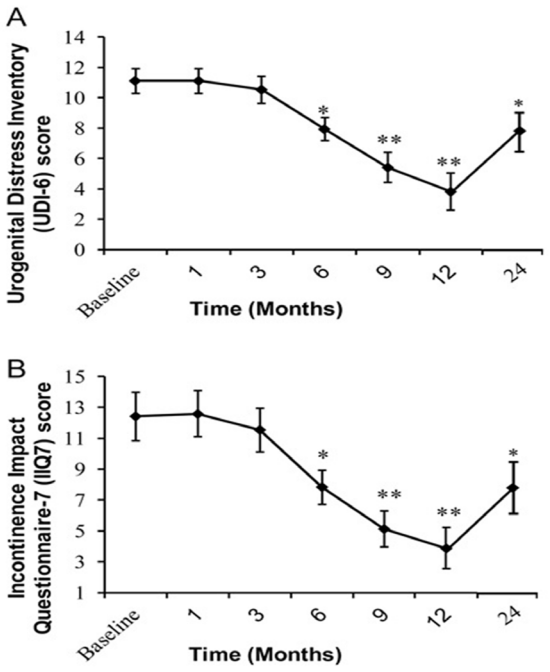

Figure 2. (A) Changes in Urogenital Distress Inventory (UDI-6) scores from the baseline to the end of 24th months follow-up in stress urinary incontinence (SUI) patients. *: $p < 0.05$ and **: $p < 0.0001$ as compared to the baseline. **(B)** Changes in Incontinence Impact Questionnaire-7 (IIQ-7) scores from baseline to the end of 24th months follow-up in SUI patients. * $p < 0.001$ and ** $p < 0.0001$ as compared to the baseline.

IIQ-7 scores were recorded at 3- and 6-months follow-up visits, which lasted up to 24 months (**Figures 2A and 2B**).

We observed complete response (as the primary endpoint) in 10 out of 17 (59%) patients at 12 months.

The site of the muscle biopsy healed after one week in all patients. Two years after cell injection, we detected no serious AEs (as the secondary endpoint) related to the intervention following comprehensive patient examination with respect to urinary tract infections, urinary retention, pain, hematoma, or infection at the site of muscle biopsy and cell injection. **Table 1** lists the patients' demographic data and reveals patients' parameters assessed by urinary tract ultrasound (related to bulking agent effects), and urine analysis and culture.

DISCUSSION

Our study revealed the potential efficacy and safety of transurethral injection of MDCs in female patients suffering from SUI who were unresponsive to conservative management, during a 2-year follow-up period. In this trial, we observed a gradual process of healing and improvement that started three months after the cell transplantation. Although at 12th month follow-up visit results were promising, half of the cured patients and all partial responders experienced SUI recurrence during the second year.

In 2000, Chancellor et al. for the first time, reported the positive effect of myoblasts transplantation for treatment of SUI in a rat model[13]. Several preclinical studies followed this concept and demonstrated the efficacy of cell therapy for treatment of urethral sphincter injuries[13]. Yokoyama et al. indicated that labeled MDCs differentiated into myotubes and myofibrils in the bladder wall of a rat model[14]. Injection of MDCSs into the periurethral regions of a mice model of SUI resulted in significant improvement of LPP in comparison with the control group[15,16]. In 2008, Mitterberger et al. reported that the formation of new myofibrils after a single injection of myoblasts into a guinea pig with SUI, produced no inflammation, infection, nor scar at the injection site. Another remarkable finding of this study was the direct correlation between increment of LPP and the amount of injected cells, suggesting that a sufficient number of cells is required to improve SUI[8].

Along with preclinical experiments, clinical trials that assessed the effect of MDCs as treatment of SUI have shown promising results. Injection of MDCs in SUI patients was found to be safe, which was further supported by lack of AEs in our study[8,17-27]. In another study, 12 women with a history of failed surgical intervention for treatment of SUI, received MDCs; results showed complete response in 3 and partial response in 7 patients after 12 months of follow-up[23]. Although the results of the current study indicated an acceptable improvement rate at one year follow up, half of these individuals experienced SUI recurrence. Stangel-Wojcikiewicz et al. reported that injection of 0.6 to 25×106 MDCs in 16 SUI women caused complete and partial response in 50 and 25% of the patients, respectively after 2 years of follow-up, which indicated a response rate similar to that observed in our study[25]. Improved thickness, contractility and electro-activity of the rhabdosphincter confirmed integration of MDCs into the rhabdosphincter 2 years after the MDCs injection in 20 women with SUI[24]. The efficacy of an intraurethral injection of fresh skeletal muscle in 35 women with uncomplicated and complicated SUI was reported. Uncomplicated SUI cases had a cure rate 25% and 63% improvement whereas the complicated group had a 7% cure rate and 57% improvement,[19] which was nearly comparable to the findings of the present trial.

Of note, the efficacy results might be attributed to the quantity of injected cells. Carr et al. reported that injection of $18\text{-}22\times10^6$ MDCs improved 5 and cured 1 patient out of 8 subjects with SUI. They indicated that the improvement began 3 and 8 months after the cell injection. This trend was in line with our results[17]. Later, they confirmed the positive effect of higher numbers of injected cells in 30 patients[28]. Therefore, to ensure a positive effect, all patients received at least 5×10^7 cells. In addition, injection of MDCs led to a complete response in 50% and partial response in 25% of 16 SUI women, which was in line with the results of the current study[25]. On the other hand, a larger single-arm trial performed on 123 female patients with SUI, reported complete response in 79% of the patients after a single injection of 3.8×107 fibroblasts and 5.1×106 myoblasts, which were considerably higher numbers of cells compared to our trial, but with almost the same response rate. Also, Mitterberger et al. showed that in most patients, continence score, Urinary Incontinence Quality of Life Scale (I-QOl) and the thickness, contractility, and electromyographic activity of the rhabdosphincter were significantly improved[27].

Subsequently, it was shown that injection of MDCs positively impacted the quality of life of female patients with SUI, 2 and 4 years after the injection[29].

In the majority of trials, cells were directly injected into the damaged sphincteric area. Both subjective and objective assessments reported that the cure rate in these trials ranged from 13 to 50%, and indicated 50-86% improvement at short-to-medium term follow-up periods. In 2018, Cui et al. compared the effect of muscle-derived stem cells (MDSCs) and adipose tissue-derived stem cells (ADSCs) for treatment of SUI in a rat model. Also, after cell injection, rats were killed and their urethra was studied. Histologic analysis showed that the MDSCs- and ADSCs-treated groups had significantly higher myosin and α-smooth muscle actin (α-SMA) content compared to the control group[30].

CONCLUSIONS

MDC therapy was found to be a minimally invasive and safe procedure for treatment of female patients with SUI with 24 months follow-up. Although 59% of patients were cured at the 12-month follow-up, the positive results declined at 24th month and half of those responders demonstrated evidence of SUI recurrence. The efficacy should be evaluated by a larger multi-center randomized clinical trial.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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