THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH & REVIEWS

The Effect of Transendocardial Stem Cell Injection on Erectile Function in Men With Cardiomyopathy: Results From the TRIDENT, POSEIDON, and TAC-HFT Trials

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ABSTRACT

Background: Despite limited human data, there is a growing interest in the use of stem cell therapy (SCT) for erectile dysfunction (ED).

Aim: To determine the effect of transendocardial stem cell injection on erectile function on men with cardiomyopathy and ED.

Methods: We used International Index of Erectile Function (IIEF) scores collected from men enrolled in 3 separate randomized controlled trials: Comparison of Allogeneic vs Autologous Bone Marrow—Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy (POSEIDON), Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy (TAC-HFT), and Dose Comparison Study of Allogeneic Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy (TRIDENT). These trials recruited patients with ischemic cardiomyopathy and ejection fraction less than 50%. Inclusion and exclusion criteria were identical in all 3 trials. The primary intervention in these trials included transendocardial stem cell injection of stem cells or placebo via cardiac catheterization. The follow-up period was 1 year. IIEF data were collected at baseline and at multiple time points in each trial.

Outcomes: We investigated erectile function over time based on cell dose, cell source (autologous vs allogenic), cell type (mesenchymal stem cells vs bone marrow mononuclear cells), and comparing men who received SCT with those who received placebo.

Results: A total of 36 men were identified with complete IIEF data. 8 men received placebo injection, and 28 received SCT. The median age was 66.5 years. Comorbidities were similar among all men. Analysis was performed on men with ED, defined by an IIEF-EF score of 24 or less. In the placebo and all-comer SCT group, the median IIEF-EF score was 5 [1—8] and 5 [1—15] at baseline and was 3.5 [3—5.8] and 7 [1—18] at 12 months ($P > .05$). When analyzed by cell dose, the IIEF-EF score in men who received 200 million cells increased significantly over 12 months (14 [4—23] to 20 [15—24.5], $P = .014$.) Similarly, an autologous cell source resulted in a similar increase from baseline to 12 months (14 [3.8—23.3] to 20 [12—22], $P = .030$).

Clinical Implications: Erectile function may improve after systemic delivery of SCT in men with ischemic cardiomyopathy and at least mild ED.

Strengths & Limitations: This post hoc analysis is the first to investigate the effect of SCT on erectile function using randomized, placebo-controlled data. Weaknesses include that ED was not a primary end point, and men were not originally recruited based on erectile function.

Conclusion: Future trials on systemic delivery of SCT for ED should focus on high cell dose and autologous cell source, as these seem to provide the best response in men with at least mild ED. **Ory J, Saltzman RG,**

Received November 17, 2019. Accepted January 4, 2020.

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https://doi.org/10.1016/j.jsxm.2020.01.003

Blachman-Braun R, et al. The Effect of Transendocardial Stem Cell Injection on Erectile Function in Men With Cardiomyopathy: Results From the TRIDENT, POSEIDON, and TAC-HFT Trials. J Sex Med 2020;XX:XXX-XXX.

Key Words: ED; Erectile Dysfunction; IIEF; Regenerative Medicine; Stem Cells

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to attain or maintain a penile erection sufficient for satisfactory sexual performance. ED is common, impacting almost 40% of men older than 40 years, with the incidence only increasing with age.[1] Vasculogenic ED is the most common subtype experienced by men, and its incidence is especially high in men with cardiovascular disease.[2] ED and cardiovascular disease share many of the same risk factors such as diabetes, hypercholesterolemia, and smoking, and up to 70% of men with coronary artery disease (CAD) have ED.[3,4]

Men with ED and CAD often cannot take phosphodiesterase type 5 inhibitors because of medication interactions with nitrates.[5] If men are not interested in intracavernosal injections or if they are ineffective, these men are left with few alternative options outside of a penile implant. The field of regenerative medicine via stem cell therapy (SCT) may play a role in the amelioration of ED in these men, with goals to go beyond symptom control and instead restore original tissue function.[6] This is hypothesized to take place either via improved endothelial function; improving blood flow to the penis, or from local implantation of the cells into the corporal tissue and reversal of damage via paracrine effects.[6,7] There currently is no consensus on the optimal delivery route of SCT to enact meaningful changes in erectile function. Animal research has shown positive results in a variety of ED models, with data showing that intracavernosal injection is similar to systemic delivery of cells in their effect.[8] Human research in this field has explored a wide range of modalities and delivery techniques. Intravenous SCT was shown to improve female libido in one randomized trial.[9] In addition, 5 phase I/II trials investigating intracavernosal SCT for ED have been published thus far, with mixed results.[10] Only one of these included a sham arm of 3 patients.[11] No trials to date have investigated the use of SCT in men outside of a phase II trial, and none have used a double-blinded placebo control.

Table 1. Description of the trials used in our analysis

Trial name	POSEIDON (2012)[12]	TAC-HFT (2014)[13]	TRIDENT (2017)[14]
Trial type	Phase I/II randomized, blinded	Phase I/II randomized, controlled, blinded	Phase II randomized, blinded
N	30	67	30
N with IIEF data	2	17	17
Intervention	Autologous v allogenic hMSC, varying doses	Autologous hMSC v hBMC v placebo	Allogenic hMSC, varying doses
Cell doses (million)	20, 100, 200	200	20, 100
When was IIEF data collected (months)	Baseline, 1, 2, 3, 4, 5, 6, 12	Baseline, 1, 2, 3, 4, 5, 6, 12	Baseline, 3, 6, 12
Endothelial function data	No	No	Yes
Major changes in stem cell groups	1. All groups showed improved functional capacity, ventricular remodeling, QoL. 2. Improved walk test and MLHF in autologous group. 3. The 20 million dose showed better EF.	1. Improved infarct size, regional myocardial function, walk distance with hMSC. 2. Improved MLHF in both stem cell groups.	1. All doses showed reduced cardiac scar size. 2. The 100 million dose showed increased EF.

hBMC = human bone marrow mononuclear cells; hMSC = human mesenchymal stem cells; IIEF = International Index of Erectile Function; MLHF = Minnesota Living with Heart Failure Questionnaire; POSEIDON = Comparison of Allogeneic vs Autologous Bone Marrow—Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy; TAC-HFT = Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy; TRIDENT = Dose Comparison Study of Allogeneic Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy; QoL = quality of life.

Table 2. Clinical and demographic characteristics of the pooled stem cell group and placebo group in men with ED

Treatment group	Placebo, n = 8 (%)	Stem cell therapy, n = 28 (%)
Age ± SD	65 ± 11.75	65 ± 10.94
BMI ± SD	28.67 ± 4.94	29.6 ± 3.96
History of coronary interventions	7 (87.5)	27 (96.4)
History of hypertension	6 (75)	18 (64.3)
History of congestive heart failure	6 (75)	21 (75)
History of valvular heart disease	2 (25)	4 (14.3)
Smoking history		
Never smoked	2 (25)	7 (25)
Former smoker	4 (50)	20 (71.4)
Current Smoker	2 (25)	1 (3.6)
History of hyperlipidemia	6 (75)	21 (75)
History of diabetes mellitus	1 (12.5)	5 (17.9)
History of renal insufficiency	2 (25)	1 (3.6)
History of cancer	1 (12.5)	3 (10.7)
History of TIA or CVA	0	3 (10.7)
Specify genitourinary reproductive condition		
BPH	0	3 (10.7)
Nocturia	0	1 (3.6)
Urolithiasis	0	1 (3.6)
Baseline IIEF-EF [IQR]	5.5 [1.5–8.5]	5 [1.3 – 14]
3 months IIEF-EF [IQR]	6.5 [2.5–20]	6 [1–20.8]
6 months IIEF-EF [IQR]	6 [1.5–16]	4 [1–21]
12 months IIEF-EF [IQR]	3.5 [3–5.8]	7 [1.5–20]

CVA = cerebrovascular accident; IIEF = International Index of Erectile Function; TIA = Transient ischemic attack.
Data were pooled from all 3 trials described in Table 1.

SCT has been investigated in multiple randomized controlled trials (RCTs) in men with ischemic cardiomyopathy to investigate possible improvement in cardiac function. The proposed mechanisms behind cardiac improvement may also have an effect on erectile function. We reviewed 3 RCTs in which men with ischemic cardiomyopathy received transendocardial stem cell injection (TESI). These 3 trials collected IIEF-EF questionnaires in these men. We hypothesized that SCT for men with ischemic cardiomyopathy would improve ED because of either improvement in systemic endothelial function or from local paracrine effects of implanted stem cells. We performed a post hoc analysis of 3 previously published RCTs to evaluate this hypothesis.

MATERIALS AND METHODS

Data from 3 previously published trials were used in our analysis. The Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy (POSEIDON trial), Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy (TAC-HFT trial), and the Dose Comparison Study of Allogeneic Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy (TRIDENT study) all recruited men with ischemic cardiomyopathy and ejection fraction less than 50%.[12–14] All trials involved TESI of SCT with 1-year follow-up, while the TAC-HFT trial also included a placebo group. See Table 1 for trial details. The Institutional Review Board of the University of Miami Miller School of Medicine approved all 3 original RCTs, and all participants gave written informed consent. The data used for this post hoc analysis were deidentified from the original manuscripts, and so additional approval was not required.

Our primary outcome was change in the IIEF score in the erectile function domain (IIEF-EF). Other outcomes we investigated included the mean IIEF score and patient comorbidities. We excluded men with a history of a penile prosthesis and those without baseline data or at least 6 months of follow-up. We also excluded men who did not undergo the catheterization procedure. We limited our analysis to men with ED, as defined as an IIEF-EF score of less than 25.

The TRIDENT trial also collected data on endothelial function, which were measured via brachial artery flow-mediated vasodilation (FMD%) and quantification of endothelial progenitor cell-colony forming units (EPC-CFUs). Patients with lower FMD are considered to have endothelial dysfunction, and higher counts of circulating EPCs indicate greater capacity for endothelial self-regeneration.[15,16] As an exploratory outcome, we analyzed these data in male TRIDENT participants to investigate any association with the IIEF-EF score.

Because the patients recruited in these 3 trials had identical inclusion criteria, we pooled data for some of our analyses. We investigated IIEF outcomes between autologous and allogenic

Table 3. IIEF data in men with ED stratified by the number of stem cells received

Stem cell dose	Placebo, n = 8	20 million, n = 9	100 million, n = 8	200 million, n = 11	*P*-value
Age ± SD	65 ± 11.7	70.3 ± 9.9	71 ± 3.8	56.3 ± 9.8	.005
Baseline IIEF-EF [IQR]	5.5 [1.5–8.5]	4 [1–12]	2 [1–5.8]	14 [4–23]	.072
3 month IIEF-EF [IQR]	6.5 [2.5–20]	2 [1–13]	2.5 [1–8.5]	21 [7–23]	.079
6 month IIEF-EF [IQR]	6 [1.5–16]	1 [1–18.5]	1 [1–4.5]	21 [3–27]	.052
12 month IIEF-EF [IQR]	3.5 [3–5.8]	1 [1–15]	3 [2–9.3]	20 [15–24.5]	**.014**

IIEF = International Index of Erectile Function.
Bold indicates statistically significant ($P < .05$).
Data were pooled from all 3 trials described in Table 1, restricted to men with an IIEF score <25.

cell sources, by cell dose, by cell type (human mesenchymal stem cells versus human bone marrow mononuclear cell), and in all men, when compared with placebo.

For the statistical analysis, the program SPSS, version 24.0, for Windows (IBM, NY, USA) was used. Categorical variables were presented as absolute values and frequencies and analyzed with the chi-square or Fisher's exact test as required. The normality test of Shapiro-Wilk was used to determine data distribution. Continuous variables were presented as a mean ± standard deviation, or median, and interquartile range [25–75]. Depending on their distribution, data were analyzed with the Student's t-test or Mann-Whitney U test (or analysis of variance or Kruskal-Wallis test) as required, and paired sampled analysis (baseline versus post-treatment) was performed with the Wilcoxon rank test. A P value $< .05$ was considered statistically significant.

RESULTS

A total of 36 men were identified from the 3 trials who had IIEF data collected before and after TESI and had at least mild ED at baseline (IIEF-EF $\leq$ 24).

8 men received placebo injection with saline, and 28 men received stem cell injections. Of the men who received injections of cells, 18 received allogenic human bone marrow–derived MSCs (in the TRIDENT and POSEIDON trials) and 10 received autologous-derived cells, of which 4 were treated with BMCs, and 6 were treated with MSCs (from the TAC-HFT trial). Concerning the doses of cells received, 9 men received 20 million, 8 received 100 million, and 11 received 200 million.

The median participant age was 66.5 [57.3–73] years. The incidence of hypertension, congestive heart failure, smoking history, diabetes, dyslipidemia, stroke, and prior genitourinary conditions were similar among men who received placebo and cell injection ($P > .05$).

The median baseline IIEF-EF score of the placebo and cell group (all doses) was 5.5 [1.5–8.5] and 5.0 [1.3–14] ($P = .878$), respectively. At 12-month follow-up, the median IIEF-EF score of the placebo and cell group was 3.5 [3–5.8] and 7 [1–20] ($P = .486$), respectively (Table 2). When comparing the change from baseline to 12-month follow-up within each group, there was no difference over time (placebo and cell $P > .05$).

We then analyzed IIEF-EF changes over time based on the dose of cells received (Table 3), the source of the cells received (autologous versus allogenic, Table 4), and the type of cells received (hMSCs versus hBMCs, Table 5). In each subgroup analysis, the IIEF-EF score largely did not change over time. In the analysis involving the number of cells, there was a significant change between groups from baseline (14 [4–23]) to 12 months (20 [15–24.5]) in men who received 200 million cells ($P = .014$). Similarly, men who received autologous cells displayed a similar increase from 14 [3.8–23.3] at baseline to 20 [12–22] at 12 months ($P = .030$). After accounting for the difference between groups at baseline, it is difficult to know the true

Table 4. IIEF data in men with ED stratified by the source of stem cells received

Stem cell source	Placebo, n = 8	Autologous, n = 10	Allogenic, n = 18	*P* value
Age ± SD	55.6 ± 10.1	70.2 ± 7.5	65 ± 11.7	.001
Baseline IIEF-EF [IQR]	5.5 [1.5–8.5]	14 [3.8–23.3]	3.5 [1–11.5]	.079
3 month IIEF-EF [IQR]	6.5 [2.5–20]	20 [5.5–22.3]	2.5 [1–12]	.138
6 month IIEF-EF [IQR]	6 [1.5–16]	16.5 [2.8–24.8]	1 [1–15.5]	.131
12 month IIEF-EF [IQR]	3.5 [3–5.8]	20 [12–22]	3 [1–13]	**.030**

IIEF = International Index of Erectile Function.
Bold indicates statistically significant ($P < .05$).
Data were pooled from all 3 trials described in Table 1, restricted to men with an IIEF score <25.
Autologous: stem cells derived from each individual patient. Allogenic: stem cells derived from healthy stem cell donors.

Table 5. Clinical characteristics in men with ED stratified by the type of stem cells received

Stem cell type	Placebo, n = 8	hMSCs, n = 24	hBMCs, n = 4	*P* value
Age ± SD	65 ± 11.7	66.2 ± 11.3	57.8 ± 4.3	.370
Baseline IIEF-EF [IQR]	5.5 [1.5–8.5]	4.5 [1.3–14]	9.5 [2.3–20.5]	.854
3 month IIEF-EF [IQR]	6.5 [2.5–20]	4.5 [1–21.8]	9 [2.5–17]	.887
6 month IIEF-EF [IQR]	6 [1.5–16]	4 [1–21.8]	4.5 [2.3–10.5]	.981
12 month IIEF-EF [IQR]	3.5 [3–5.8]	7 [1–18.5]	19 [9–20.8]	.225

hBMC = human bone marrow mononuclear cells; hMSC = human mesenchymal stem cells; IIEF = International Index of Erectile Function.
Data were pooled from all 3 trials described in Table 1, restricted to men with an IIEF score <25.

significance of this difference. It is interesting as an exploratory outcome, as these statistically significant differences reach the threshold for a minimally clinically important difference of 4 in the IIEF-EF domain.[17]

As part of our secondary analysis, we investigated endothelial function in men in the TRIDENT trial and whether this correlated to a change in the IIEF-EF scores. Twenty-one men from the TRIDENT trial completed measurements of endothelial and erectile function before and 3 months after treatment. Of these men, the median age was 68 years [63–72.5]. Endothelial function measured at baseline showed a median FMD of 4.7 [3.4–6.8] and EPC-CFUs of 3 [1–5.5]. Follow-up assessment at 3 months showed median FMD improved to 7.2 [5.5–8.9] ($P < .001$) and median EPC-CFUs improved to 8 [3–16.5] ($P = .004$). Despite improvements in systemic endothelial function, we did not identify any association with changes in IIEF-EF scores.

DISCUSSION

SCT is part of a new armamentarium that may provide novel treatment options to men with ED. Treatment options for ED have remained relatively unchanged for several decades, and SCT may offer a way to go beyond simply treating symptoms and instead reverse disease. RCTs of SCT for men with ED are absent in the literature. Data on SCT are limited to phase I trials in a few clinical scenarios, not including vasculogenic ED in men with CAD. This analysis is the first to our knowledge to show erectile function outcomes for men who have received SCT using RCT data. We hypothesized that SCT would improve endothelial function and erectile function compared with placebo. We retrospectively analyzed prospectively collected RCT data from 3 separate trials, pooling results to address our hypothesis. We did not find any difference in erectile function based on the IIEF when comparing SCT with placebo, but did find small, significant differences in erectile function in men who received 200 million cells, and in men who received autologous cells. These subgroup analysis findings are of uncertain significance. We did find significant improvement in endothelial function in men in the TRIDENT trial over time, but there was no correlation to changes in the IIEF in these men. These results have meaningful implications for researchers. Systemically delivered SCT may not affect distal, off-target tissues, and future trials on SCT for ED should focus on locally delivered, intracavernosal SCT. If systemic trials were to be pursued, high cell doses and autologous cell sources should be used based on the results from our analysis. In addition, men with severe CAD as per the trials in this review may be more resistant to regenerative therapies targeting ED, and a less comorbid population with possibly less corporal fibrosis and endothelial dysfunction may be a better target for future trials.

There are several explanations for our findings. Haahr et al[18] reported results from a pilot study of 21 men who received intracavernosal injections of stem cells after radical prostatectomy (RP). In their study design, they planned to inject men within 6–18 months of RP. They imposed the 18-month time limit to only include men early in the process of ED development and avoid recruiting men who had undergone corpus cavernosus fibrosis and permanent, irreversible ED. Perhaps, the men in our analysis, with advanced cardiac comorbidities and likely chronic vasculogenic ED, were outside of a range of reversibility that may be received by some men with ED.

Another likely explanation is that not enough stem cells reached corporal tissue to enact an effect. While animal studies that show improvement in ED after intravenous injection of stem cells exist, it is unclear what the best delivery method is for SCT when trying to elicit changes on erectile function.[8] In some investigative animal models, 45% of transendocardially injected stem cells reach systemic circulation, with cells reaching multiple sites, including pelvic organs after injection.[19,20] Quantifying the amount reaching target tissues is difficult, and it is possible that very few reached the corporal tissue in the men in our trials. In addition, animal studies show that most stem cells injected directly into the corpora migrate out of the penis within days to weeks. If this is similar in humans, it is possible that the window for clinical change is very short.[21,22] This observation may also explain the trend in our own data, where significance was seen at higher doses of 200 million cells, possibly due to more cells reaching target tissues. This trend mirrors the findings in the parent studies, as higher doses of cells tended to improve outcomes in these trials.

Finally, the most prudent suggestion would simply be that it is possible that stem cells, regardless of route or dose, do not lead to improved erectile function in men with vasculogenic ED. Currently, only a small number of phase I trials in men with ED

receiving SCT have been performed.[11,18,23] Results from these trials are promising but cannot be interpreted broadly due to the lack of control group and the nature of spontaneously improving erectile function in men after RP beyond 2 years, and the spontaneous changing nature of symptoms in men with Peyronie's.[24,25]

There are several strengths and limitations to our study. This post hoc analysis is the first to investigate erectile function among men who received SCT using randomized, placebo-controlled data. Compliance within the original RCTs was 95%. The study's weaknesses include that ED was not a primary end point in any of these trials, and men were not recruited based on erectile function. In addition, many men with ED in these trials had severe disease, which may impose more resistance to a small clinical improvement possibly present with SCT. Including data from 36 men, despite being the largest number investigated with this intervention to date, is insufficient to detect a clinically meaningful difference in IIEF-EF scores. If future prospective trials targeted an improvement in erectile function of 15% with SCT, these trials should aim to recruit at least 175 men per arm to detect a statistically significant difference in IIEF scores, based on calculations described by Charan et al[26] A 15% difference may also translate to a clinically significant difference, but this will depend on the assessment tool used in future trials.[17] Finally, most of the animal research lending support to SCT for ED comes from direct intracavernosal injection of cells, not from TESI or systemically delivered SCT, and so its theoretical basis for efficacy is weaker than other modalities.

CONCLUSION

In men with ischemic cardiomyopathy and ED, delivery of high dose, autologous SCT into the myocardium had a possible effect on erectile function in pooled results from 3 RCTs. These men did notice improvement in endothelial function, but this did not appear to translate to improvement in erectile function. Research in this area has focused mainly on exploratory phase I/II trials, and the population of men who may benefit has not been clearly defined. Given the high quality data that produced our results, our data can encourage researchers to explore different patient populations who may benefit, as well as to focus on high cell dose and autologous cell source if pursuing systemic SCT for ED.

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Conflict of Interest: Joshua M Hare and Ranjith Ramasamy are co-inventors on provisional US Patent #32286/51807. Joshua M Hare discloses a relationship with Vestion Inc that includes equity, board membership, and consulting; is the Chief Scientific Officer, a compensated consultant, and advisory board member for Longeveron; holds equity in Longeveron; and is also the co-inventor of intellectual property licensed to Longeveron. All other authors indicated no potential conflicts of interest. Joshua M Hare is supported by National Institutes of Health grants 1R01 HL137355, 1R01 HL107110, 1R01 HL134558, 5R01 CA136387, and 5UM1 HL113460 and Soffer Family Foundation.

Funding: None.

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