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Original Article

Intracavernosal Injection of Autologous Adipose-Derived Mesenchymal Stem Cells as an Efficient Alternative Treatment for Patients with Erectile Dysfunction

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HIGHLIGHTS

- The treatment of ED using autologous adipose-derived MSCs with the injection of papaverine is an effective and safe method.
- To evaluate the treatment efficacy of autologous adipose-derived mesenchymal stem cells (MSCs) in patients with erectile dysfunction (ED).

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ABSTRACT

Introduction

This study aimed to evaluate the treatment efficacy of autologous adipose-derived mesenchymal stem cells (MSCs) in patients with erectile dysfunction (ED).

Methods

This study included 14 ED patients (aged 29-75 years) referred to our ED clinic from 2020 to 2022. The patients had a healthy mental status, no history of malignancies, and no prior use of psychiatric medications. Papaverine was used to achieve an erection to improve the efficacy of stem cell injection. The clinical assessment of the patients was conducted using the International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) before and 3 months after the injection of stem cells. The follow-up visit was performed 3 months after the injection of stem cells.

Results

The mean age of the study participants was 46.42 ± 10.62 years. Ten patients had a history of treatment with platelet-rich plasma (PRP) for ED. The EHS and IIEF scores of the patients were significantly higher 3 months after the injection compared to the pre-treatment period (P-value=0.000 and P-value=0.001, respectively). Only three patients had minor ecchymosis on their penises.

Conclusions

The treatment of ED using autologous adipose-derived MSCs with the injection of papaverine is an effective and safe method. The main goal of this treatment method is to repair the damaged tissues or the vascular system of the corpus cavernosum to improve the erectile function of the patients.

Keywords: Erectile Dysfunction; Mesenchymal Stem Cells; Papaverine; Platelet-Rich Plasma

Introduction

The inability to sustain a sufficient erection of the penis for successful penetration is called erectile dysfunction (ED) (1). The underlying cause of ED may be organic and/or psychogenic. Organic ED may be developed

by various causes, including neurogenic, hormonal, or vasculogenic causes (2, 3). It has been reported that organic etiologies of ED are responsible for more than 80% of ED causes, among which the most common etiology is vasculogenic disorders. Vasculogenic



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disorders can lead to arterial blood flow and venous outflow abnormalities of the corpus cavernosum (4). The incidence of ED was estimated to be 25.9 cases per 1,000 man-years, based on the results of a longitudinal study. Moreover, there is a higher risk of developing ED in men with diabetes mellitus, lower education, coronary artery disease, hypertension, and pelvic injuries (5-8). An erection happens when nitric oxide (NO) is released. NO is released from the terminals of parasympathetic nerves. As a result, it leads to the relaxation of smooth muscles of the corpus cavernosum, resulting in an increased blood flow and, thus, erection (9, 10). A defect in NO synthesis is associated with endothelial dysfunction, which can lead to ED. Currently, there are multiple management options for ED, including phosphodiesterase type 5 inhibitors, vasoactive intracavernosal injections (ICIs), prostaglandin urethral suppositories, vacuum erection devices and penile implants (2, 11-13). In addition, the ICIs of platelet-rich plasma (PRP) have been used as a potential treatment option for ED with increasing demand (14). Regarding the treatment of ED patients, stem cell therapy has attracted the attention of researchers. Mesenchymal stem cells (MSCs) are a type of stem cells that can differentiate into multiple tissues, including bone, fat, cartilage, and muscle (15). Mesenchyme is a mesoderm-derived embryonic connective tissue that can be obtained from tissues that it generates. The main benefit of MSCs is not their capability of differentiation into other organs or target tissues. In fact, the efficacy of MSCs is mostly based on the paracrine effect, whereby releasing of growth factors and cytokines which promote healing and decrease inflammation (16-18). In the present study, we used autologous adipose-derived MSCs to treat ED in non-end-stage patients who have been under other treatment options, such as phosphodiesterase type 5 inhibitors, with some complications, including adverse effects of the drug or drug interactions. Autologous adipose-derived MSCs can be an alternative treatment modality.

Methods

Study design

This clinical trial was performed in an institutional center (Tehran University). The Ethics Committee of Tehran University of Medical Sciences approved this study (code: IR.TUMS.MEDICINE.REC.1399.438). The ethical committee of Tehran University of Medical Sciences approved this study and sampling was started after receiving the Iranian Registry of Clinical Trials (IRCT20190624043991N11) on 27/11/2020. This study is adhered to CONSORT guidelines and include a completed CONSORT checklist.

Eligibility criteria

A total of 14 ED patients referred to ED clinic at Sina

Hospital from 2020 to 2022 were enrolled in this study. Inclusion criteria were ED patients aged 18-65 years with a healthy mental status, no history of malignancies, and no prior use of psychiatric medications. The enrolled patients had reversible ED and were unsatisfied with their current treatment or experienced side effects.

Isolation of autologous adipose-derived MSCs

To obtain autologous adipose-derived MSCs, the fat grafts obtained from the patients' abdomens by a surgeon with traditional liposuction were harvested. In this regard, a solution containing 1200,000 of epinephrine with 0.5% lidocaine in Ringer lactate solution was infiltrated into the abdomen using a small incision. Then, an aspiration cannula was used to harvest adipose particles by connecting to the liposuction machine with a negative pressure of less than 20 cmH₂O. The adipose particles were transferred to the laboratory and centrifuged at 500 rpm for 10 minutes to separate the adipose tissue from soluble liquid and oil. The middle layer of the adipose particles was taken for further evaluation. Specimens were then washed with phosphate-buffered saline (PBS), mixed with type 1 collagenase, and incubated for 1 hour. For the assessment of cellular functions, the glycerol-3-phosphate dehydrogenase assay was used. In addition, the hematoxylin and eosin staining was used for histologic evaluation of the specimens to confirm the adipose-derived MSCs. The final products were injected into the patients 2 to 3 weeks after the initial preparation of the adipose-derived MSCs.

Study protocol

A solution containing 5 million autologous adipose-derived MSCs in 10 mL of normal saline was injected via ICI. To improve the treatment effects and prevent migration of the autologous adipose-derived MSCs to other organs by the blood flow, an erection was induced in the penis. To achieve a rigid erection, ICI of papaverine (20mg) was used. Papaverine is best known as a potent direct-acting smooth muscle relaxant and a vasodilator. The erection was maintained at least 30 minutes after the end of stem cell injection; in the case of early relaxation of the penis, the erection duration was extended using ICI of papaverine (5mg). The maximum duration of the erection was considered 45 minutes from the initial injection. The erection was then ended using epinephrine 110000 in normal saline if no relaxation occurred after 90 minutes from the first dose of papaverine. All patients were monitored for 3 hours after the initial injection and then were discharged.

Clinical assessment

The International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) were used for the therapeutic assessment of the patients. IIEF is widely

Table 1. Baseline characteristics of the participants

	Age	Medical history	History of PRP
Patient No. 1	36	Multiple sclerosis	Yes
Patient No. 2	39	None	Yes
Patient No. 3	49	None	Yes
Patient No. 4	46	Diabetes mellitus	Yes
Patient No. 5	29	None	Yes
Patient No. 6	48	Diabetes mellitus	Yes
Patient No. 7	50	Diabetes mellitus and hypertension	Yes
Patient No. 8	48	Diabetes mellitus, hypertension, and dyslipidemia	Yes
Patient No. 9	47	Diabetes mellitus and hypertension	No
Patient No. 10	35	Diabetes mellitus, hypertension, and dyslipidemia	Yes
Patient No. 11	75	Diabetes mellitus	Yes
Patient No. 12	50	Diabetes mellitus	No
Patient No. 13	48	Diabetes mellitus	No
Patient No. 14	50	Diabetes mellitus and hypertension	No

Abbreviation: PRP, platelet-rich plasma

used to evaluate male sexual function (19, 20). This index consists of 5 domains, including erectile function, orgasmic function, intercourse satisfaction, sexual desire, and overall satisfaction. The maximum score of IIEF is 75. Further, EHS has 4 domains regarding the hardness of the penis during penetration. The maximum score of EHS is 4. IIEF and EHS were measured before and 3 months after the injection of stem cells. The follow-up visit was performed 3 months after the injection of stem cells.

Statistical analysis

A paired-sample t test was used to compare the EHS and IIEF scores before and after the injection of stem cells. All statistical analyses were performed using SPSS version 26 (IBM SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered statistically significant.

Results

The mean age of the participants was 46.42±10.62 years (29 to 75 years). Ten patients had a history of treatment with PRP for ED. Among those, 6 patients had temporary improvements in their erections, and 4 were unsatisfied regarding the results of the PRP treatment. Three patients had drug interactions, 4 were unsatisfied with their routine treatment for ED, 2 experienced side effects, and 5 had no improvement in their erections after consumption of their medications. The baseline characteristics of the participants are presented in Table 1.

The IIEF scores of the patients were significantly higher 3 months after the injection of autologous adipose-derived MSCs compared to the pre-treatment period (P-value=0.000). In addition, the EHS scores

of the participants were significantly higher 3 months after the injection compared to the pre-treatment period (P-value=0.001; Tables 2 and 3). Only 3 patients had minor ecchymosis on their penises.

Discussion

Stem cell therapy has attracted the attention of researchers in various fields, though its exact mechanism is still unclear. To date, stem cells have been used for many medical goals, including urological disorders and ED (21). MSCs are a type of stem cells that are capable of differentiation into several tissues and self-renewal. Moreover, MSCs can be isolated from the adult organs which they form, including adipose tissue. The major hypothesis of this study is that MSCs are able to enhance the vascular system and the abnormal function of penile smooth muscle cells via a paracrine release of various cytokines and growth factors. An important concern regarding the treatment with stem cells is the migration of injected cells through the blood flow to other proximal or distal organs, such as the lungs. According to several studies, fatal pulmonary embolism may occur due to the intravenous injection of stem cells (22, 23). The corpus cavernosum structure, which is spongy, has many vessels (24). Therefore, ICI is similar to intravenous injection. Although this concern has not been answered clearly in the literature, some strategies have been performed regarding this concern. Lin et al., (25) used magnetic-forced cell retention using magnetized stem cells to achieve a therapeutic benefit in the penis. However, the major limitations of this strategy are the damage caused by the implantation and removal of magnetic rods, as well as the cytotoxicity of nanoparticles. Another method mentioned in some studies (26, 27) is the use of large-size microcarriers to trap stem cells within the

Table 2. The IIEF and EHS scores of the patients before and after the injection of stem cells

	Before injection Mean (\pm SD)	3 months after injection Mean (\pm SD)	P-value
IIEF	41.85 (\pm 8.56)	63.78 (\pm 4.87)	0.000
EHS	2.64 (\pm 0.49)	3.35 (\pm 0.63)	0.001

* IIEF, International Index of Erectile Function ; EHS, Erection Hardness Score

corpus cavernosum. In the study by Koga and Horiguchi (28), the exfoliated deciduous dental pulp stem cells were injected into the corpus cavernosum using a small hairband attached to the base of the penis for 6 hours to ensure the treatment efficacy. In the study by Bahk et al., (29), the penile root was clamped for 30 minutes to increase the residence time of injected cells. It retained more cells within the corpus cavernosum; however, many cells still can escape from the corpus cavernosum, mainly due to the short time of penile clamping. Haahr et al., (30) conducted a clinical trial on 17 men with ED after radical prostatectomy and injected autologous adipose-derived regenerative cells via an intracavernosal injection. The therapeutic effect of stem cells was absent in patients with urinary incontinence, mainly due to disruption of the neurovascular bundle. In the present study, we used autologous adipose-derived MSCs to treat ED patients. We injected 5 million autologous adipose-derived MSCs using an intracavernosal injection. With the aim of increasing the efficacy of our treatment, we are the first to use papaverine to induce a temporary blood flow stasis following a penile erection. This allows stem cells to function in the target organ, which is cavernosal tissue. In addition, we conducted our random patient selection from the patients with ED, which was not secondary to end-stage urologic diseases, such as post-operative ED following radical prostatectomy in prostate cancer. The underlying reason for our patient selection is the important fact that the therapeutic effects of stem cells can improve the function of damaged—but not destroyed—tissues and organs. Most of our patients had DM, dyslipidemia, or hypertension leading to vascular damage. Our results showed a promising efficacy regarding the ICI of autologous adipose-derived MSCs in ED patients who have difficulties with their current treatment options, including side effects, drug interactions, and high cost of medications. While our study reports positive results regarding safety and functional recovery, future studies should explore the impact of additional injections, mid and long-term results.

Conclusions

This is the first report of the treatment of ED with autologous adipose-derived MSCs using papaverine as a method to inhibit the migration of injected stem cells

Table 3. Comparison of the EHS scores of the patients before and after the injection of stem cells

Time	EHS score	Before injection	3 months after injection
1		$n = 0$	$n = 0$
2		$n = 5$	$n = 1$
3		$n = 9$	$n = 7$
4		$n = 0$	$n = 6$

* EHS, Erection Hardness Score

from the target organ. The main goal of this treatment was to repair the damaged tissues or the vascular system of the corpus cavernosum to improve the erectile function of the patients.

Authors' contributions

SAM and RAB wrote the manuscript. PDF analysed the data. LOR edited the manuscript. ES and RR and VAY found the sources.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

The Ethics Committee of Tehran University of Medical Sciences approved this study (code: IR.TUMS.MEDICINE.REC.1399.438).

Data availability

Data will be provided on request.

Abbreviations

ED	Erectile dysfunction
EHS	Erection Hardness Score
IIEF	Index of Erectile Function
MSCs	Mesenchymal stem cells
PRP	Platelet-rich plasma

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