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Intracavernous Stem Cell Injection for Erectile Dysfunction: Safety and Efficacy Review

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ABSTRACT

Background: Erectile dysfunction is a common condition in men characterized by the inability to maintain an erectile state. Current treatment using phosphodiesterase-5 inhibitors treatment may leave significant side effects and effectivity problems in some patients. The use of stem cell transplantation in erectile dysfunction has been emerging as a replacement therapy for erectile dysfunction. The effectiveness of stem cell therapy for the treatment of erectile dysfunction has been investigated in several animal studies and one clinical trial in humans. The intracavernous injection is one of the methods to deliver stem cell treatment for erectile dysfunction besides intravenous and intraperitoneal. It was believed to improve erectile function by promoting cavernosal tissue regeneration, vascularization, and smooth muscle relaxation. However, the intracavernous injection of stem cells for erectile dysfunction treatment in clinical settings requires further investigation since its long-term efficacy and safety concerns regarding swelling, priapism, and fibrous plaque. **Objective:** This review aims to summarize the available evidence on the safety and efficacy of intracavernous stem cell injection for erectile dysfunction treatment in clinical studies only from PubMed. **Conclusion:** In conclusion, while the available evidence suggests that intracavernous stem cell injection is considered safe and effective for the treatment of erectile dysfunction, further large-scale clinical studies are needed to determine its long-term safety, efficacy, and optimal dosing regimens.

Keywords: *Erectile dysfunction, MSC, intracavernous injection, stem cells therapy*

INTRODUCTION

Erectile dysfunction is a common condition that affects men of various ages, with approximately 50% of men between the ages of 40 and 70 experiencing some degree of erectile dysfunction.[1] Despite the availability of oral medications, such as phosphodiesterase-5 inhibitors, a substantial number of patients do not respond to these treatments or experience significant side effects.[2–4] In recent years, cell-based therapy using bioengineered replacement of cavernosal tissue has been proposed as a promising approach for the treatment of erectile dysfunction.[5,6] Specifically, intracavernous stem cell injection has been investigated as a potential treatment option.[7]

The success of this therapy is based on its safety and ease of application, as well as its being the only therapy that seeks to modify the pathophysiology of the disease.[8–10] Studies have shown that intracavernous stem cell injection is effective in improving erectile function by promoting the regeneration of cavernosal tissue, increasing vascularization, and enhancing smooth muscle relaxation.[11,12] Intracavernous stem cell injection therapy has emerged as a promising approach for

treating erectile dysfunction that offers several advantages over traditional oral medications.[13,14] This treatment has the potential to address the underlying causes of erectile dysfunction rather than just treating symptoms.[15,16]

A case report of intracavernosal injection using autologous bone-marrow stem cells on diabetic patients with erectile dysfunction showed that there is an improvement in overall erectile function but not with the penile systolic and diastolic velocity after 12 weeks, moreover, there are quality decline of erectile function after 12 weeks of treatment.[17] Even though this procedure was considered safe, rare major adverse events such as swelling, priapism, and fibrous plaque are still concerning.[15] Recent studies have also explored combinatory therapies by supplementing stem cells with angiogenic proteins such as endothelial growth factor to enhance the therapeutic effects of intracavernous stem cell injection.[18,19]

However, while stem cell transplantation shows promise as a treatment option for erectile dysfunction, some studies have suggested that satisfactory efficacy is not always achieved by the application of stem cells alone.[20,21] Moreover, the safety issues regarding side effects after injection was also concerning such as pain, intracavernosal bleeding, or site infection. Therefore, further clinical research is needed to enhance its effectiveness and safety issues.

This review aims to provide a safety and efficacy overview of intracavernous stem cell injection therapy as a potential treatment for erectile dysfunction in clinical phases. The therapy has emerged as a promising approach for treating erectile dysfunction, with advantages in terms of addressing the underlying causes of the disease.

This review focuses only on clinical studies using stem cell injected intracavernous for the treatment of erectile dysfunction. A literature search was done using PubMed with specific keywords including "intracavernous stem cell injection" and "erectile dysfunction treatment". The search was narrowed to only include clinical research and under 10 years of publication.

Stem Cell Therapy for Erectile Dysfunction

Stem cells are cells that are not fully developed and can replicate and specialize in a wide variety of cell types.[22] They can be categorized into different groups including totipotent, pluripotent, multipotent, or unipotent depending on their ability to differentiate into numerous cell lines.[23] When stem cells divide, the new cells can either remain stem cells or transform into specialized cell types, such as nerve and muscle tissue cells.[24] Stem cells are influenced by their surrounding environment, which can support their self-renewal and transformation into specialized cells.[25,26] The secretion of growth factors and the migration of stem cells to injury sites can lead to tissue regeneration.[27,28] Hence, it is possible that the use of stem cells could be beneficial for the treatment of urinary system diseases or pathological conditions.

Recently, stem cell therapy has emerged as a potential treatment for erectile dysfunction (ED) since stem cells can differentiate into endothelial, neuronal, or smooth muscle cells, which could help repair any structural damage to the penile tissue.[7] Studies have shown success in animal models that demonstrated improvement in ED after stem cell therapy.[9,19,29] However, the exact mechanism of how stem cells work in ED has not been fully confirmed, and the paracrine action of stem cells is another possible mechanism shown in animal models.

Preclinical studies have utilized different types of stem cells, including adipose tissue-derived, bone marrow-derived, muscle-derived, and embryonic stem cells.[30] Clinical studies have also yielded positive results, but determining the ideal type, number, and method of preparing and administering stem cells for clinical use still requires further research.

Stem Cell Delivery in Erectile Dysfunction

There have been several suggested and examined methods for administering stem cells. Studies have explored the effects of intraperitoneal and intravenous injections, with suggestions that intravenous injection is more effective in improving erectile function.[31,32] Other studies have looked at periprostatic implantation, which appears to be equally as effective as intracavernosal injection.[33,34] However, even though less than 1% of injected stem cells may remain in the target tissue and dissipate within a few days after injection, several studies have recommended direct injection into the organ of concern as the most effective method.[33,35] This is because even a limited number of stem cells remaining in the target tissue can trigger endogenous mechanisms of regeneration and promote the differentiation and propagation of progenitor cells, ultimately leading to the recovery of the target tissue.[36,37] Furthermore, these cells have been shown to secrete growth factors and anti-inflammatory cytokines that promote tissue regeneration, angiogenesis, and neuroprotection.[38,39]

Efficacy of Intracavernosal Stem Cell Injection

Intracavernosal stem cell injection has shown promise in treating erectile dysfunction. Several studies have reported increased erectile function scores and improved penile hemodynamics following this treatment (Table 1). We have selected five clinical studies published in the last ten years, which investigated the therapeutic efficacy of intracavernosal injection of various types of stem cells for erectile dysfunction. These studies have demonstrated the efficacy of stem cell therapy in improving erectile function, with specific parameters such as peak systolic velocity, end-diastolic velocity, and resistive index showing significant improvements post-treatment.

A small sample of early clinical studies was made by Levy et al. in 2016.[13] One milliliter of placental matrix mesenchymal stem cells (PM-MSCs) diluted in 2 mL of isotonic saline and injected into the base of corpora cavernosum in 8 patients. International Index of Erectile Function (IIEF), peak systolic velocity (PSV) and end-diastolic velocity (EDV) stretched penile length (SPL), penile width, and rigidity testing were measured 6 weeks, 3 months and 6 months after treatment. This study found that there is a significant increase in PSV at 3 months and 6 months but not in IIEF scores, SPL, and penile width. However, After PM-MSC injection, 3 of 8 patients were able to achieve erections with no pharmacologic assistance.

An open-label phase 1 clinical trial was done in 2018.[14] Four diabetic patients with erectile dysfunction mellitus were given 30 × 106 cells/4 mL bone marrow MSCs intracavernous at 4 sites; one proximal and one distal injection at each side. The primary outcome of IIEF and Erection Hardness Score (EHS) was evaluated in 1, 3, 6, 12 months intervals. This study found that overall IIEF in 12 months was significantly better compared to pre-treatment scores. EHS was found to have a significant effect on the 1st month of the treatment and lower after 3 months. However, overall EHS in 12 months was found to be significantly improved compared to baseline scores. This study overall is the first study to demonstrate the safety and efficacy of intracavernous injection of bone marrow MSCs in humans for the treatment of diabetic patients with erectile dysfunction with promising outcomes in 12 months of follow-up.

A single-blind clinical trial conducted in 2021 reported that intracavernosal injection of oral mucosal stem cells significantly improved erectile function in diabetic patients with erectile dysfunction.[40] A total of 20 patients were selected for this study and received intracavernosal injections of 50-60 x 106 oral mucosal stem cells and control therapy using a randomization method. They evaluated using IIEF, PSV, EDV, and resistance index (RI) 6 months after treatment. Six months after the treatment, significant improvements were observed in IIEF scores. However, an improvement was shown in PSV, EDV, and RI but was not statistically significant. The beneficial impact of stem cells on erectile dysfunction in patients with diabetes is potentially linked to their paracrine effects on the penis,

which can encourage the development of smooth muscle cells, endothelial cells, and neurons. However, the exact mechanisms through which this occurs are not yet fully understood.

A phase 1/2 clinical trial conducted in 2021 further investigated stem cell therapy for erectile dysfunction in diabetic patients.[15] A 20 x 106 Wharton's jelly-derived mesenchymal stem cells were injected intracavernosally in 22 patients. Maximum improvement in IIEF-5 scores was observed after 6 months compared to the baseline. A significant improvement in IIEF-5 scores was recorded in 12 months. EHS score was significantly higher compared to baseline after 6 months. PSV was significantly better after 3 months of injections. However, no significant improvement was observed in EDV and RI.

Table 1. List of clinical studies of intracavernous injection of MSCs in erectile dysfunction in the last ten years.

The study, Year of publication	Source of Stem cells	Pre-Existing Condition	Additional Treatment	Period of Follow-up
Levy et al., 2016[13]	Placental matrix	None	None	6 months
Al Demour et al., 2018[14]	Bone marrow	Diabetes mellitus	None	12 months
Mirzaei et al., 2021[40]	Oral mucosa	Diabetes mellitus	None	6 months
Al Demour et al., 2021[15]	Wharton's jelly	Diabetes mellitus	None	6 months
You et al., 2021[16]	Bone marrow	Post prostatectomy and Diabetes mellitus	None	12 months

Another open-label phase 1 clinical trial conducted in 2021 investigated the efficacy of bone marrow stem cells for the treatment of erectile dysfunction.[16] Ten participants were enrolled in this study and nine completed the clinical trial. A total of 3 x 107 BM-MSCs were injected into the corpus cavernosum. The primary endpoint of this study was IIEF score, Sexual Encounter Profile Score (SEP) 2 and 3, Global Assessment Question (GAQ) scores, PSV, EDV, and RI. The results showed there is an improvement in the IIEF score, but not statistically significant. However, a significant IIEF score was only recorded in the 1st month of treatment, and the improvement was not maintained after 3 months. A hemodynamic analysis using PSV, EDV, and RI all showed no significant improvements. Patient satisfaction levels were measured using SEP 2 and 3 and GAQ 1 and 2. Results showed that the rate of successful vaginal penetration was maintained at 30-40% for up to a year after the injection. Additionally, 20-40% of patients reported an improvement after injection.

All clinical trials in this review have shown similar results. A full comparison of efficacy outcomes was shown in Table 2. Intracavernous injection of stem cells has shown potential for the treatment of erectile dysfunction, particularly in diabetic patients. The IIEF score was reportedly consistent in most studies, indicating the potential efficacy of this treatment. One study showed IIEF score was not significant and the other study showed that improvement did not maintain the effect after 1 month. Furthermore, the hemodynamic analysis using PSV, EDV, and RI did not show statistically significant improvements in any of the studies reviewed. Only one study showed that there is an improvement in PSV. These findings suggest that while the injection of stem cells into the corpus cavernosum may have a positive effect on erectile function, further research is needed to understand its mechanisms and to achieve consistent and long-lasting results.

Table 2. Comparison of clinical outcomes in each study.

p-value of clinical outcomes	Clinical Studies				
	Levy et al., 2016	Al Demour et al., 2018	Mirzaei et al., 2021	Al Demour et al., 2021	You et al., 2021
IIEF score	ns	0.04	0.02	0.0002	0.184
EHS	-	0.02	-	<0.0001	-
PSV	<0.01	-	0.25	0.0332	ns
EDV	ns	-	1	-	ns
RI	-	-	0.057	0.6719	ns

Safety and Ethical Considerations

The efficacy of intracavernosal stem cell injection for the treatment of erectile dysfunction has been demonstrated in numerous studies. This may be due mainly to the ability of mesenchymal stem cells to promote tissue regeneration, angiogenesis, and neuroprotection through their secretion of growth factors and anti-inflammatory cytokines. Potential risks of stem cell therapy include infection, tumor formation, and thrombosis.

Similarly, ethical considerations should include obtaining informed consent from patients regarding the experimental nature of the therapy and adequate monitoring for potential adverse effects. While stem cell therapy for erectile dysfunction shows great promise, further research is needed to optimize the delivery of stem cells and evaluate long-term safety and efficacy.

The first clinical study of intracavernous stem cell injection for erectile dysfunction did not include any long-term safety data.[13] In the second clinical study, patients reported experiencing well-tolerated pain during intracavernous injections, with VAS pain scores ranging from 2 to 4. No bleeding, bruising, pain, swelling, hypo- or hyperthermia, erythema, urticarial, or priapism was observed at the site of intracavernous injection.[14] Physical examination did not reveal any significant changes in body temperature, blood pressure, heart rate, or respiratory rate from baseline. There were no significant adverse events related to the nervous, cardiovascular, respiratory, or gastrointestinal systems, and no significant changes were detected in the hormonal profile.

The third clinical study did not include any safety data related to site injection.[40] Only hormonal adverse events such as lipid and glucose profiles were reported, which remained within normal ranges. The fourth clinical study focused on ensuring the safety and tolerance of the procedure, and no serious adverse effects were reported by patients.[15,41] During the injection procedure, ten patients had mild pain at the injection site, with VAS pain scores ranging from 0 to 3. Most patients did not experience any pain, bleeding, erythema, urticaria, bruising, swelling, priapism, hypothermia, or hyperthermia at the injection site during follow-up. Two patients experienced minimal redness and swelling at the base of the penis. During follow-up, there were no systemic adverse events detected, including in the cardiovascular, respiratory, urinary, nervous, and gastrointestinal systems.

In the fifth clinical trial, three out of 10 patients experienced a total of seven treatment-emergent adverse events (TEAEs).[16,42] One patient with post-prostatectomy ED experienced pyrexia and back pain, while two patients with DM-associated ED experienced a viral upper respiratory tract infection, prostatitis, pruritus, and two cases of hyperglycemia. One patient with DM-associated ED experienced two serious TEAEs, both episodes of hyperglycemia. Five of the seven TEAEs were mild, while the other two were moderate and reported in patients with DM-associated ED. Even though not all adverse events were recorded in all clinical studies, all of the studies reported no significant safety concerns associated with intracavernous injection of stem cells for the treatment of erectile dysfunction. The overall safety findings suggest that this procedure is safe and well-tolerated by patients.

Conclusion and Future Directions

In conclusion, studies suggest that intracavernous injection of stem cells for the treatment of erectile dysfunction is a safe and well-tolerated procedure. While further research is necessary to establish the efficacy of this procedure, the current data demonstrate promising potential for stem cell therapy in restoring erectile function through IIEF scores. However, mechanisms of action and the optimal dose, frequency, and duration of treatment need to be further explored.

Given the limited number of clinical studies conducted on humans and inconsistencies in study methods and treatment protocols, caution should be exercised when interpreting the current findings

and implementing stem cell therapy in clinical practice. Further controlled studies with larger sample sizes, longer follow-up periods, and standardized treatment protocols are necessary to establish the efficacy and safety of intracavernous injection of stem cells for the treatment of erectile dysfunction. As the field of stem cell therapy continues to evolve, researchers and clinicians must remain vigilant in their approach to evaluating new treatment methods.

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AUTHORS' CONTRIBUTIONS

ASL concept and design the study and made the academic review and revisions, PHA had the literature search and review and FRM were drafting the manuscript.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

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