Health Tech Asmnt Act. 5(2). doi: 10.18502/htaa.v5i2.8004

Research Article

Safety and Efficacy of Stem Cell Therapeutics in Wound Healing: A Rapid Review of Available Evidence

Zeinab Shaker[1], Zohreh Shaker[2], Mohsen Barouni*[3]

[1] School of Management and Medical Information Science, Kerman University of Medical Sciences, Kerman, Iran
[2] School of Management and Medical Information Science, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Health Services Management Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

*Corresponding author: Health Services Management Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran. Email: mohsenbarooni@gmail.com

Received 2021 February 15; Accepted 2021 March 17.

Abstract

Background: Skin and wound injuries are important health problems with great mortality rates. While there are different alternative therapies, there is no agreement on the best therapy for burn wounds and wound complications. Stem cell therapy has an optimistic prospect in many preclinical studies of burn wounds and diabetic wounds.

Objectives: In this study, we performed a rapid review to evaluate the efficacy and safety of stem cell therapy in wound treatment.

Methods: This rapid review of the evidence aimed to evaluate the potential effects of stem cells on wound healing to create a policy guide for policymakers in the health care system. We searched such databases as PubMed and Scopus on March 13, 2021 using keywords, including "stem cells and wound healing", "safety", and "efficacy". The references of retrieved studies were also checked to ensure the capture of the literature. Studies evaluating the safety and efficacy of stem cells on wound healing published in Persian and English were included. Generally, we used the PICO (population, intervention, control, and outcomes) model for search strategy.

Results: Out of a total of 92 retrieved papers, 22 studies were eligible for inclusion. The overall review showed that stem cell therapy improved wounds. Also, studies showed that using stem cell technology in a non-invasive way could be a good alternative. However, the limitations of this technology consisted of the need to improve cell delivery methods, cell sustainability, heterogeneity in the research of mesenchymal stem cells, and wound substrate. Further studies are needed to determine its safety and efficacy.

Conclusions: Although the evidence on the safety and efficacy of using stem cells for wound healing was limited, studies showed that stem cell technology is a good alternative to traditional therapies. Future clinical studies should consider the differences in the studies to achieve maximum effectiveness.

Keywords: Stem Cell, Wound Healing, Safety, Efficacy

1. Background

Skin and wound injuries are serious challenges that can affect mortality and morbidity rates. The skin of the body has multiple vital tasks; it is a barrier to prevent the entry of pathogens, modifies body temperature, provides sensation, and stops dehydration. Thus, healing wounds and damaged skin is very important (1).

Serious wounds and injuries that heal during a procedure are usually associated with benign scars. Stem cell therapy is a new treatment that has been considered in the treatment of several types of wounds, including diabetic and burn wounds (2).

Mesenchymal stromal cells (MSCs) can self-renew and transform into any adult diversity cell in the body with different potentials (3).

Bone marrow and other tissues such as adipose tissue, nerve tissue, cord blood, and dermis with phenotypic heterogeneity are the sources of MSCs (4).

Given that recent trend on wound care is associated with low efficacy and high cost, stem cell therapy can be a good alternative with higher efficacy and affordability. The difference between this treatment and other treatments is that they can regenerate themselves and differentiate into multiple cells and regenerate physiologically damaged tissue. The current review aimed to evaluate the role of stem cells in wound repair (5).

2. Objectives

Accordingly, this rapid review of the evidence aimed to evaluate the potential effects of stem cells on wound healing to create a policy guide for policymakers in the health care system.

3. Methods

We searched such databases as PubMed and Scopus on March 13, 2021, using keywords, including "stem cells and wound healing", "safety", and "efficacy". The titles and abstracts of the articles were reviewed, and the studies were selected based on the inclusion and exclusion criteria. In addition, references of retrieved studies were checked to ensure the capture of the literature. All studies published in Persian or English investigating the safety and efficacy of using stem cells in wound healing were included. Also, animal clinical trials were excluded from the study. It should also be noted that economic evaluation could not be performed due to time constraints. Since the data in the included studies was not sufficient for meta-analysis, these articles were reviewed qualitatively. Table 1 illustrates the search strategy.

Table 1. Search Strategy

Databases	Keywords	Regulation
PubMed	#1 ((injection OR treatment [All Fields]) AND (wound OR "wound diabetic" [All Fields] OR burn) AND ("Stem cell" [MeSH Terms] OR " Mother cell" OR "Stem cell mesenchymal" [All Fields] OR "Mesenchymal Stem Cells" [All Fields]) AND (Efficacy) AND (Safety)) #2 ((wound OR "wound diabetic" OR burn) AND ("Stem cell" OR " Mother cell" OR "Stem cell mesenchymal" OR "Mesenchymal Stem Cells")) AND (injection OR treatment)) AND (Efficacy(AND (Safety))	503
Google Scholar	((Injection) AND ("wound diabetic" OR burn) AND ("Stem cell" OR "Stem cell mesenchymal") AND (Efficacy) AND (Effectiveness) AND (Safety))	11270
Scopus	(Injection OR treatment) AND (wound OR "wound diabetic" OR burn) AND ("Stem cell" OR " Mother cell" OR "Stem cell mesenchymal" OR "Mesenchymal Stem Cells") AND (Efficacy) AND (Safety)	204

4. Results

Out of a total of 11,977 papers retrieved, 22 studies published from 2011 to 2020 were included after removing duplicates and applying the inclusion criteria. Table 2 shows the number of selected studies. We included review studies and case reports because human studies were limited (Figure 1).

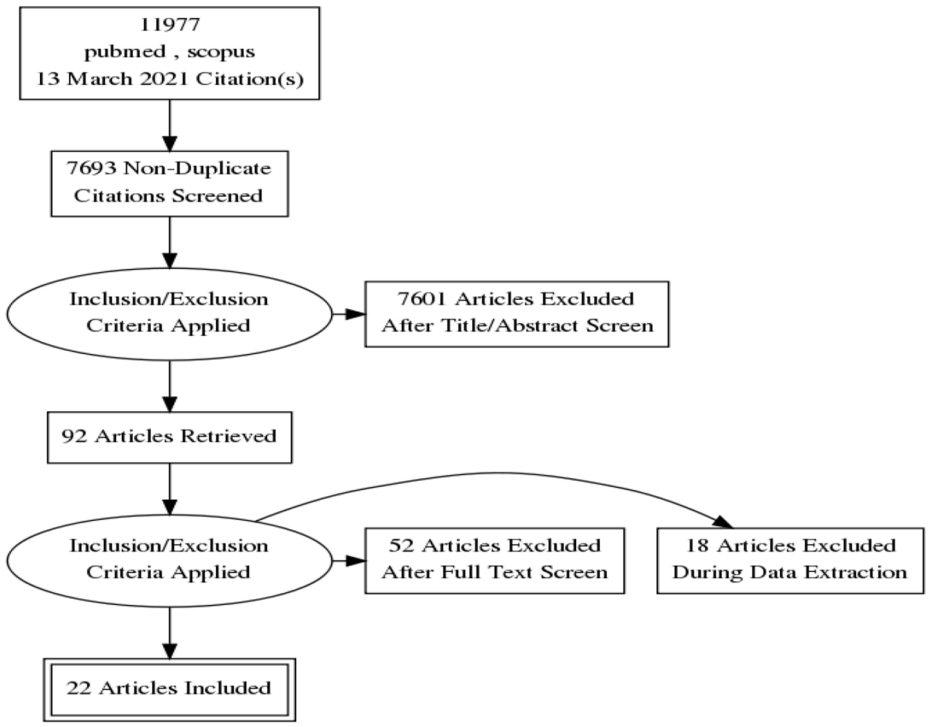

Figure 1. The search process of the study

Table 2. Included Studies

Author (s)	Type of Study	Population	Intervention	Comparison	Outcomes
Gentile et al. (6)	Systematic review	-	-	-	In 84% of articles, the injuries improved; in some cases, mild side effects were seen 48 - 72 hours after injection; and safety was seen.
Sierra-Sanchez et al. (7)	Systematic review	1316	0.5 × 106 - 150 × 106	Some studies had a control group	Wound healing was observed in 60 to 100% of cases; 25% of cases presented early complications (infection or partial loss of graft) and 45% late complications (hypo- or hyperpigmentation, contracture scar or hypertrophic scar).
Maslowski et al. (8)	Clinical trial	11	5.6 × 106 ± 4 × 106 cells per milliliter	Standard and general treatment	Improvement was observed in 75% of ulcers.
Malik et al. (9)	Systematic review	389	1 - 11 times 0.5 to 21 mL	Some studies had a control group	Further studies are needed, and there were no side effects.
Kosaric et al. (10)	Review	131	In 1 - 2 phases of injection, the amount of injection was unspecified	Some studies had a control group	High recovery and efficacy; and safety was seen.
Domaszewska-Szostek et al. (11)	Review	-	-	-	Safety, pain relief, and wound healing were seen; however, more studies were needed in this area
Francis et al. (12)	Review	-	-	-	The treatments were effective on different wound beds.
Lopes et al. (13)	Review	396	At least 1 × 106 cells	All studies had a control group	In all studies, improvement and safety were observed.
Holm et al. (14)	Systematic review	187	Injection between 1.5 × 106 to 60 × 108 cell/mL	Out of nine studies, three articles had a control group	66.7 to 100% of injuries improved; and safety was seen.
Luck et al. (15)	Systematic review	-	-	Control group studies	-
Gadelkarim et al. (16)	Review	-	-	-	Efficacy
Zhang et al. (17)	Review	127	1.5 × 106 - 3 × 108	-	Compared to either of the therapies, there were more clinical effects.
Zeng et al. (18)	Case report	1	1× 106 cell	-	No recurrence or complication was seen; and safety was seen

Cao et al. (19)	Review	227	2 - 10 mL	-	In one of the articles, 79% of patients' limbs were saved.
Kanji and Das (20)	Review	-	-	-	Effective in the wound healing process.
Kim et al. (21)	Review	716	-	Out of 17 articles, three studies had a control group	-
Portas et al. (22)	Case report	1	1 × 106 cell/mL Wound size 12 cm × 4 cm	-	Significant improvement was seen in signs and symptoms; quality of life increased; and safety was seen.
Hassan et al. (23)	Review	-	2 × 104 to 5 × 107	-	Wound healing.
Jayaraman et al. (24)	Review	-	Gave each excision wound 80 mL MSC-CM by subcutaneous injection and 20 mL by topical	-	Promoting wound healing.
Kirana et al. (25)	Clinical trial	30	4 × 106 to 106 cell/mL		Safety and improvement in pain and wound size were seen.
Sung et al. (26)	Case report	2	4 × 106 to 6 × 106 cell/mL		Satisfactory results and side effects were not seen.
Cherubino et al. (27)	Review	-	-	-	Efficacy and safety were seen.

In this study, we included 12 review studies, five systematic reviews, three case reports, and two clinical trials.

4.1. Systematic Review Studies

In this study, we included five systematic reviews:

(1) In the study by Gentile P et al., 22 papers were selected. This systematic review presented the efficacy of platelet-rich plasma (PRP), adipose-derived (AD)-MSCs, and biomaterials in treating cerebral salt wasting (CSW, sexually transmitted diseases (STDs), and skin defects. Because cell therapy is technically different, further studies should be performed to determine the protocol and its standardization, and also large-scale clinical trial studies should be performed to ensure the effectiveness of this treatment (6).

(2) The study by Holm et al involved all clinical trials from PubMed and Embase. 14 studies were found. The results showed that cell therapy was effective, and it could heal wounds and reduce the pain. The results of studies showed the positive effect of cell therapy on treating various wounds; however, further studies are required (14).

(3) Luck J, et al. evaluated the efficacy and safety of cell therapy in chronic wounds. All autologous fat grafting (AFG) techniques were performed on the intervention group and meta-analysis was performed, and different techniques were compared. The results showed that all techniques were effective and safe in wound healing (15).

(4) In the study by Malik D et al., 10 observational case series were included in the qualitative synthesis. There were no randomized controlled trials. Autologous fat cell transplantation was associated with satisfactory wound healing and few complications, but the quality of evidence in the studies was low (9).

(5) Sierra-Sanchez et al. expressed that using MSCs advanced therapies for skin pathology can improve patients' quality of life. Treatment of psoriasis or atopic dermatitis was effective. They also highlighted the need for more studies in terms of effectiveness and safety. Despite many studies, the studies did not have sufficient quality and control group (7).

4.2. Clinical Trial Studies

In this study, we included two clinical trials.

(1) Eleven patients participated in a clinical trial by Maslowski et al. The mean age of this group was 9.5 + 66.6 years with the chronic venous ulcer. Adipose tissue was col-

lected by aspiration. Cells were implanted subcutaneously on and around the wound, and patients were followed up every two weeks for six months. All patients received topical and standard treatment. The average amount of cells injected into patients was $5.6 \times 10^6 \pm 4 \times 10^6$. Eventually, 75% of the wounds healed). There was no association between age and recovery, and no serious side effects were observed. Finally, the authors stated that adipose tissue stem cells can be a promising and safe treatment for chronic venous ulcers (8).

(2) In a clinical trial by Kirana et al., 24 patients were randomized to receive bone marrow mononuclear cells (BMCs) (BMCs or tissue repair cells) TRCs (and 22 patients were in the control group. One patient in the TRC group and two patients in the BMC group were excluded during follow-up, and one patient died before the end of the study. During the study, while the BMC group improved, the TRC group did not show any improvement. Eighteen patients recovered 3.8 times fewer cells than the other group after 45 weeks of recovery, but TRC patients were injected with some CD90 + tubes. Improvement in micro vascularization was seen in some patients, and improvement was seen in both groups (25).

4.3. Case-control Studies

In this study, we included three case-control studies.

(1) In a study by Sung et al., a 23-year-old female patient was injected by a non-medical specialist in the forehead and nose. Inflammation with necrosis was seen in an area of 3 x 3 cm. In another case, a 30-year-old woman in a private clinic had cells injected into the back and tip of her nose; she developed swelling at the injection site, but the wounds gradually healed, leaving only fine lines after six months. Using fat mesenchymal cells, the wounds healed completely, and the results were satisfactory (injection: $6 - 4 \times 10^6$ cells) (26).

(2) Portas et al. evaluated a case of chronic wound with more than 30 years of non-response to treatment with other MSCs with a volume of 1×10^6. The area of the wound was 12 x 4 cm after two years of follow-up after injection. Finally, the wounds healed, the signs and symptoms decreased, and the patient's quality of life increased dramatically (22).

(3) In a case report by Zeng et al., a 57-year-old woman with a diabetic ulcer on the back of her right leg that wound did not heal with other treatments. MSCs were injected at a concentration of 1×10^6. After the stem cell injection, her foot ulcer healed, and her foot function was well maintained while walking, and cell therapy did not cause any side effects after six months of follow-up (18).

4.4. Review Studies

The summary of the results of 12 articles reviewed is as follows:

- Using stem cell technology as a non-invasive approach can be a good alternative to improving wound problems.
- MSC transplantation can accelerate wound closure, improve clinical parameters, and prevent amputation.
- The short-term evidence of this technology in terms of efficiency and effectiveness, and to some extent cost-effectiveness, has been declared positive.
- Limitations of stem cells to wound healing may include the need to improve cell delivery methods, cell viability, and heterogeneity in the preparation of MSCs. Further studies may be needed to determine its safety (10-14, 16, 17, 19-21, 23, 24, 27).

5. Conclusions

Based on the findings, evidence on the safety and efficacy of using stem cells in treating patients with wound problems is sufficient. However, there are still few clinical trials in this regard. Hence, further studies are needed to confirm the results. Most clinical studies are in the animal phase. The preliminary finding of our research showed that MSCs can be a hopeful strategy to improve wound injury, and these were effective and safe in most studies, but most of the research agree that more studies need to be done, but anyway, Stem cells accelerate burn wound healing.

References

1. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. Exp Dermatol. 2008;17(12):1063-72.
2. Atiyeh BS, Ioannovich J, Al-Amm CA, El-Musa KA. Management of acute and chronic open wounds: the importance of moist environment in optimal wound healing. Curr Pharm Biotechnol. 2002;3(3):179-95.
3. Nakagawa H, Akita S, Fukui M, Fujii T, Akino K. Human mesenchymal stem cells successfully improve skin-substitute wound healing. Br J Dermatol. 2005;153(1):29-36.
4. Lee OK, Kuo TK, Chen WM, Lee KD, Hsieh SL, Chen TH. Isolation of multipotent mesenchymal stem cells from umbilical cord blood. Blood. 2004;103(5):1669-75.
5. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13(12):4279-95.
6. Gentile P, Garcovich S. Systematic Review: Adipose-Derived Mesenchymal Stem Cells, Platelet-Rich Plasma and Biomaterials as New Regenerative Strategies in Chronic Skin Wounds and Soft Tissue Defects. Int J Mol Sci. 2021;22(4).
7. Sierra-Sanchez A, Montero-Vilchez T, Quinones-Vico MI, Sanchez-Diaz M, Arias-Santiago S. Current Advanced Therapies Based on Human Mesenchymal Stem Cells for Skin Diseases. Front Cell Dev Biol. 2021;9:643125.
8. Maslowski L, Paprocka M, Czyzewska-Buczynska A, Bielawska-Pohl A, Dus D, Grendziak R, et al. Autotransplantation of the Adipose Tissue-Derived Mesenchymal Stromal Cells in Therapy of Venous Stasis Ulcers. Arch Immunol Ther Exp (Warsz). 2020;68(1):1-9.
9. Malik D, Luck J, Smith OJ, Mosahebi A. A Systematic Review of Autologous Fat Grafting in the Treatment of Acute and Chronic Cutaneous Wounds. Plast Reconstr Surg Glob Open. 2020;8(5):e2835.
10. Kosaric N, Kiwanuka H, Gurtner GC. Stem cell therapies for wound healing. Expert Opin Biol Ther. 2019;19(6):575-85.
11. Domaszewska-Szostek A, Krzyzanowska M, Siemionow M. Cell-Based Therapies for Chronic Wounds Tested in Clinical Studies: Review. Ann Plast Surg. 2019;83(6):e96-e109.
12. Francis E, Kearney L, Clover J. The effects of stem cells on burn wounds: a review. Int J Burn Trauma. 2019;9(1):1.
13. Lopes L, Setia O, Aurshina A, Liu S, Hu H, Isaji T, et al. Stem cell therapy for diabetic foot ulcers: a review of preclinical and clini-

cal research. Stem Cell Res Ther. 2018;9(1):1-16.
14. Holm JS, Toyserkani NM, Sorensen JA. Adipose-derived stem cells for treatment of chronic ulcers: current status. Stem Cell Res Ther. 2018;9(1):1-11.
15. Luck J, Smith OJ, Malik D, Mosahebi A. Protocol for a systematic review of autologous fat grafting for wound healing. Syst Rev. 2018;7(1):1-5.
16. Gadelkarim M, Abushouk AI, Ghanem E, Hamaad AM, Saad AM, Abdel-Daim MM. Adipose-derived stem cells: Effectiveness and advances in delivery in diabetic wound healing. Biomed Pharmacother. 2018;107:625-33.
17. Zhang W, Bai X, Zhao B, Li Y, Zhang Y, Li Z, et al. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing via the PI3K/Akt signaling pathway. Exp Cell Res. 2018;370(2):333-42.
18. Zeng X, Tang Y, Hu K, Jiao W, Ying L, Zhu L, et al. Three-week topical treatment with placenta-derived mesenchymal stem cells hydrogel in a patient with diabetic foot ulcer: A case report. Medicine (Baltimore). 2017;96(51):e9212.
19. Cao Y, Gang X, Sun C, Wang G. Mesenchymal Stem Cells Improve Healing of Diabetic Foot Ulcer. J Diabetes Res. 2017;2017:9328347.
20. Kanji S, Das H. Advances of Stem Cell Therapeutics in Cutaneous Wound Healing and Regeneration. Mediators Inflamm. 2017;2017:5217967.
21. Kim KH, Blasco-Morente G, Cuende N, Arias-Santiago S. Mesenchymal stromal cells: properties and role in management of cutaneous diseases. J Eur Acad Dermatol Venereol. 2017;31(3):414-23.
22. Portas M, Mansilla E, Drago H, Dubner D, Radl A, Coppola A, et al. Use of Human Cadaveric Mesenchymal Stem Cells for Cell Therapy of a Chronic Radiation-Induced Skin Lesion: A Case Report. Radiat Prot Dosimetry. 2016;171(1):99-106.
23. Hassan WU, Greiser U, Wang W. Role of adipose-derived stem cells in wound healing. Wound Repair Regen. 2014;22(3):313-25.
24. Jayaraman P, Nathan P, Vasanthan P, Musa S, Govindasamy V. Stem cells conditioned medium: a new approach to skin wound healing management. Cell Biol Int. 2013;37(10):1122-8.
25. Kirana S, Stratmann B, Prante C, Prohaska W, Koerperich H, Lammers D, et al. Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients. Int J Clin Pract. 2012;66(4):384-93.
26. Sung HM, Suh IS, Lee HB, Tak KS, Moon KM, Jung MS. Case Reports of Adipose-derived Stem Cell Therapy for Nasal Skin Necrosis after Filler Injection. Arch Plast Surg. 2012;39(1):51.
27. Cherubino M, Rubin JP, Miljkovic N, Kelmendi-Doko A, Marra KG. Adipose-derived stem cells for wound healing applications. Ann Plast Surg. 2011;66(2):210-5.