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Original Research

Intracavernous injection of stem cell-derived bioactive molecules for erectile dysfunction—a pilot phase non-randomized controlled trial

Ernst R von Schwarz[1,2,3,*], Nathalie Busse[1,4], Karen Mulholland Angelus[1,4], Ahmed Omair[2], Aubriana A von Schwarz[1,2], Paul C Bogaardt[1,4]

[1]Heartstem, Inc., Beverly Hills, CA 90212, USA
[2]Southern California Hospital Heart Institute, Culver City, CA 90232, USA
[3]Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
[4]Nustem, Inc., Beverly Hills, CA 90212, USA

***Correspondence:** Dr.ernstschwarz@gmail.com (Ernst R von Schwarz)

Abstract

Background and objective: Experimental and few clinical studies have indicated great potential of stem cell treatments as both a causal and symptomatic approach for the treatment of male erectile dysfunction (ED). We investigated the effect of a one-time injection of stem-cell derived bioactive molecules in patients with self-reported ED.

Materials and methods: Twenty self-referred male patients with at least one-year history of ED received a one-time intra-penile injection of acellular stem cell-derived bioactive molecules. ED was evaluated by the International Index of Erectile Function questionnaire (IIEF-5), and quality of life was assessed by the Short-Form-36 questionnaire, (SF-36) at baseline and at 6 months. Six male patients with ED, who received a similar injection using saline served as a historic control. Primary outcome was erectile function as measured by IIEF-5 scores. Secondary outcomes were quality of life, assessed by SF-36 questionnaire.

Results: IIEF-5 scores improved from 12.9 $\pm$ 4.47 at baseline to 18 $\pm$ 3.37 at follow-up ($p < 0.05$). No significant difference of IIEF-5 scores were observed in the historic controls during the observation period (11 $\pm$ 2.53 at baseline vs 10.67 $\pm$ 3.5 at follow-up; $p > 0.05$). Patients, who received stem cell injections, demonstrated significantly enhanced IIEF-5 scores compared to the historic control ($p < 0.05$). Quality of life scores were significantly improved (role limitations due to physical health issues 56.25 $\pm$ 42.82 at baseline vs 68.75 $\pm$ 40.45 at follow-up, $p < 0.05$, energy 51.57 $\pm$ 19.33 at baseline vs 57.75 $\pm$ 12.3 at follow-up, $p < 0.05$, emotional wellbeing 56.32 $\pm$ 16.28 at baseline vs 68.1 $\pm$ 11.73 at follow-up, $p < 0.05$, and social functioning 67.5 $\pm$ 23.79 at baseline vs 76.25 $\pm$ 18.98 at follow-up, $p < 0.05$).

Conclusions: A one-time intracavernous acellular stem cell-derived bioactive molecule injection improves IIEF-5 scores and quality of life in men with ED in this small pilot phase study (ClinicalTrials.gov Identifier: NCT04684602).

Keywords

Erectile dysfunction; Stem cell therapy; Umbilical cord blood; Exosome; Secretome

JOMH
Journal of Men's Health

1. Introduction

Erectile dysfunction (ED) is defined as the inability to attain and maintain an erection with sufficient rigidity to permit satisfactory sexual intercourse [1]. While oral pharmacotherapies such as phosphodiesterase-5 inhibitors (PDE5i) exhibit clear benefits, their effects are transient as opposed to an etiological therapy approach and treatment is relatively costly [2].

Impaired erectile function represents a complex, yet common medical condition, which profoundly impacts the quality of life of those affected [3]. According to cross-sectional studies, 50% of men above the age of 50 years suffer from some degree of ED. There appears to be a substantial association between vascular disorders and ED with significant implications exceeding the treatment of the primary condition by an adequate cardiovascular risk assessment [4]. In the longitudinal, population-based "Massachusetts Male Aging Study", heart disease, diabetes mellitus, and hypertension were identified as major risk factors for ED in males aged 40–69 years [5]. Moreover, the prevalence of ED is predominant in men suffering from chronic diseases including renal insufficiency, liver dysfunction and heart failure [6–11]. Other causes include a reduction of sexual hormones due to acquired hypogonadism, chronic diseases as well as urologic and traumatic issues. Of interest, among younger men an overexposure to pornographic videos on social media and widely accessible websites has been related to psychologically based sexual dysfunction [6–9].

Stem cells have the ability to either multiply through division of daughter cells or transform into specialized cell types, thus holding the potential for enhanced tissue repair and maintenance of numerical capacity [12]. The classification underlies the cells' multi-lineage differentiation properties and distinguishes totipotency, pluripotency, multipotency, and unipotency, in descending order based on differentiation capacities [13]. In that context, embryonic stem cells are pluripotent and can serve as progenitors for all tissue types. Adult stem cells, however, are further advanced in differentiation and develop into specialized structures in a more tissue-restricted manner [14]. Cells can be extracted from human tissues including bone marrow, adipose tissue, neonatal teeth, umbilical cord blood, placenta, and Wharton's Jelly, with the two latter preparations being reflected upon in the consecutive analysis [15–17]. More recently, exosomes - extracellular vesicles containing components of the mesenchymal stem cell (MSC) secretome (i.e., DNA, RNAs, miRNA, lipids, and functional proteins) [18]—have emerged as a potential addition to the clinical deployment of stem cell therapeutics [19]. Beneficial results have been reported in the frame of preclinical studies exploring effects on central nervous [20], cardiovascular [21, 22], hepatorenal [23, 24], and metabolic [25, 26] conditions.

Stem cell therapy has been proposed in the management of ED with respect to complete replacement of lost or damaged cells or protection of threatened host cells via immunomodulatory effects, provision of trophic factors or gene delivery [27]. A number of case reports and small clinical studies using stem cell preparations in men with ED have been published—with promising results. A recent report by our group suggested beneficial effects of stem cell injections as a curative approach for ED, however, limited present data due to small sample sizes accounts for reduced external validity [28].

We report the first study evaluating a larger group of 20 patients with ED undergoing an intracavernous injection of acellular stem cell-derived bioactive molecules.

2. Materials and methods

The present study was approved by the institutional review board of the International Cell Surgical Society (Palm Desert, CA, USA).

Twenty self-referred men with ED were recruited for stem cell injections as part of an ongoing larger study investigating the effects of acellular stem cell preparations on vascular disease presentations. Furthermore, six male ED patients with a similar medical history, who received similar intracavernosal injections using saline, served as a historic control. All patients signed an informed consent form, agreed to follow up, and were informed about the experimental nature of the treatment. Data regarding the participants' medical history, past surgical history, and relevant current medication was extracted from medical records.

Inclusion criteria were as follows:

(1) Self-reported ED for at least one year;

(2) Age 18-80 years;

(3) Availability for follow up visits.

Exclusion criteria were:

(1) History of any known malignancy within the last two years;

(2) Inability to provide consent;

(3) Current use of anticoagulants (except low dose aspirin);

(4) Uncontrolled diabetes mellitus;

(5) Uncontrolled hypertension;

(6) Any life-threatening condition with a life expectancy of less than one year.

During the procedure, study participants were comfortably placed in supine position. The penis was prepared with topical 2% lidocaine cream for local anesthesia. Subsequently, the aspirate containing the allograft suspension was injected intra-cavernosal into the penis at three injection sites bilaterally along the penile shaft (total of 6 injections of 0.33 cc per patient, 2 cc total) using a new 22 G sterile needle. The patients were watched for 20 minutes before being discharged. All patients received a follow-up phone call the following day and were advised to contact the clinic in case of occurrence of local and/or systemic changes, symptoms potentially related to the procedure or any events. Recipient records were maintained for the purpose of post-injection tissue tracing according to the Joint Commission standard QC.5.310.7 and FDA 21 CFR 1271.290 regulation requirements.

At the initial office visit and at follow-up at six months, study participants underwent an assessment of their general health. ED was assessed within the context of a personal interview and the International Index of Erectile Function

Questionnaire (IIEF-5; [29]) was provided. The following parameters were obtained at baseline and at six months follow-up:

-Blood pressure (mmHg) at rest,

-Heart rate (beats per minute, bpm) at rest,

-IIEF-5 questionnaire,

-Six Minute Walk Test (6MWT, measured in meters (m) [30]), and

-Short-Form-36 Quality of Life Questionnaire (SF-36; [31]).

The 36-Item Short Form Health Survey (SF-36) is a self-reported quality of life measure that was developed as a component of the Medical Outcomes Study to explain variation in patient outcomes. Thirty-six questions that span 8 domains of health are used to measure clinical parameters with regards to the health status of specific patient groups in order to extrapolate to the efficacy of clinical interventions [31]. Erectability and intercourse success were assessed and evaluated based upon personal interviews on patient satisfaction in the frame of a clinical follow-up.

The stem cell-derived product is a highly concentrated acellular solution derived from umbilical cord tissue containing no blood cells or blood products. This tissue allograft was processed in an FDA approved "Human Cell and Tissue Establishment" (HCTERS) for the recovery, screening, donor testing, packaging, processing, storage, labeling, and distribution of human umbilical cord and related tissue allografts. Each intervention consisted of a 2 milliliter (cc) aliquot of PrimePro^{TM} (Thomas Advanced Medical, Los Angeles, CA, USA) sourced from donated human umbilical cord tissue, which was obtained by an FDA approved "Tissue Procurement" facility. The cord tissue allograft was deemed qualified for transplantation by an authorized recovery agency after confirmation of results from donor pre-screening lab tests, specifying the latter to be free from risk factors and active infections of applicable communicable disease agents and diseases as required by the FDA, including (but not limited to) HIV I/II Ab: Human Immunodeficiency Virus Types 1⁄2 and O Antibody, HIV/HCV/HBV nucleic acid testing (NAT): Human Immunodeficiency/Hepatitis C/B, HBc Ab: Hepatitis B Core Antibody, HBx Ag: Hepatitis B viral Protein, rapid plasma reagin (RPR)/serologic test for syphilis (STS) or Equivalent: Syphilis, HCV Ab: Hepatitis C Virus, and HTLV I/II: Human T-Cell Lymphotropic Virus. The aforementioned investigational drug contains little to no human leucocyte antigens (HL-A), hereby accounting for a significantly reduced risk of HL-A antibody production and thus increased immunologic safety [32].

In accordance with FDA Article 21 CFR Part 1271, the product was stored in a cryopreserved vial and maintained at –80 °C or colder using an ultra-low temperature freezer or liquid nitrogen until preparation for treatment. Each vial was intended for use in one patient, on a single occasion only and administered by the principal investigator.

Suspension material was transported frozen in liquid nitrogen just prior to the application. The frozen vials containing the acellular suspensions were opened in a sterile working area. The material was allowed to thaw at room temperature for 15–20 minutes. The therapeutic suspension was then aspirated through a 22 G needle under sterile conditions into a sterile 2 cc syringe and then injected.

Similarly, six patients received a single-time intracavernosal injection using 2 cc of saline. The procedure was performed as described above. IIEF-5 scores as well as blood pressure and resting heartrate were obtained at baseline and follow-up. In addition, sexual intercourse success and erectability were investigated in the frame of interviews during both visits.

Statistical analysis was performed in SPSS Version 26 (IBM, Armonk, NY, USA). Data are presented as mean $\pm$ standard deviation (SD). A paired student's t-test was used to test for significant variations before and after the investigated treatment. Furthermore, the two groups (stem cell injections vs historic control) were compared using an independent samples Welch t test. Differences with p values < 0.05 were considered statistically significant.

3. Results

Twenty male patients ages 31 to 77 (53.05 $\pm$ 12.71 years) years were included in the analysis, six additional patients served as a historic control (57.67 $\pm$ 14.19 years; $p = 0.5$ vs intervention group). All participants self-reported ED with a significant impact on their quality of life since at least one year prior to the clinic visit. ED was considered vasculogenic in origin for all patients. All patients reported to have a sexual partner. None of the patients were diagnosed with Peyronie's disease or a history of prostate cancer, prostatectomy or hormone therapy. In the intervention group, one patient had diabetes and was controlled with medication and diet. Three patients had a history of controlled hypertension and were on oral antihypertensives. One patient had a history of coronary artery disease in the past and was in a stable condition. Moreover, the medical history of patients in the historic control group complied with both inclusion and exclusion criteria for the active trial arm. All controls had a history of controlled hypertension, three presented with hyperlipidemia, two had prediabetes, and one patient had a history of a minor stroke. No other significant internal diseases or surgical histories were reported in either subcohort. All twenty patients in the intervention group reported a prior history of PDE5i use, however, no further treatment methods were undertaken by any of the participants. Equally, all six individuals in the control reported a history of unsuccessful PDE5i use, which was discontinued before the intervention. At the time of study enrollment all patients were advised not to use any therapeutic agents or mechanic treatment methods (i.a. PDE5i, hormone therapy, local injections, intraurethral suppositories, vacuum erection devices) until the end of the observation period. At follow-up, none of the patients reported any change in their home medication regimen and confirmed that they did not use PDE5i, hormone substitution such as testosterone injections, and there was no other significant change regarding the use of supplement or changes in dietary habits. Demographics are presented in Table 1.

JOMH
Journal of Men's Health

TABLE 1. Patient data.

Characteristics (n = 26)		Baseline	6-month- Follow-up	
Age (years)			$p = 0.5$	
	Intervention group (n = 20)		53.05 ± 12.71	
	Historic control (n = 6)		57.67 ± 14.19	
IIEF-5		$p = 0.21$	$p \leq 0.05$	
	Intervention group	12.9 ± 4.47	18 ± 3.37	$p \leq 0.05$
	Historic control	11.00 ± 2.53	10.67 ± 3.5	$p = 0.064$
6MWT (m)		324.41 ± 188.33	353.11 ± 192.59	$p \leq 0.05$
RR Sys (mmHg)		$p = 0.38$	$p = 0.21$	
	Intervention group	133.5 ± 16.01	130.25 ± 13.03	$p = 0.12$
	Historic control	140.5 ± 16.06	138.67 ± 13.17	$p = 0.55$
RR Dia (mmHg)		$p = 0.8$	$p = 0.5$	
	Intervention group	79.9 ± 8.72	77.85 ± 7.1	$p \leq 0.05$
	Historic control	81.33 ± 12.09	81.5 ± 11.74	$p = 0.94$
HR (bpm)		$p = 0.25$	$p \leq 0.05$	
	Intervention group	70.15 ± 12.13	66.95 ± 7.28	$p \leq 0.05$
	Historic control	74 ± 4.52	74.67 ± 5.32	$p = 0.6$
SF-36 Scores				
	Physical function	87.75 ± 25.21	89 ± 22.80	$p = 0.17$
	RL physical health	56.25 ± 42.82	68.75 ± 40.45	$p \leq 0.05$
	RL emotional problems	51.67 ± 39.71	61.67 ± 43.63	$p = 0.32$
	Energy/Fatigue	51.57 ± 19.33	57.75 ± 12.3	$p \leq 0.05$
	Emotional wellbeing	56.32 ± 16.28	68.1 ± 11.73	$p \leq 0.05$
	Social functioning	67.5 ± 23.79	76.25 ± 18.98	$p \leq 0.05$
	Bodily pain	82 ± 22.98	82.63 ± 19.01	$p = 0.89$
	General health	58.75 ± 19.86	60.5 ± 18.77	$p = 0.46$
	Health change	51.25 ± 24.97	58.75 ± 20.32	$p = 0.14$

Data are mean ± SD (SD, Standard Deviation); RL, Role Limitations; IIEF-5, International Index of Erectile Function 5 Questionnaire; 6MWT, Six Minute Walk Test (m, meters); SF-36, Short Form Health Survey; HR, Heart rate (bpm, beats per minute); RR, Blood Pressure (sys, systolic; dia, diastolic) (mmHg, millimeters of mercury).
6MWT and SF-36 results are only available for group 1. *p* values are presented for differences between treatment group and historic control as well as before and after the respective intervention in each group.

3.1 Erectile Function

At follow-up, every patient in the treatment group self-reported improved erectability including prolonged erectile capabilities and improved intercourse success. At baseline, IIEF-5 scores ranged from 5 (severe ED) to 21 (mild ED) and averages at 12.9 ± 4.47 (mild to moderate ED) at baseline. At follow up, IIEF-5 scores were 18 ± 3.37 ($p < 0.05$ vs baseline) with a range of 13 (= mild to moderate ED) to 22 (= no ED; Fig. 1). Among the historic controls, no significant changes regarding erectability and intercourse success were reported at the end of the follow-up period. IIEF-5 at baseline ranged from 7 to 13 (mean score = 11 ± 2.53; $p = 0.21$ vs intervention group). At follow-up, mean scores were 10.67 ± 3.5 and ranged from 5 to 15 ($p = 0.64$ vs baseline; $p = 0.002$ vs intervention group, Fig. 2). No data were obtained with regard to the frequency of sexual activity before recruitment and during follow-up in both groups.

3.2 Physical examination and functional capacity

At baseline, the six minute walking distance was 324.41 ± 188.33 m (range 76 m–700 m). At follow-up, the walking distance was 353.11 ± 192.59 m (range 100 m–780 m, $p < 0.05$ vs baseline; Fig. 3).

A physical examination was performed by a physician prior to the procedure and at follow-up. All participants were hemodynamically stable on both dates. No major changes regarding the over-all health of subjects were reported.

Among patients in the intervention group, heart rate at baseline was 70.15 ± 12.13 bpm and 66.95 ± 7.28 bpm ($p < 0.05$) at follow-up, respectively. Historic controls measured heart rates of 74 ± 4.52 bpm ($p = 0.25$ vs intervention group) at baseline and 74.67 ± 5.32 bpm ($p = 0.6$ vs baseline) at follow-up. At the end of the observation period, patients, who received stem cell injections, exhibited significantly lower heart rates than individuals in the historic control ($p < 0.05$). In the intervention group, blood pressure at baseline was 133.5 ± 16.01 over 79.9 ± 8.72 mmHg. Blood pressure at follow-up was 130.25 ± 13.03 ($p = 0.12$ vs baseline) over 77.85 ± 7.1 mmHg ($p < 0.05$ vs baseline). In the historic control, blood pressure at baseline was 140.5 ± 16.06 ($p = 0.38$ vs intervention group) over 81.33 ± 12.09 mmHg ($p = 0.8$ vs intervention group). At follow-up, no significant changes were observed (138.67 ± 13.17 over 81.5 ± 11.74 mmHg, $p > 0.05$ vs baseline). Moreover, differences between the follow-up blood pressure values of patients in the active trial group and the historic control, respectively, were non-significant ($p > 0.05$).

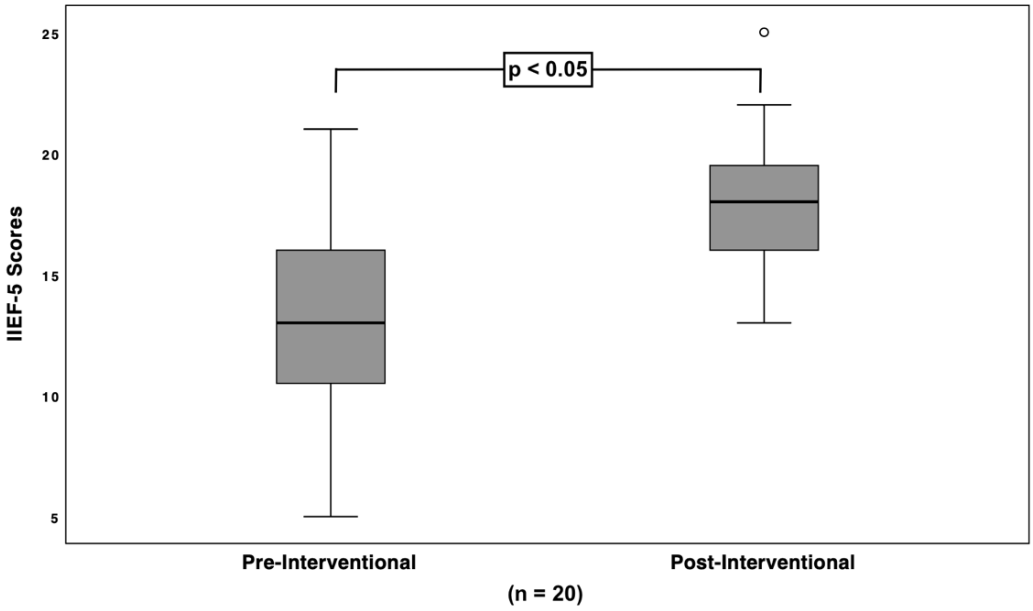

FIG. 1. IIEF-5 Results at Baseline vs Follow-up after acellular stem cell-derived bioactive molecule injections.

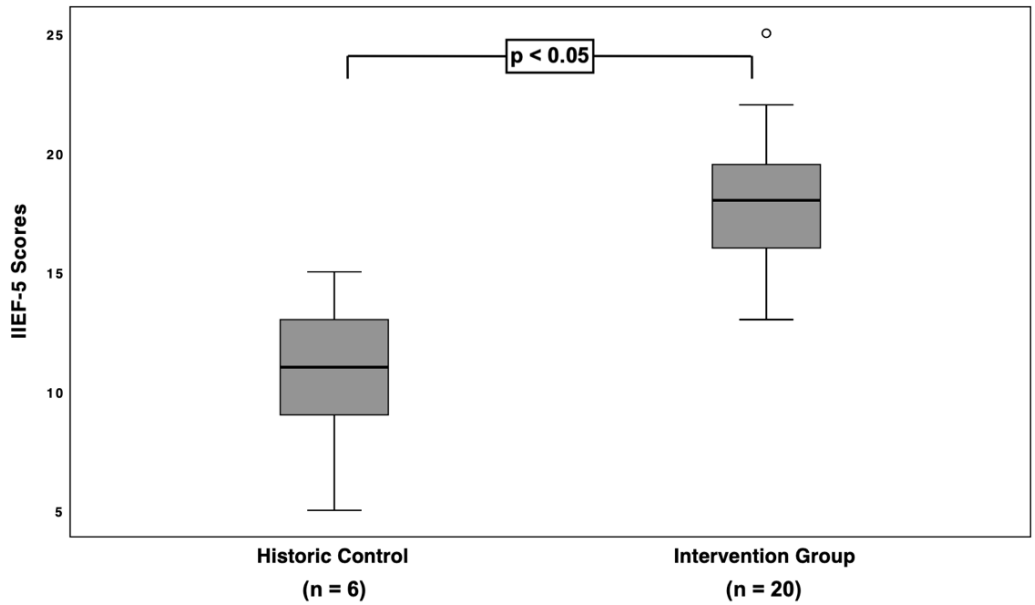

FIG. 2. Comparison of IIEF-5 results between control and intervention group.

3.3 Quality of life

SF-36 questionnaire scores for role limitations due to physical health issues increased from 53.62 ± 41.74 at baseline to 64.33 ± 40.39 at follow-up ($p < 0.05$), energy scores increased from 49.16 ± 18.85 to 55.05 ± 12 ($p < 0.05$), emotional wellbeing scores were 53.69 ± 15.88 at baseline and 64.90 ± 11.45 at follow-up ($p < 0.05$), and social functioning scores were 64.33 ± 23.19 at baseline and 72.67 ± 18.51 at follow-up ($p < 0.05$). Scores regarding physical function, role limitations due to emotional problems, general health, and bodily pain increased slightly but not significantly. Similarly, health changes were 48.86 ± 24.34 at baseline and 56 ± 19.81 at follow-up but did not reach statistical significance ($p > 0.05$).

3.4 Tolerability and adverse events

Injections were well tolerated by all patients. Seven patients reported mild-to-moderate pain during stem cell injections, which subsided in all shortly after completion. Similarly, two patients of the historic control group proclaimed injection-associated pain, which also receded within minutes after the procedure. No adverse events such as bleeding from the injection sites, hematoma, swelling, discomfort or prolonged pain were reported. No other adverse events were observed or reported during the follow-up period.

JOMH
Journal of Men's Health

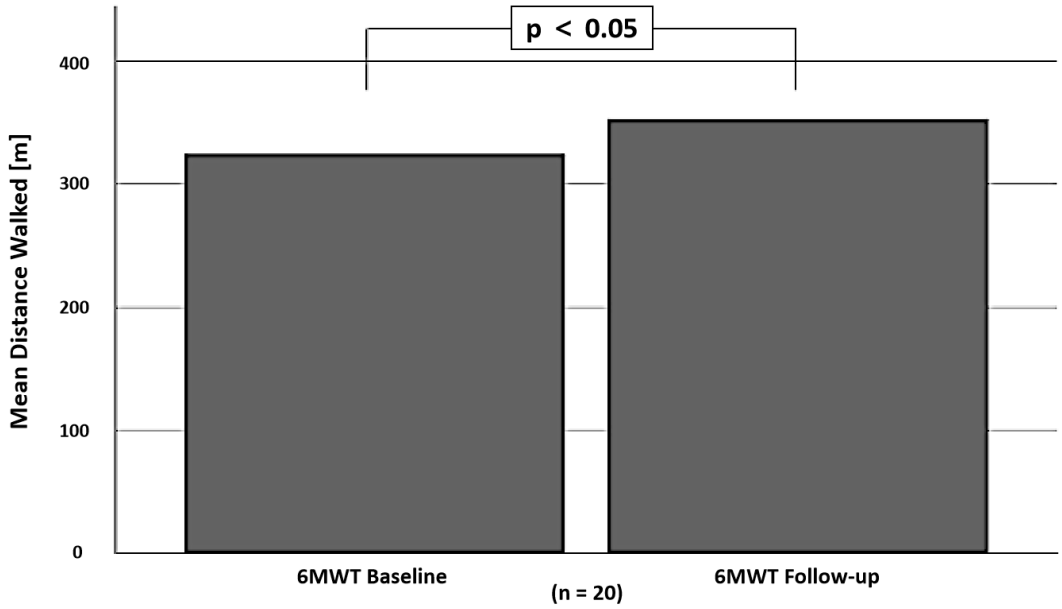

FIG. 3. Six Minute Walk Test Results at Baseline vs Follow-up after acellular stem cell-derived bioactive molecule injections (intervention group).

4. Discussion

We report the results of the largest ever reported study investigating the effects of intracavernous injections of acellular stem cell-derived bioactive molecules for ED. Stem cell injections resulted in a significant improvement of erectile function as assessed by a standardized IIEF-5 questionnaire. Furthermore, the one-time penile injection was associated with an increased walking distance in a 6-minute walk test implying possible systemic effects despite a strictly local injection. The Quality of Life questionnaire (SF-36) demonstrated improvements in role limitations due to physical health, energy, emotional wellbeing, and social functioning.

Our data are in concordance with preclinical studies that showed stem cells targeting ED-related vasculogenic insufficiencies such as impaired local vasodilation [33], hypoperfusion of sinusoidal spaces [34], and corporeal venous leakage due to veno-occlusive failure [35] through the induction of endothelial cell proliferation secondary to proangiogenic characteristics [33, 36, 37]. In that context, stem cell therapy generated an increase in the concentration of VEGF [38–44]. Consequently, endothelial cell proliferation was facilitated, thereupon enhancing endothelium content in cavernous tissue as a functional indicator of regenerative processes in the local vasculature [43, 45, 46]. In general, stem cell therapy was associated with the secretion of a multitude of growth factors, suggesting subsequent facilitation of tissue repair [42, 47]. Concomitant with structural modifications, a reversal of intracavernous endothelial malfunction as a result of improved endothelium-derived NO/cGMP signaling [48] has been demonstrated, based on increased cavernous tissue cyclic guanosine monophosphate (cGMP) levels [39] and enhanced concentration of endothelial nitric oxide synthase (eNOS) [38, 42] promoting vasodilation in sinusoidal vascular spaces [49].

Furthermore, *in vitro* analyses of acellular stem cell preparations revealed the presence of proangiogenic and antifibrotic microRNAs (miRNAs) [38, 41]. These findings indicate that the therapy could ameliorate anatomic impairments of ED [50–53], thus promoting endogenous regeneration processes. Of interest, the expression of miRNAs was found to be higher in acellular preparations compared to regular stem cell solutions [41].

In addition to expediting tissue regeneration, stem cell contents promote the modulation of the recipients' immune response. In that context, the production of inflammatory factors (e.g., Interleukin-6, Interleukin-1b, and Tumor-Necrosis Factor α) was shown to be reduced [39]. Further, stem cells effectuated higher activity of superoxide dismutase and reduced malondialdehyde concentration in animal models. Consequently, oxidative stress in form of superoxide radicals, which prevail in aging or diseased organisms, were diminished [42, 47].

Moreover, the effect of transplanted stem cells exceeded mere engraftment in damaged tissues but included paracrine activity [54]. In that regard, stem cells were able to both alter their secretome according to the demands of the impaired anatomic structure and modify the paracrine function of host cells in a tissue-specific manner [44].

Administration of mesenchymal stem cells in animal models resulted in a partial improvement of erectile function [45] as demonstrated by a significant increase of the maximal intracavernosal pressure to mean arterial pressure ratio (ICP/MAP ratio) [36–41, 45–47, 55] with an accumulative tendency upon protracted follow-up periods [49] and higher bioactive factor concentration [41]. While the exact modes of action underlying the treatment responses are still largely elusive, an accretive body of scientific evidence suggests tissue regeneration, anti-inflammatory properties and immunomodulation as pivotal mechanisms [56].

Small scale clinical trials demonstrated beneficial effects of bone-marrow derived [57] and umbilical cord derived [58] MSC injections on ED due to diabetes mellitus. Erectile function significantly improved as measured by IIEF-15 questionnaire and Erection Hardness Survey [57]. Furthermore, patients reported more frequent occurrence of morning erections and improved rigidity, and a decrease of blood glucose was observed, which resulted in a temporary diminution of diabetes medication dosages [58].

In a case series on eight patients with organic ED due to diabetes mellitus, hypertension, hypercholesterolaemia or Peyronie's disease, Protogerou *et al.* [59] demonstrated the therapeutic effects of adipose tissue-derived compared to platelet lysate-derived MSCs. The intracavernous injection augmented erectile function as measured by IIEF5 scores, improved penile perfusion and resulted in improved morning erections. No adverse events or side effects were documented. The comparison of platelet-derived and adipose-derived stem cells showed no significant advantage of preparation.

Furthermore, our findings are in concordance with the investigations of Levy *et al.* on the effects of placental matrix derived stem cells in ED with in-depth investigation of Peyronie disease. Injections were placed intracavernosally, if applicable in and around plaques. Peak systolic velocity increased ($p < 0.01$ vs baseline) and a reduction of penile curvature and a decrease of plaque volume were observed. In addition, mild but not significant changes in stretched penile length, penile girth, and end-diastolic velocity were noted [60, 61].

Moreover, the effect of MSC-derived products on ED following prostatectomy has been investigated [62–64]. A significant increment of erectility as displayed by IIEF-15 domains intercourse satisfaction and erectile function was noted, with alleviating tendencies after one year upon completion of therapy [62, 63]. Equally, an increase of Erection Hardness Scale scores and augmentation of penile peak systolic velocity as well as nitric oxide release were observed [63]. Of interest, continent men profited to a greater extent from the intervention (n = 8 recovered patients, IIEF at 6 months follow-up = 17; $p = 0.0069$, vs baseline) compared to individuals presenting with incontinence (n = 0 recovered patients, IIEF at 1/3/6 month follow-up = 5; $p = 0.9999$, vs baseline) [64].

We propose that the improvement of erectile function in our study may be caused in part by the proangiogenic properties of stem cell-derived products [33, 36, 37]. Enhanced penile vascularization and augmented perfusion account for recovered erectability. Furthermore, we did not expect to find changes with regard to physical capacity or quality of life (which is part of our routine evaluation before and after any vascular treatment), however, walking distance and certain domains of quality of life according to the SF-36 questionnaire improved significantly. While direct measurements of vascular properties and reactions exceed the frame of the present study, there can be multiple reasons for the observed data:

(1) Stem cell-derived molecules might exert systemic effects despite the local penile application. Stem cells might provide systemic regenerative effects to restore endothelial function, consequently ameliorating cardiovascular impairments [65, 66]. However, this study was not designed to investigate the aforementioned mechanisms.

(2) Increased sexual satisfaction does have a significant impact on emotional wellbeing and overall quality of life [67, 68].

We report a small pilot phase study but it has the largest patient sample reported to date using stem cell-derived products for the treatment of ED. There are several limitations to our study as outlined here:

(1) Our findings are based on subjective reporting as well as established questionnaires for sexual function and quality of life.

(2) We did not perform any blood flow measurements or tissue analyses which was beyond the frame of the current pilot phase study.

(3) We did not perform a prospective placebo-controlled study. However, we used historic controls, who received saline injections and had the IIEF-5 questionnaire at baseline and 6 months follow-up (but no SF-36 questionnaire).

(4) There is a lack a long-term follow-up beyond 6 months.

In conjunction with these promising results, there is a rationale for adding diagnostic techniques (i.a. ultrasound, laboratory testing, and nocturnal penile tumescence) for further objectification and consolidation of these findings as well as the conduction of a randomized controlled study in a larger patient cohort.

5. Conclusions

The presented study is the first to demonstrate beneficial effects of intracavernosal injections containing stem cell-derived bioactive molecules on ED in the largest patient sample reported to date. Stem cell treatment of impaired erectile function is a promising therapeutic approach. Large scale clinical controlled trials are warranted to demonstrate further evidence for a generalized acceptance of stem cell treatment for ED outside of clinical studies.

Author contributions

ERS, NB and PB Designed the research study. ES, KMA, NB and AO performed the research. KMA, AO and AAS collected the data. PB provided help and advice on medical analytics. ES, NB and AAS analyzed the data. ES, NB and AAS drafted the article. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board (IRB) of the International Cell Surgical Society (approval number: ICSS-2020-032).

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Conflict of interest

The authors declare no conflict of interest. None of the study personnel were payed for their participation in the research project, funds were solely used to cover the cost of the investigational drug.

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