Effects of Stem Cell Treatment in Human Patients With Peyronie Disease

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Context: Peyronie disease (PD) is a connective tissue disorder involving the formation of fibrous plaques in the tunica albuginea. Abnormal plaques and scar tissue create a chronic state of inflammation, causing increased curvature of the penis as well as erectile dysfunction.

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

Methods: In a prospective study, patients with PD were injected with PM-MSCs, and followed up at 6-week, 3-month, and 6-month intervals to assess changes in plaque volume, penile curvature, and erectile function status (measured using peak systolic velocity, end-diastolic velocity, and the International Index of Erectile Function questionnaire).

Results: In the 5 patients enrolled in the study, statistically significant increases in peak systolic velocity occurred after PM-MSC injection ($P<.01$). Of a total of 10 plaques managed, 7 had disappeared completely at 3-month follow-up. Changes in end-diastolic velocity, stretched penile length, and penile girth were not statistically significant.

Conclusion: To our knowledge, this study is the first on the use of stem cells to manage PD in humans. The results suggest that PM-MSCs may be beneficial and effective as a nonsurgical treatment in patients with PD. Future studies with long-term follow-up in a larger sample of patients are warranted. (ClinicalTrials.gov number NCT02395029)

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Peyronie disease (PD) is characterized by the presence of a fibrous plaque in the tunica albuginea that causes pain, deformity, curvature, and erectile dysfunction.[1] Its prevalence varies, but it has been estimated to be as high as 7.1% in the general population.[1] Patients with PD and erectile dysfunction have been found to have abnormal arterial blood flow in the penis and venoocclusive dysfunction,[2] and one study group speculated that the fibrous plaque is the cause of this dysfunction.[3]

Multipotent mesenchymal stem cells—a possible management for PD—can originate from fetal tissue, umbilical cord blood, or adult tissues and can form cell types within the embryonic lineage to which they belong.[4] Mesenchymal stem cells may also exert beneficial effects in a paracrine-dependent fashion, promoting local growth, repair, and regeneration of the tissue in which they reside.[5,6] These cells have been found in adipose tissue, the liver, and muscle, as well as in the placenta, amniotic fluid, and umbilical cord blood.[5,6]

Studies[7,8] involving rat models have been performed to determine the effects of stem cell treatment in PD. Injection of adipose tissue–derived stem cells into the tunica albuginea in rat models with PD prevented formation of fibrosis and elastosis in the tunica and corpus cavernosum and statistically significantly improved erectile function.[7] Another study[8] demonstrated that adipose tissue–derived stem cells prevented or reduced Peyronie plaques by decreasing the expression of tissue inhibitors of metalloproteinases.

In the current study, we assessed the use of placental matrix–derived mesenchymal stem cells (PM-MSCs) to manage PD in humans.

Methods

The present prospective study took place from August 2013 to March 2015 at a private practice urology clinic. The study was approved by the Western Institutional Review Board and registered at ClinicalTrials.gov (NCT02395029). All participants provided informed consent.

Patients who presented to the clinic with Peyronie disease and who did not want to pursue surgical options at that time were selected for study enrollment. Participants were included in the study if they were aged 18 years or older and had an acquired penile curvature associated with a palpable penile plaque at physical examination and penile plaque at ultrasonography screening.

Patients with any of the following conditions were excluded: current warfarin treatment; inability to achieve adequate erections with penile injection to allow assessment of penile curvature; history of definitive treatment for prostate, bladder, or other pelvic cancer (eg, surgery, external-beam radiation therapy, brachytherapy, cryotherapy); any history of prostate cancer, hematologic disorders, chronic liver disease (eg, cirrhosis, hepatitis C), immune system disorders (eg, human immunodeficiency virus infection), psychiatric disorders (eg, major depression, schizophrenia, bipolar disorder), cerebrovascular accident or deep venous thrombosis within the past 5 years, or severe sleep apnea; clinically significant abnormal laboratory results that (in the opinion of the investigator) would put the participant at increased risk or compromise the integrity of the study data; or any receipt of investigational drugs within the past 30 days.

Placental matrix–derived mesenchymal stem cells are a placental stem cell product that mixes mesenchymal stem cells with growth factors, cytokines, and an extracellular matrix to promote wound healing, angiogenesis, and tissue repair. Our PM-MSCs were derived from the chorionic placenta.

Patients were evaluated using penile ultrasonography to count and measure their Peyronie plaques. Before receiving any PM-MSC and trimix injections, they answered the International Index of Erectile Function (IIEF) questionnaire to determine their erectile function status.

Next, patients were injected with 0.2 mL of a trimix compounded solution as a control and for standardization of data to produce a penile erection. The trimix solution consisted of papaverine (30 mg), phentolamine (5 mg), and prostaglandin (50 μg). While the penis was erect, a protractor was used to measure the baseline angle of penile curvature. Curvature was measured on the concave side of the penile shaft, with the angle of curvature used as a fulcrum; essentially, the middle of the protractor was placed over the angle of curvature. Doppler ultrasonography was used to measure peak systolic velocity (PSV) and end-diastolic velocity (EDV). Stretched penile length and penile girth were also measured at this visit.

At a second visit 1 to 3 weeks after the initial (baseline) visit, the patients received PM-MSCs, which were injected intracavernosally. First, 1 mL of PM-MSCs was diluted with 2 mL of isotonic saline solution, to a total of 3 mL. Up to 2 mL of the diluted PM-MSC solution was then injected in and around the Peyronie plaques. The rest of the PM-MSC solution was then injected evenly into both corpora at the base at the base of the penis. No patient received additional PM-MSC injections after this visit during the course of the study.

Patient follow-up included visits for reevaluation 6 weeks, 3 months, and 6 months after the PM-MSC injections, with measurement of PSV, EDV, stretched penile girth, and angle of curvature. Plaque volume was calculated by multiplying plaque length by plaque width and height. Patients also filled out IIEF questionnaires before any injection at 6-week, 3-month, and 6-month visits.

Statistical analysis was performed, with differences considered statistically significant at $P<.05$. Two-tailed P values were calculated for all measured criteria, including PSV, EDV, stretched penile length, penile girth, and IIEF score. Plaque volumes were presented as raw data, and P values were not calculated for these measurements.

Results

In total, 5 patients aged 45 to 59 years were enrolled in the trial. Patient 3 was included in the study because of a painful Peyronie plaque and erectile dysfunction, although he had no penile curvature (0°). At physical examination, he had no visible curvature but had an easily palpable fibrotic Peyronie plaque, which was then confirmed sonographically.

The baseline PSV, after trimix injection and before PM-MSC treatment, ranged from 14.1 to 25.5 cm/s. The PSV range increased from 23 to 42.6 cm/s at 6 weeks after PM-MSC injection, 38.9 to 49 cm/s at 3 months, and 50.5 to 67.1 cm/s at 6 months. These increases were statistically significant in all patients and for all intervals ($P<.01$; unpaired t test). Patients 1 and 2 refused trimix reinjection at 3 and 6 months because they were satisfied with their results and did not want another penile injection, and patient 5 refused follow-up at 6 months. The initial (baseline) EDV ranged from 0.1 to 4.3 cm/s after injection of trimix. Although these values improved slightly after PM-MSC injection, the changes did not reach statistical significance.

At the beginning of the study, 1 patient had 3 Peyronie plaques, 3 had 2 plaques each, and 1 had a single plaque. Plaque volume decreased statistically significantly by 6 weeks, 3 months, and 6 months. At 6 weeks, plaque volume had decreased from 33.33% to 98.67%, and at 3 months, from 45.83% to 100%, with reductions greater than 90% in 4 of 5 (80%) patients. Seven of the 10 plaques initially seen with ultrasonography disappeared completely. At 6 months, plaque volumes were measured in 4 patients, all with decreases close to 100%.

Penile curvature varied from 0° to 120° before PM-MSC injection. After PM-MSC injection, it improved dramatically, with 30° to 120° of improvement in the patients with curvature. At 6 weeks, penile curvature had decreased by 14.29% to 100% in the 4 patients with curvature; patient 3 had no initial curvature and thus demonstrated no change. *Table 1* and *Table 2* show the PSV, EDV, and penile measurements in the 5 patients at 6-week and 3-month follow-up, respectively. The 2 patients who refused reinjection of trimix at 3 and 6 months both self-reported an improvement in curvature; patient 1 measured his curvature at 40° at 3 months, and patient 2 reported that his curvature had resolved.

The IIEF scores ranged from 27 to 73 before PM-MSC injection and from 36 to 73 after injection. This difference was not statistically significant. Stretched penile length and penile girth (*Table 1* and *Table 2*) also did not change statistically significantly.

Patient 1 eventually underwent 16-dot plication. In patient 2, another plaque developed during the study, as did priapism, which had to be aspirated at his 6-week visit. No complications involving penile hematomas, corporal rupture, or penile edema occurred.

Discussion

Although our sample was small (n=5), the effects of PM-MSCs in patients with PD were statistically significant. Both PSV and penile curvature significantly improved at 6 weeks, 3 months, and 6 months after

Table 1.
Baseline and 6-Week Follow-up Findings in Patients with Peyronie Disease Treated With Penile Stem Cell Injections[a]

	Patient				
Measurement	**1**	**2**	**3**	**4**	**5**
Age, y	54	46	45	59	52
PSV (After Trimix Injection)					
Baseline, cm/s	25.5	14.1	23.5	22.1	23.4
6-wk follow-up, cm/s	35.4	23	42.6	37.6	33.3
Change, %	+38.82	+63.12	+81.28	+70.14	+42.31
EDV (After Trimix Injection)					
Baseline, cm/s	0.1	3.3	4.3	0.7	3.1
6-wk follow-up, cm/s	0	0	0	4.3	0.3
Change, %	−100	−100	−100	+514.29	−90.32
Stretched Penile Length					
Baseline, cm	14	15	12.8	17.5	16.5
6-wk follow-up, cm	15	15.3	12.8	17.7	16.7
Change, %	+7.14	+0.02	0	+1.14	+1.21
Penile Girth (After Trimix Injection)					
Baseline, cm	13.5	14	9.5	12.7	12.5
6-wk follow-up, cm	14	13.3	12	13	12.7
Change, %	+3.70	−5.0	+26.32	+2.36	+1.60
Penile Curvature/Angle					
Baseline, °	70	60	0[b]	120	70
6-wk follow-up, °	40	0[c]	0[b]	70	60
Change, %	−42.86	−100	0	−41.67	−14.29
IIEF Score					
Baseline score	41	63	73	34	27
6-wk follow-up score	35	50	74	68	39
Change, %	−14.63	−20.63	+1.37	+100	+44.44

[a] For changes from baseline, positive percentages represent increases; negative percentages, decreases; 0, no change.
[b] After trimix injection.
[c] Patient 3 had no curvature.

Abbreviations: EDV, end-diastolic velocity; IIEF, International Index of Erectile Function (questionnaire); PSV, peak systolic velocity.

Table 2.
Baseline and 3-Month Follow-up Findings in Patients With Peyronie Disease Treated With Penile Stem Cell Injections[a]

	Patient				
Measurement	**1**	**2**	**3**	**4**	**5**
PSV[b]					
Baseline, cm/s	25.5	14.1	23.5	22.1	23.4
3-mo follow-up, cm/s	Refused[c]	Refused	49	43.5	38.9
Change, %	…[d]	…	+108.51	+96.83	+66.24
EDV[b]					
Baseline, cm/s	0.1	3.3	4.3	0.7	3.1
3-mo follow-up, cm/s	Refused	Refused	4	0.2	4.9
Change, %	…	…	−6.98	−71.43	+58.06
Stretched Penile Length					
Baseline, cm	14	15	12.8	17.5	16.5
3-mo follow-up, cm	15	15.2	12.8	17.9	16.8
Change, %	+7.14	+1.33	0	+2.29	+1.82
Penile Girth[b]					
Baseline, cm	13.5	14	9.5	12.7	12.5
3-mo follow-up, cm	Refused	Refused	12.5	13.3	12.9
Change, %	…	…	+31.58	+4.72	+3.2
Penile Curvature/Angle					
Baseline, °	70	60	0[e]	120	70
3-mo follow-up, °	Refused	Refused	0[e]	35	40
Change, %	…	…	0	−70.83	−42.86
IIEF Score					
Baseline score	41	63	73	34	27
3-mo follow-up score	45	57	73	32	47
Change, %	+9.76	9.52	0	−5.88	+74.07

[a] For changes from baseline, positive percentages represent increases; negative percentages, decreases; 0, no change.
[b] After trimix injection.
[c] Patients 1 and 2 refused reinjection with trimix at 3-month follow-up because they were satisfied with their results and did not want to undergo subsequent injection.
[d] Unable to calculate change.
[e] Patient 3 had no curvature.

Abbreviations: EDV, end-diastolic velocity; IIEF, International Index of Erectile Function (questionnaire); PSV, peak systolic velocity.

PM-MSC injection, but EDV did not prove to demonstrate a statistically significant improvement. As seen in 2 animal studies,[7,8] stem cells seem to be an effective form of nonsurgical treatment in patients with PD.

Our study was not without limitations, however. Because our sample was small (n=5), our findings need to be replicated in a single-center or multicenter study with a much larger population. Although most cases of PD are idiopathic, causes of Peyronie plaques should be identified if possible, including any history of trauma, surgery, or inherited conditions, in addition to the length of time the plaques have been present.

Another limitation is that our trial was nonrandomized. A double-blinded trial in which one cohort of patients received PM-MSCs and another received a control or placebo would be highly beneficial. Finally, our study included patient follow-up only at 6 weeks, 3 months, and 6 months; future studies should include long-term follow-up for 1 to 5 years, documenting any changes in PD state and any adverse effects (eg, priapism).

Conclusion

To our knowledge, this was the first feasibility study on the use of stem cells (PM-MSCs) to manage PD in humans. Although the sample was small, the results were statistically significant and seem promising. They show that PM-MSC treatment may be a future nonsurgical treatment option for patients with PD. The PM-MSC injections also statistically significantly increased PSV. Further studies of PM-MSC treatment in patients with PD should be conducted to confirm its efficacy.

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; Dr Zahalsky gave final approval of the version of the article to be published; and Dr Zahalsky agrees 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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