Determining the Feasibility of Managing Erectile Dysfunction in Humans With Placental-Derived Stem Cells

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Abstract

Introduction: Stem cell therapy is thought to improve wound healing and promote vasculogenesis and has also been investigated as a treatment for patients with erectile dysfunction (ED), which is usually caused by a microvascular disease such as diabetes mellitus or hypertension.

Objective: To determine the feasibility and effects of using placental matrix–derived mesenchymal stem cells (PM-MSCs) in the treatment of patients with ED.

Methods: Participants were recruited from a private practice urology in Coral Springs, Florida. Each patient received an injection of PM-MSCs and was followed up with at 6 weeks, 3 months, and 6 months to assess peak systolic velocity (PSV), end diastolic velocity, stretched penile length, penile width, and erectile function status based on the International Index of Erectile Function questionnaire.

Results: Eight patients were injected with PM-MSCs. At the 6-week follow-up, PSV ranged from 25.5 cm/s to 56.5 cm/s; at 3 months, PSV ranged from 32.5 cm/s to 66.7 cm/s. Using unpaired *t* tests, the increase in PSV was statistically significant ($P<.05$). At 6 months, PSV ranged from 50.7 cm/s to 73.9 cm/s ($P<.01$). Changes in measured end diastolic velocity, stretched penile length, penile width, and International Index of Erectile Function scores were not statistically significant. At the 6-week follow-up, 2 patients for whom previous oral therapies failed had the ability to sustain erections on their own. At the 3-month follow-up, 1 additional patient was able to achieve erections on his own.

Conclusion: To our knowledge, this is one of the first human studies to report on the feasibility of using stem cell therapy to treat patients with ED. The results indicate that this treatment may be beneficial, and further investigations with larger sample sizes should be conducted. (ClinicalTrials.gov number NCT02398370)

Erectile dysfunction (ED) is the inability to obtain or maintain an erection satisfactory for sexual intercourse.[1] By 2025, experts predict that 322 million men will have ED worldwide, which is an increase from the estimated 152 million men with ED in 1995.[2] Aging has been associated with resistance in penile blood flow, possibly due to decreases in nitric oxide synthase–containing nerve fibers.[3] Erectile dysfunction is frequently associated with vascular risk factors such as diabetes mellitus, coronary artery disease, and hypertension. In particular, 50% to 75% of men with diabetes mellitus have ED regardless of their age.[4]

Multipotent mesenchymal stem cells can form in the embryonic lineage to which they belong.[5] These cells can originate from fetal tissue, umbilical cord blood, or adult tissues and have been found in placenta, amniotic fluid, adipose tissue, liver, muscle, and umbilical cord blood.[6,7] Mesenchymal stem cells may also exert beneficial effects through a paracrine-dependent fashion to assist in local growth and regeneration of the tissue in which they reside.[6,7]

Animal models have demonstrated that intracavernosal injections of autologous and allogenic mesenchymal stem cells improve erectile functions in rats with cavernous nerve injury by increasing the mean maximum intracavernosal pressure.[8] Intracavernosal transplant of bone marrow–derived mesenchymal stem cells in rats with diabetes had beneficial effects compared with controls by increasing the content of endothelium and smooth muscle in the corpus cavernosum.[9]

The present study seeks to determine the feasibility of using placental matrix–derived mesenchymal stem cells (PM-MSCs) in the management of ED in humans.

Methods

The PM-MSCs in this study, which are thought to increase vasculogenesis and ultimately improve penile blood flow, were derived from the chorionic placenta. We recruited patients with ED who could not tolerate oral therapy and did not want a penile prosthesis from a private practice urology clinic. At the initial visit (baseline), patients provided written informed consent and answered the International Index of Erectile Function (IIEF) questionnaire to determine the status of their erectile function. A score of 5 indicates severe erectile dysfunction, and a score of 75 indicates no erectile dysfunction. The present study was reviewed and approved by the Western Institutional Review Board to perform a prospective, open-label, nonrandomized, single-center study.

Inclusion criteria were men aged 40 to 70 years who had chronic, organic ED for at least 6 months; had a baseline IIEF score greater than or equal to 21; were involved in a monogamous, heterosexual relationship for at least 3 months in which both partners were motivated to have or attempt sexual intercourse at least 4 times per month beginning 2 weeks after the study treatment; were willing to limit alcohol intake and eliminate use of recreational drugs for sexual encounters; were willing to undergo an injection; were mentally competent and able to understand all study requirements; were willing to be available for all baseline, treatment, and follow-up examinations required by protocol; and were willing to forego participation in any other study throughout the duration of the present study. In addition, participants were not allowed to take oral phosphodiesterase-5 inhibitors for the first 6 months after receiving the study treatment, and those who were taking phosphodiesterase-5 inhibitors were required to go through a 4-week washout period to allow clearance of the drug before completion of the baseline erectile function assessments and study treatment.

Exclusion criteria were clinically evident penile anatomical deformities (eg, Peyronie disease) or a history of priapism; participation in any nonstudy intervention for ED within 4 weeks of study treatment; uncontrolled hypertension or hypotension (systolic blood pressure >170 mm Hg or <90 mm Hg and diastolic blood pressure >100 mm Hg or <50 mm Hg); untreated hypogonadism or low serum total testosterone (<200 ng/dL); body mass index greater than or equal to 30; major medical conditions; prostate cancer; previous pelvic or abdominal radiation therapy; previous, concomitant, or scheduled use of antiandrogen therapy; skin irritation, infection, wound, sore, or disruption in the immediate areas of skin entry for penile injection; previous penile implant or penile vascular surgery; current or previous malignancy other than localized prostate cancer; unstable cardiovascular disease (eg, unstable angina, myocardial infarction within the past 6 months, cardiac failure or life-threatening arrhythmia, congestive heart failure); symptomatic postural hypotension within 6 months before screening; current urinary tract or bladder infection; systemic autoimmune disorder; substantial active systemic or localized infection; immunosuppressant medications; drug, alcohol, or substance abuse within the past 3 years; sexual partner (aged 18 years or older) with a gynecologic disorder; and any other factors that would limit participation in sexual intercourse to less than 4 times per month.

After completing the IIEF questionnaire, patients were injected with 0.2 mL of a trimix compounded solution as a control and for standardization of data. The trimix (30-4-50) composition consisted of 30 mg of papaverine, 4 mg of phentolamine, and 50 µg of prostaglandin. Patients then underwent penile Doppler ultrasonography, which measured baseline peak systolic velocity (PSV) and end diastolic velocity (EDV). Measurements of stretched penile length (SPL) and penile width were taken, and rigidity testing was performed.

Approximately 2 weeks after baseline and control injection, patients returned to the clinic to receive the study treatment. A solution comprising 1 mL of PM-MSCs diluted in 2 mL of isotonic saline was prepared, and 1.5 mL was injected into the base of each corpora cavernosum. The number of PM-MSCs in 1 mL was not quantified by the company the cells were obtained from. No immunosuppressive therapy was used, and no additional PM-MSC injections were given.

Patients returned to the clinic 6 weeks, 3 months, and 6 months after the PM-MSC injection to have PSV, EDV, SPL, and penile width reevaluated. At each follow-up visit, patients' erectile function was reassessed using the IIEF questionnaire.

Statistical analysis was calculated with statistical significance set at $P<.05$. Unpaired t tests and a 2-tailed P value were calculated for each measured PSV, EDV, SPL, penile width, and IIEF scores.

Results

In total, 8 patients were enrolled in the study. All of the patients had been using injectable medications to sustain an erection. All but 1 of these patients passed the rigidity testing after the trimix injection.

Baseline PSV was measured in each of the 8 patients after trimix injection (*Table*) and initially ranged from 23.1 cm/s to 49.3 cm/s. Six weeks after PM-MSC injection, PSV ranged from 25.5 cm/s to 56.5 cm/s. At 3 months, PSV ranged from 32.5 cm/s to 66.7 cm/s. This increase proved to be statistically significant ($P<.05$). Patients 4 and 8 were lost to follow-up at this time. At 6 months, PSV ranged from 50.7 cm/s to 73.9 cm/s. This finding also proved to be statistically significant ($P<.01$). Patients 4 and 6 were lost to follow-up, and patient 7 refused further evaluation at the 6-month follow-up. Although patient 8 did not participate in the 3-month follow up, he was present for the 6-month follow-up.

Table.

Outcome Measures at 6-Week, 3-Month, and 6-Month Follow-Up for Patients Treated With Placental Matrix–Derived Mesenchymal Stem Cells for Erectile Dysfunction (N=8)

Outcome Measure	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
PSV With Trimix								
Initial, cm/s	26.5	49.3	32.1	29.8	31.6	23.1	31.8	35.0
6-wk follow-up, cm/s (% change)[a]	45.1 (+70.19)	56.5 (+14.60)	40.1 (+24.92)	31.4 (+5.37)	45 (+42.41)	25.5 (+10.39)	36.0 (+13.21)	48.8 (+39.43)
3-mo follow-up, cm/s (% change)[a]	40.3 (+52.08)	66.7 (+35.29)	41.2 (+28.35)	NA	47.3 (+49.68)	32.5 (+40.69)	53.0 (+66.67)	NA
6-mo follow-up, cm/s (% change)[a]	53.2 (+100.75)	73.9 (+49.9)	50.7 (+57.94)	NA	54.4 (+72.15)	NA	NA	53.2 (+52.0)
EDV With Trimix								
Baseline, cm/s	7.1	6.9	12.3	6.1	5.5	2.5	2.5	0
6-wk follow-up, cm/s (% change)[a]	5.4 (-23.94)	10.6 (+53.62)	9.2 (-25.2)	8.1 (+32.79)	7.0 (+27.27)	0.7 (-72.0)	6.4 (+156.0)	5.8 (NA)
3-mo follow-up, cm/s (% change)[a]	10.1 (+42.25)	17.9 (+159.42)	8.9 (-27.64)	NA	6.1 (+10.91)	4.0 (+60.0)	11.0 (+340.0)	NA
6-mo follow-up, cm/s (% change)[a]	7.7 (+8.45)	6.4 (-7.25)	9.5 (+22.76)	NA	7.3 (+32.73)	NA	NA	8.7 (+100.0)
Stretched Penile Width								
Baseline, cm	19.0	15.2	14.0	20.3	15.0	12.7	17.0	15.8
6-wk follow-up, cm (% change)[a]	19.4 (+2.11)	16.0 (+5.26)	15.0 (+7.14)	21.0 (+3.45)	15.2 (+1.33)	13.3 (+4.72)	17.3 (+1.76)	16.0 (+1.27)
3-mo follow-up, cm (% change)[a]	19.5 (+2.63)	16.5 (+8.55)	15.2 (+8.57)	NA	15.4 (+2.67)	15.0 (+18.11)	17.5 (+2.94)	NA
6-mo follow-up, cm (% change)[a]	19.5 (+2.63)	18.0 (+18.42)	16.0 (+14.29)	NA	15.5 (+3.33)	NA	NA	16.0 (+1.27)
Penile Width After Trimix								
Baseline, cm	14.0	10.5	10.5	17.5	12.7	10.5	12.7	13.0
6-wk follow-up, cm (% change)[a]	14.4 (+2.86)	12.6 (+20.0)	13.0 (+23.81)	18.0 (+2.86)	12.9 (+1.57)	12.0 (+14.29)	12.9 (+1.57)	14.0 (+7.69)
3-mo follow-up, cm (% change)[a]	15.5 (+10.71)	14.0 (+33.33)	14.0 (+33.33)	NA	13.3 (+4.72)	12.2 (+16.19)	13.0 (+2.36)	NA
6-mo follow-up, cm (% change)[a]	15.5 (+10.71)	14.5 (+38.1)	14.5 (+35.1)	NA	13.5 (+6.3)	NA	NA	13.5 (+3.85)
IIEF Score[b]								
Baseline	23.0	42.0	38.0	36.0	54.0	31.0	21.0	32.0
6-wk follow-up (% change)[a]	43.0 (+86.96)	43.0 (+2.38)	24.0 (-36.84)	26.0 (-27.78)	22.0 (-59.26)	21.0 (-32.26)	21.0 (-4.76)	61.0 (+90.63)
3-mo follow-up (% change)[a]	30.0 (+30.43)	51.0 (+21.43)	52.0 (+36.84)	NA	44.0 (-18.52)	28.0 (-9.68)	11.0 (-47.62)	NA
6-mo follow-up (% change)[a]	23.0 (0)	43.0 (+2.38)	63.0 (+65.79)	NA	48.0 (-0.11)	NA	NA	67.0 (+109.38)

[a] Percent change is calculated from follow-up to initial visit.

[b] The IIEF score is based on a scale of 5 to 75. A score of 5 indicates severe erectile dysfunction, and a score of 75 indicates no erectile dysfunction.

Abbreviations: PSV, peak systolic velocity; NA, not applicable; EDV, end diastolic velocity; IIEF, International Index of Erectile Function.

View Large

Baseline EDV was measured in each of the 8 patients after the trimix injection. At 6 weeks, 3 months, and 6 months after PM-MSC injection, the change in EDV was not found to be statistically significant. The *Table* demonstrates the 8 patients' PSV, EDV, SPL, penile width, and IIEF scores from baseline over the course of 6 weeks, 3 months, and 6 months, respectively. Increases in PSV reached statistical significance at 3 months and 6 months. At 6 weeks, 3 months, and 6 months, the changes in IIEF scores, SPL, and penile width were not statistically significant.

Before this study, all 8 patients required injectable medications to achieve erections. After PM-MSC injection, 3 patients were able to achieve erections with no pharmacologic assistance. Of 8 patients, 4 needed low-dose oral medication, and 1 patient continued to use the trimix solution to achieve erections. Three of the 8 patients stated that they had irritation at the injection site, which resolved after 48 hours. No patients went on to develop any other adverse effects, such as priapism, penile hematomas, or infection.

Discussion

Stem cell therapy for patients with ED has been investigated in more than 30 studies, and a study from South Korea[10] used umbilical cord blood stem cells injected into the corpora cavernosum. The study[10] involved 7 patients with both type 2 diabetes mellitus and ED and found that stem cell injections improved erectile function.

A variety of stem cells can be sourced from different sites, such as placenta, bone marrow, and adipose tissue. The present study shows that chorionic PM-MSC injection caused a statistically significant improvement in blood flow into the penis, which was sustained at 6 months. Although all of the patients did not obtain completely satisfactory erections without the aid of oral medications or injectables for assistance, no patients went on to need or request a penile prosthesis.

We believe it is unlikely that 1 injection of any substance would be able to restore erectile function completely, but this treatment may help maximize penile blood flow and improve erectile function.

A limitation of the present study is the small sample size (n=8) and smaller sample at the 6-month follow-up (n=5). Further investigations should study a larger population to determine whether the results of the current study are consistent and to examine long-term outcomes. In addition to a larger population, randomized double-blinded controlled trials need to be conducted to evaluate efficacy, safety, and adverse outcomes over long-term follow-up at 1 year and 5 years.

Conclusion

To our knowledge, the present study is one of the first human studies to report on the feasibility of using stem cell therapy to manage ED. We believe this treatment may be especially beneficial to men who have been unable to achieve erections after oral medications. Although the results of the present study appear promising, stem cells and other biologic products must be further evaluated to understand the precise mechanism of action of these injections. The placental matrix comprises stem cells from the chorionic layer of the amniotic sac, which also contains growth factors. Further studies should evaluate whether it was the stem cells, growth factors within the cells, or both that led to the improvement in erectile function.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Student Doctor Levy and Dr Zahalsky drafted the article or revised it critically for important intellectual content; Student Doctor Levy and Dr Zahalsky gave final approval of the version of the article to be published; and Student Doctor Levy and Dr Zahalsky agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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