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REVIEW ARTICLE

Stem-cell therapy for erectile dysfunction: a review of clinical outcomes

Mingyue He[1] · Ernst R. von Schwarz[1,2,3,4]

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Abstract

The prevalence of erectile dysfunction (ED) has increased in recent decades. Although many treatments offer some benefits for patients with ED, unmet therapeutic needs remain, and promising new approaches are under investigation. One of these approaches is the use of stem-cell (SC) therapy for ED. We comprehensively reviewed the published literature and ongoing phase 1 and phase 2 trials and identified 27 trials by using SC therapy to treat ED. Of the 27 trials, three have been withdrawn, nine have published results, six are complete but without published results, and nine trials are ongoing or have an "unknown" status. Our analysis revealed that SC therapy represents a promising option to treat ED, although published data exist for less than 100 patients. Large placebo-controlled trials with longer follow-up are needed to confirm the long-term safety and efficacy of SC therapy for ED.

Introduction

Erectile dysfunction (ED) is a common major sexual disorder among men and can significantly impact quality of life for both patients and their partners with a high incidence and an increasing prevalence worldwide [1, 2]. It is suggested that over 600,000 new cases of ED are expected annually in the USA [3].

The increasing prevalence of ED may result from a concurrent increase in the number of patients with one or more ED risk factors. It has also been shown that the risk for developing ED increases with hypertension, diabetes, heart disease, age, and lower education [3]. Smoking, obesity, depression, psychological causes, and spinal injuries are also risk factors for developing ED [4–6]. An increasing number of patients also suffer from post-operative ED following radical prostatectomy despite nerve-sparing surgery [7]. There are many localized conditions related to ED, such as Peyronie's disease (PD), which is an acquired pathological curvature of the penile shaft due to progressive fibroblastic proliferation of collagenous plaques in the tunica albuginea [8, 9].

The American Urological Association guidelines suggest patients with ED should see a mental health professional as adjunctive therapy [10], which has been shown to improve adherence to treatment plans and enhance the effects of other treatment approaches, resulting in improved erectile function [11]. Other therapeutic options include non-invasive approaches such as lifestyle changes or oral medications, in addition to more invasive treatments such as vacuum constriction devices, intraurethral and intracorporeal injection, and surgically implanted penile prostheses.

Most international clinical guidelines suggest the use of oral phosphodiesterase type 5 inhibitors (PDE5-Is) as first-line therapy for ED because of their excellent efficacy and safety profiles. However, 30–35% of ED patients are not responsive to PDE5-Is [12]. Moreover, PDE5-Is only provide temporary symptom relief and rarely address the underlying etiology of a patient's ED. Thus, unmet needs in the treatment for ED have prompted the development of novel minimally invasive therapeutic modalities, including stem-cell (SC) therapy.

SC are unique, undifferentiated cells with three essential features: unlimited proliferation, multi-differentiation potency, and perpetual self-renewal. SC also possess unique

✉ Ernst R. von Schwarz
ernst.schwarz@cshs.org

1 Southern California Hospital Heart Institute, Culver City, CA 90232, USA

2 Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

3 University of California, Los Angeles, Los Angeles, CA 90095, USA

4 University of California, Riverside, Riverside, CA 92521, USA

proangiogenic, antifibrotic, and antiapoptotic characteristics [13] and are subdivided into four main classifications: adult SC (ASC), embryonic SC (ESC), induced pluripotent SC, and amniotic fluid SC [14]. Of these, ASCs are the chief focus of existing research for multiple diseases because of fewer ethical concerns, decreased oncogenic potential, and reduced genetic instability versus other SC groups. ASCs are abundant throughout the body, are able to repair damage and restore function in different tissues [15]. They are named and distinguished by their origin, such as mesenchymal stem cells (MSCs), first described by Friedenstein et al. [16] and hematopoietic stem cells. MSCs have a broad differentiation potential comparable to that of ESCs. Their regenerative capacity has been extensively studied in many conditions, including ED. Initially derived from bone marrow stroma, MSCs have been isolated from a variety of other tissues, such as adipose tissue (ADSC), umbilical cord blood, placenta, umbilical Wharton's jelly, muscle tissue, fallopian tissue, cartilage, skin, menstrual blood, and urine [17, 18]. MSCs are abundant in nearly all well-vascularized tissues and are related to pericytes, the perivascular cells that wrap around blood capillaries [19]. MSCs were originally thought to restore tissue function through engraftment on to injured host tissue or differentiation into different cell types. However, the recent literature supports the idea that SC exert their regenerative effect by secreting bioactive factors (known as their secretome), which function in a paracrine manner.

Stem-cell therapy for ED: preclinical studies

Bochinski et al. [20] first reported in 2004 the injection of ESC into rat ED models with cavernous nerve injury (CNI). Subsequent studies investigated the effects of SC treatment of ED caused by aging, diabetes, hyperlipidemia, CNI, and other etiologies. The most studied SC cell types in preclinical animal models have been neural crest SC, MSC, ESC, and endothelial progenitor cells.

In 2017, Hou et al. performed a meta-analysis of 20 studies that used a total of 248 rats [21]. The results showed that ADSC therapy can regenerate damaged cavernous tissues. Subgroup analysis also suggested that ADSC modified growth factors such as nerve growth factor, vascular endothelial growth factor, hepatocyte growth factor, and neurotrophic factors such as brain-derived neurotrophic factor, which significantly improved erectile function compared with ADSC alone. Administration of a large number of cells ($>1 \times 10^6$), insulin therapy combined with ADSC, or hypoxic preconditioning of ADSC resulted in a significant improvement in ED models of diabetic rats.

Several approaches have been used to improve the efficacy of SC treatment of ED. For example, physical administration of hydrogels and biodegradable membranes coated with growth factors also has improved SC therapy in preclinical models [22, 23].

Because of these promising preclinical data, clinical translation of SC therapy for ED has emerged in recent years.

Methods

A literature search on clinical use of SC for ED was conducted

Using PubMed and the United States National Institute of Health database (www.ClinicalTrials.gov) and the European Union Clinical Trials Registry (www.clinicaltrialsregister.eu), the following search terms were used: "erectile dysfunction," "Peyronie's disease," and "stem cell." We placed an emphasis on SC use in patients with ED, regardless of the cause of ED. For the specific purpose, only phase 1 and 2 clinical trials were analyzed. Exclusion criteria were: (1) non-English literature; (2) duplicated data; (3) preclinical studies, review articles, editorials, comments, and letters.

Results

In PubMed using the terms ("erectile dysfunction") AND ("stem cell"), 339 articles were identified. Of these, nine articles reporting eight trials were found. One hundred and twenty-nine articles represented preclinical studies, 127 articles were review articles, comments, editorials and letters, and 74 articles were irrelevant for the analysis.

When using the terms ("Peyronie's disease") AND ("stem cell"), 49 articles were identified. Of these, two represented clinical trials. Eleven articles described preclinical studies, 31 articles represented review articles, comments, editorials and letters, and 5 articles were irrelevant for the analysis.

Nine clinical trials using SC therapy for ED were identified in PubMed (Table 1).

Safety is the primary endpoint for most studies (eight out of nine), and common sources of SC were adipose tissue, umbilical cord, placenta, or bone marrow. The number of transplanted SC ranged from 1.5×10^7 (15 million) cells to 2×10^9 (2 billion) cells per patient and was reported to be safe without major adverse effects during and/or after treatment.

The secondary endpoint was the efficacy of SC therapy, measured after a single (eight trials) or two consecutive intracavernous injections (one study). All studies described a significant improvement of ED (despite different ED etiologies such as diabetes, PD, or postradical prostatectomy).

Table 1 A summary of completed phase I and II clinical trials with published results of SCs therapy for ED.

Publication	Disease	Study type	Cells used	Outcomes
Bahk et al. [26]	Diabetic ED	Single blind	Allogeneic hUCB-SC 1.5×10^7 cells	No adverse events. Improved subjective outcomes
Levy et al. [24]	Peyronie's disease	Open label Nonrandomized Single center	PM-MSCs Not quantified	No adverse effect. Statistically significant increases in PSV. 7/10 plaques disappeared completely at 3 m
Lander et al. [25]	Peyronie's disease	Pilot study	SVF combined with penile shock-wave treatment Not quantified	Subjective improvement in curvature and plaque size. 7/11 patients reported improvement in erectile function.
Levy et al. [27]	Chronic organic ED	Open label, nonrandomized, single center	PM-MSC Not quantified	3/8 patients reported injection site irritation. Significant increases in PSV.
Yiou et al. [29]	ED post-RP	INSTIN clinical trial first stagenonrandomized, dose-escalation, phase I/II pilot	Autologous BM-MNCs 2×10^9 cells. 1×10^9 cells. 2×10^8 cells. 2×10^7 cells.	No serious side effects. Mild pain and hemoglobin decrease after aspiration. Significant improvement of IIEF-15 and EHS. Greater improvement with the higher doses
Yiou et al. [28]	ED post-RP	INSTIN clinical trial Second stage Phase I/II pilot	Autologous BM-MNCs 1×10^9 cells.	No adverse effect. Significant improvements in EF-15 and erectile function after 6 m.
Demour et al. [31]	Diabetic ED	Open label Phase I Single arm Single center	2 consecutive autologous BM-MSC, one at baseline, the second at day-30. 30×10^6 cells	No significant adverse effects. Significant improvement of IIEF-15 and EHS
Haahr et al. [30]	ED post-RP	Open label, nonrandomized Single arm single center phase 1	SVF and ADRC. 2.2×10^7/50 µL	No serious adverse events. 8/15 (53%) patients in the continent group reported improved erectile function. No improvements in the incontinent group.
Protogerou et al. [32]	Organic ED	Phase 1, Open label Single center, pilot study	Group A: $38.9 \pm 14.4 \times 10^6$ ADMSC in combination with 2.2 ± 0.3 mL of PL ($1708 \pm 76 \times 10^6$ PLTs) Group B: 2.3 ± 0.4 mL of PL ($1693 \pm 52 \times 10^6$ PLTs)	No severe adverse reactions Improved erectile function No statistically significant difference between group A and B

Erectile function stats: assessed using peak systolic velocity (PSV), end-diastolic velocity (EDV) with Doppler ultrasonography.

C/T Patient number: control/therapy, *hUCB-SC* human Umbilical Cord Blood Stem Cells, *ADRC* adipose-derived regenerative cell, *BM-MNC* bone marrow mononucleated cells, *RP* radical prostatectomy, *SEP* sexual encounter profile question, *GAQ* global assessment questions, *PMD-MSC* placental matrix-derived mesenchymal stem cells, *BM-MSC* bone marrow-mesenchymal stem cells, *ADMSC* adipose-derived mesenchymal stem cells, *PL* plate lysate, *SPL* stretched penile length, *PG* penile girth, *PW* penile width, *EHS* Erection Hardness Score, *IIEF-5* International Index of Erectile Function questionnaire.

Two prospective studies exploring SC therapy for PD were identified. In a 2015 study [24], five patients received placental matrix-derived MSC. No adverse effects were observed. Significant increases in peak systolic velocity (PSV) ranging from 23 cm/s to 42.6 cm/s at 6 weeks, 38.9 cm/s to 49 cm/s at 3 months, and 50.5 cm/s to 67.1 cm/s at 6 months ($P < 0.01$) were reported. In addition, penile curvature improved, and seven out of ten plaques disappeared at 3 months follow-up.

Lander et al. assessed stromal vascular fraction (SVF) efficacy in patients with PD [25]. SVF is comprised of a mixture of immune modulatory cells, adipose-derived SCs, and endothelial precursor cells, which act synergistically to promote angiogenesis and epithelial cell differentiation. This study examined the effects of combined SVF and shock-wave therapy on Peyronie's plaque disruption. All 11 PD patients were injected with autologous SVF and received one to six shock-wave treatments. All patients reported subjective improvement in curvature and reduction in plaque size with minimal adverse events. Mean PD questionnaire scores decreased from 15.0 to 8.7, while mean Erectile Hardness Score (EHS) improved from 2.7 to 3.5 over 6 months.

In 2010, Bahk et al. reported the results of a single intracavernous infusion of allogenic human umbilical cord blood stem cells (HUCB-SC) in seven diabetic patients with

ED [26]. HUCB-SC (1.5×10^7) were injected into the corpora cavernosa of each patient. Following SC injection, blood flow into the penis, libido, and blood glucose improved without immune suppression. There were no safety concerns during follow-up.

Another phase 1 trial tested the efficacy and safety of placental matrix-derived mesenchymal SC in eight organic ED patients [27]. Three patients reported irritation at the injection site, which disappeared after 2 days, but no other adverse effects were reported. Significant increases in PSV ranging from 25.5 cm/s to 56.5 cm/s at 6 weeks, 32.5 cm/s to 66.7 cm/s at 3 months, and 50.7 cm/s to 73.9 cm/s at 6 months ($P < 0.01$) were reported.

Yiou et al. [28, 29] conducted a phase 1 and 2 clinical trial (INSTIN: Intro-Cavernous Stem-Cell Injection Clinical Trial) to treat postradical prostatectomy-ED with BM-MNC. This was the first phase 2 human trial to use SC therapy for ED. In the first phase, four escalating doses of autologous BM-MNCs (2×10^7, 2×10^8, 1×10^9, and 2×10^9) were tested in 12 patients with ED refractory to medical therapy. At 6 months, no serious side effects occurred. Intercourse satisfaction (6.8 ± 3.6, 3.9 ± 2.5, $P < 0.05$) and erectile function (17.2 ± 8.9, 7.3 ± 4.5, $P < 0.05$) domains of the IIEF-15 as well as erection hardness scale (2.6 ± 1.1, 1.3 ± 0.8, $P < 0.05$) improved significantly. The clinical benefits correlated with the improvement of PSV, which was sustained at a 1-year follow-up. In phase 2, six additional patients were included and received 1×10^9 BM-MNC. No serious side effects were reported, and erectile function improved. After a mean follow-up of 62.1 ± 11.7 months, erectile function scores appeared lower compared with the 1-year follow-up. The authors discussed that repeated injections might be necessary to prevent a gradual decline in erectile function over time.

In 2018, Haahr et al. [30] revealed the results of a phase 1 clinical trial that included 21 patients with ED following radical prostatectomy. All patients received a single intracavernous injection of autologous adipose-derived regenerative cells freshly isolated after liposuction and were followed for 1 year. Eight reversible minor events were reported because of liposuction and one scrotal and penile hematoma. Eight of 15 patients in the continent group had recovery of erectile function and regained the ability to perform sexual intercourse, IIEF-5 scores were significantly improved at 6 months and 12 months. Incontinent patients reported no significant improvements in erectile function.

Demour et al. conducted an open label, phase 1 clinical trial [31]. Two consecutive intracavernous autologous BM-MSC injections were given at baseline and at 30 days later to treat four diabetic patients with refractory ED. No major adverse effects were reported. The authors found significant improvements of IIEF-15 scores, sexual desire, intercourse satisfaction, EHS, erectile function, and overall satisfaction ($P < 0.05$ for all comparisons).

In 2019, Protogerou et al. [32] conducted a phase 1 study testing the safety and efficacy of ADMSCs and platelet lysate (PL) for ED. Five men with organic ED received autologous ADMSC suspended in PL, three organic ED patients received PL alone. No severe adverse reactions were reported (except minor pain at the injection site). Both patient groups showed improved IIEF-5 scores at 1 ($P < 0.05$) and 3 months ($P < 0.05$). All patients reported increased morning erections and improved penile triplex. No difference was observed between the two groups.

Search in registered trials

Twenty-two trials using the search terms "stem cell" and "erectile dysfunction" were found in the United States National Institute of Health database (www.ClinicalTrials.gov). One trial was excluded (irrelevant for the investigated topic) and three studies were withdrawn. Of the remaining 18 trials, 3 were published (Table 1). Six completed trials lacked publications, five are actively recruiting, one trial is not yet recruiting, and three trials are "unknown."

Two trials using the search words "stem cell" and "Peyronie's Disease" were found in the United States National Institute of Health database (www.ClinicalTrials.gov). One was published (Table 1), the other is "unknown."

One single "ongoing" trial was identified using the search words "stem cell" and "erectile dysfunction" or "Peyronie's Disease" in the European Union Clinical Trials Registry (www.clinicaltrialsregister.eu).

A total of 15 registered trials without the full results were found (Table 2).

Discussion

When performing a Google search using the terms "erectile dysfunction" and "stem cells," within 0.48 s, 1,520,000 results appear. Of interest, the majority of these results represent advertising from venders trying to sell unapproved and undifferentiated SC therapies (for the treatment of sexual dysfunction). The social medial content is in large contrast to the actual amount of published data in the scientific literature. Despite a huge public interest in sexual dysfunction and SC therapy, only nine clinical trials using SC therapy for ED in men were published. Collectively, the results show significant improvements in penile hemodynamics and improved erectile function scores. No major adverse effects were

Table 2 A table of registered completed or ongoing trials without full published results.

Status	Study director/contact	Interventions	Locations
Completed in 2018 full results awaited	Chungsu Kim	Mesenchymal stem cell phase 1	Korea
Completed in 2018 full results awaited	Abdallah Awidi Sophia Al-Adwan	Wharton Jelly Mesenchymal stem cells, phase 1	Jordan
Completed in 2019 full results awaited	Abdallah Awidi Sophia Al-Adwan	Wharton Jelly Mesenchymal stem cells phase 1 and phase 2	Jordan
Completed in 2018 full results awaited	Jacob Rajfer	CaverStem	Los Angeles
Completed in 2017 full results awaited	Mark H Berman	Administration of autologous adipose-derived SVF	Rancho Mirage, CA
Completed in 2016 full results awaited	Andrey A Pulin, Mikhail E Chalyy	Intracavernosal administration of autologous ADRC phase 1 and phase 2	Moscow
Not yet recruiting	Rabih EL OSTA	Autologous bone marrow derived Mesenchymal Stem Cells phase 1	France
Recruiting estimated completion: 2022	Chungsu Kim	Follow-up	Korean
Recruiting estimated completion: 2020	Jianwu Dai	NeuroRegen scaffold/BMMCs transplantation NeuroRegen scaffold/HUC-MSCs transplantation phase 1 and phase 2	Nanjing, China
Recruiting estimated completion: 2020	Jianwu Dai	HUC-MSCs Injectable Collagen Scaffold + HUC-MSCs phase 1	Nanjing, China
Recruiting estimated completion: 2029	Dr Ayn O'Reilly David L Greene	Amniotic and umbilical cord tissue procedure phase 1	Multiple locations in the USA
Recruiting estimated completion: 2022	Jibing Chen	Very small embryonic-like stem cell (VSEL) phase 1 and phase 2	China, Guangdong
Unknown	Saleh Binsaleh	liposuction for retrieval of own stem cells from fat cells phase 2	Saudi Arabia
Unknown	Khaled A Gadalla	Adipose tissue stem cell injection	Egypt
Ongoing	Odense Universitets Hospital	Stromal vascular fraction phase 1	Denmark

described, and SC therapy has shown efficacy in ED of different etiologies.

Most studies (eight trials out of nine) have a 6- or 12-month follow-up. Two studies reported sustained effect at 1 year. Follow-up at longer period (62.1 months) suggested a decline in erectile function over time.

SCs were derived from multiple sources, prepared using various protocols, and administered at various doses. Three published studies did not give the number of cells that were administered.

The specific mechanisms underlying SC efficacy in ED treatment has not been evaluated in clinical studies. Preclinical studies have shown that the differentiation of SCs is not always present during the repair process and the therapeutic effects of SCs can persist regardless of the cell numbers or even after the disappearance of SCs. Cell-free treatments (such as secretomes) have also shown regenerative benefits [13] and are thought to be important for improving erectile functional. The MSC secretomes' proangiogenic, anti-inflammatory, antiapoptotic, and antifibrotic properties have shown preclinical potential in different animal models of ED and may be a future treatment option for ED [33, 34]. The MSC secretomes hold several advantages over traditional cell-based therapies for regenerative urology such as safety and cost effectiveness [13, 35–38]. To date, no clinical studies have been published using secretomes to treat ED in men.

Other future treatment options for ED may include injection of platelet-rich plasma, botulinum toxin injection,

and low intensity extracorporeal shock-wave therapy [39]. These therapies have shown promising initial results with few side effects. However, these methods are still considered experimental and further investigation is needed. Among all the novel ED treatment options, SC therapy appears to be the most promising. SC may also reverse in part neuronal and structural causes of ED, as shown in preclinical studies [21].

Each study has its own individualized protocol and there are no standardized protocols for SC therapy in the management of ED in general. Therefore, optimization of cellular preparation and development of a standardized method for the general application of SC therapy for ED with regards to the cell type, number, application, and outcome measures is recommended. However, ethical concerns, cost, source, ease of isolation and culture, risks, and effectiveness must be taken into account when selecting the most suitable type of SC protocol [40].

Along with different regulatory and commercial factors to consider, potential SC therapy for ED treatment is becoming increasingly complex. The guidelines put forth by professional societies as well as the FDA for clinical translation of SC therapy should be followed when designing and conducting trials [41, 42].

Conclusions

Preclinical research in animal models has generated excitement for the use of SC as a potentially curative treatment for ED. The primary mechanism proposed is paracrine effects, while possible engraftment and cellular differentiation are potential auxiliary mechanisms. Less than 100 patients have been reported to receive SC injections so far, future large-scale clinical trials with controls are necessary to assess the safety and efficacy of SC therapy for patients with ED. The use of SC in humans continues to be an ethically challenging issue and SC studies must be carefully evaluated. Long-term efficacy and safety of SC therapy for ED treatment need to be evaluated, as the field continues to gain a better understanding of the role regenerative medicine may play in ED management.

Compliance with ethical standards

Conflict of interest The authors have no financial affiliation or involvement with any organization with a financial interest/conflict associated with the studies discussed in this paper. This includes expert testimony, employment, honoraria, consultancies, stock options or ownership, grants or patents pending/received, or royalties.

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