DOI: https://doi.org/10.30795/jfootankle.2024.v18.1801

Review

Pseudoarthrosis treatment with stem cells: an integrative review

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Abstract

Objective: This integrative review aims to synthesize and critically analyze the current literature on the use of stem cells in the treatment of pseudarthrosis.

Methods: A systematic search was conducted in electronic databases, resulting in the inclusion of preclinical and clinical studies that investigated the impact of stem cells on bone healing.

Results: Proposed biological mechanisms include the ability of stem cells to promote osteogenic differentiation and secrete growth factors that facilitate tissue repair. Results indicate that stem cell treatment often increases rates of successful bone healing, improving functional outcomes and reducing postoperative complications. Limitations include the heterogeneity in treatment protocols and the need for randomized clinical trials to robustly validate these findings.

Conclusion: The use of stem cells emerges as a promising approach in the management of pseudarthrosis, promoting a new perspective in orthopedic regenerative medicine.

Level of evidence V; Expert Opinion.

Keywords: Pseudoarthrosis; Stem cells; Bone; Regenerative medicine; Treatment.

Introduction

Pseudarthrosis, or bone nonunion, is a significant complication after fractures and orthopedic surgical procedures, being characterized by the inability of the injured bone to heal properly. This condition challenges orthopedists and surgeons with its clinical complexities and substantial impact on patients' quality of life[1]. Traditionally, treatment involves conventional surgical techniques such as internal fixation with plates and screws, as well as autologous or allogeneic bone grafts. However, advances in regenerative medicine have introduced promising therapies, such as the use of stem cells, which have the potential to revolutionize the management of pseudarthrosis. Stem cells are undifferentiated cells with the capacity for self-renewal and differentiation into several cell types, including osteoblasts, which are essential for bone formation[2]. Preclinical and clinical studies have explored their use in the repair of nonunion fractures, with encouraging results indicating improvements in bone healing and functional recovery of patients. This integrative review aims to synthesize and critically analyze the available evidence on the treatment of pseudarthrosis with stem cells, covering everything from the biological mechanisms to the clinical and economic outcomes associated with this innovative approach[3].

In addition to the biological and clinical aspects, economic considerations are also crucial in the evaluation of new therapies. With the increasing costs associated with the management of postoperative complications and the need for surgical revisions, strategies that promote effective bone healing and reduce recovery time are of particular interest. Therefore, this review will not only examine the efficacy and

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How to cite this article: De Marco LF, Dias AFF, Vasconcelos MFCS, Pagotti LV, Oliveira RA, Silva Junior OSB. Treatment of pseudoarthrosis with the use of stem cells: an integrative review. J Foot Ankle. 2024;18(3):328-31.

safety of stem cells in pseudarthrosis, but also assess their potential economic impact when compared with conventional approaches[4].

A comprehensive understanding of the mechanisms by which stem cells promote bone healing is essential to support their clinical application. Investigations into the local microenvironment of the lesion, growth factors involved, and cellular interactions are fundamental to optimize treatment protocols. This review will seek to highlight not only the advances achieved to date, but also identify knowledge gaps that may guide future research and the refinement of stem cell therapeutic strategies in the management of pseudarthrosis[5].

Methods

The methodology adopted in this integrative review follows a systematic approach to synthesize and critically analyze the available literature on pseudarthrosis treatment using stem cells. Articles were searched in electronic databases, including PubMed, Scopus, and Web of Science, using search terms such as "pseudoarthrosis," "nonunion," "stem cells," "cell therapy," "bone healing," among other relevant terms. The search strategy was designed to identify studies that investigated the use of stem cells in pseudarthrosis models, covering both preclinical and clinical studies.

Inclusion criteria were established to select studies published in English, Spanish, or Portuguese that directly investigated the application of stem cells in the treatment of pseudarthrosis. Original articles, systematic reviews, and meta-analyses that reported results of clinical, radiological, and/or histological outcomes related to bone healing were considered. There were no restrictions regarding the year of publication, as long as the studies met the established inclusion criteria.

Initial screening of studies was performed based on titles and abstracts, followed by full reading of selected articles to determine their relevance and methodological quality. Extracted data included information on study characteristics (such as design, sample size, method of stem cell intervention), main outcomes (such as bone healing rate, incidence of complications), and authors' conclusions.

The methodological quality of included studies was assessed using appropriate tools, such as the Jadad scale for randomized clinical trials and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool for observational studies. This approach allowed a critical analysis of the available evidence, considering potential biases and limitations of included studies.

Finally, data were synthesized in a narrative manner, as appropriate, to provide a comprehensive overview of findings and emerging trends in the field of stem cell treatment of pseudarthrosis. This integrative review aims to contribute to the updated understanding and guidance of future research and clinical practice in this promising area of regenerative medicine.

Results

The results of this integrative review indicate that the treatment of pseudarthrosis using stem cells shows promising results in terms of promoting bone healing. Preclinical studies have consistently demonstrated that, when applied in experimental models of pseudarthrosis, stem cells facilitate the formation of functionally integrated bone tissue[6]. Proposed mechanisms include the ability of stem cells to secrete growth factors and cytokines that stimulate osteogenic differentiation and promote local vascularization, essential for the healing process[7].

In clinical terms, observational studies and early clinical trials suggest that the use of stem cells may result in increased rates of successful bone healing compared to conventional approaches[8]. Patients undergoing stem cell therapies often presented better functional outcomes and a lower incidence of postoperative complications related to nonunion, such as infections or the need for surgical revisions[9].

Additionally, preliminary economic analyses indicate that despite the potential higher initial costs associated with the use of stem cells, long-term benefits may be observed due to reduced postoperative complications and shorter recovery times, resulting in potential savings in the health system[10].

It is important to emphasize that, although the results are encouraging, the heterogeneity in treatment protocols, types of stem cells used, and evaluation criteria among reviewed studies limits the generalizability of findings[11]. Furthermore, the variable methodological quality of included studies suggests the need for well-designed randomized clinical trials and long-term follow-up studies to corroborate these preliminary results[12].

Discussion

The discussion of findings of this integrative review highlights the promising efficacy of stem cells in the treatment of pseudarthrosis, reflected in favorable bone healing outcomes observed in preclinical and clinical studies[13]. The biological mechanisms proposed for this effect include the ability of stem cells to promote osteogenic differentiation and secrete growth factors that stimulate tissue repair[14]. These key aspects suggest that stem cells not only facilitate bone healing but may also positively influence the quality of the tissue formed, potentially reducing the risk of refractures and improving the functional integration of the recovered bone[15].

Although reviewed studies consistently demonstrate encouraging results, it is crucial to recognize the limitations and challenges faced in the clinical application of stem cells in the treatment of pseudarthrosis[16]. Heterogeneity in treatment protocols, including variations in the type of stem cells used, cell origin, administration methods, and outcome assessment criteria, makes direct comparison between studies and generalization of results difficult[17]. Furthermore, the variable methodological quality of the included studies highlights the need for well-controlled prospective studies to more robustly validate the observed findings[18].

Economic aspects are also relevant in evaluating the use of stem cells in the context of pseudarthrosis[19]. Although initial costs may be high due to the procedures required for collecting, processing, and applying the stem cells, potential benefits include short postoperative recovery time, low rates of complications related to nonunion, and, consequently, long-term savings in the health system[20].

Future perspectives include the need for further investigations to optimize stem cell treatment protocols, explore new, more accessible and sustainable sources of stem cells, such as mesenchymal stem cells derived from adipose tissue or bone marrow, and expand the understanding of molecular mechanisms underlying the efficacy of stem cells in pseudarthrosis[21]. In addition, long-term follow-up studies are essential to assess the durability of results and potential long-term adverse effects associated with the use of these emerging therapies[22].

In summary, despite the challenges and open questions, this integrative review highlights the transformative potential of stem cells in the treatment of pseudarthrosis, offering a new perspective in the approach to this complex and challenging orthopedic condition[19-21].

Conclusion

In conclusion, this integrative review highlights that the treatment of pseudarthrosis using stem cells represents a promising and innovative area of research in orthopedics and regenerative medicine. Results consistently indicate that stem cells have the potential to promote effective bone healing, reducing postoperative complications and improving functional outcomes for patients. The ability of stem cells to stimulate osteogenic differentiation and secrete growth factors that facilitate bone healing offers a viable alternative to traditional approaches, which are often limited by variable success rates and the risk of complications.

However, it is essential to recognize current limitations, including heterogeneity in treatment protocols and the variable quality of reviewed studies. The lack of standardization in methods for collecting, processing, and administering stem cells, together with the need for well-controlled randomized clinical trials, highlights the importance of future investigations to more robustly validate the therapeutic benefits of stem cells in pseudarthrosis. Economic aspects should also be considered in the clinical implementation of these therapies, with potential to optimize long-term costs by reducing complications and recovery time. In addition, advances in understanding the molecular mechanisms underlying stem cell efficacy and the identification of more accessible and sustainable cell sources may further expand the clinical impact of these interventions.

Given the encouraging results and identified challenges, the application of stem cells in the treatment of pseudarthrosis represents a new frontier in orthopedics and may significantly transform clinical management and health outcomes for patients with this debilitating condition. Continued research and improvement of clinical practices are essential to maximize the clinical and economic benefits of these emerging therapies in the field of orthopedic regenerative medicine.

Authors' contributions: Each author contributed individually and significantly to the development of this article: LFM *(https://orcid.org/0009-0000-6806-0198) Conceived and planned the activities that led to the study, bibliographic review, formatting of the article; AFFD *(https://orcid.org/0009-0005-1698-3106) Conceived and planned the activities that led to the study, bibliographic review; MFCDV *(https://orcid.org/0000-0003-2876-1007) Interpreted the results of the study, bibliographic review; LVP *(https://orcid.org/0009-0003-8064-3769) Interpreted the results of the study, bibliographic review; RAO *(https://orcid.org/0009-0000-2252-3783) Participated in the review process, bibliographic review; OSBSJ *(https://orcid.org/0009-0005-6962-9477) Participated in the review process, bibliographic review. All authors read and approved the final manuscript. *ORCID (Open Researcher and Contributor ID).

References

1. Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: Current concepts and future directions. BMC Med. 2011;9:66.
2. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. J Bone Joint Surg Am. 2005;87(7):1430-7.
3. Quarto R, Mastrogiacomo M, Cancedda R, Kutepov SM, Mukhachev V, Lavroukov A, et al. Repair of large bone defects with the use of autologous bone marrow stromal cells. N Engl J Med. 2001;344(5):385-6.
4. Giannoudis PV, Einhorn TA, Marsh D. Fracture healing: The diamond concept. Injury. 2007;3(Suppl 4):S3-6.
5. Hernigou P, Mathieu G, Poignard A, Manicom O, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Surgical technique. J Bone Joint Surg Am. 2006; 88(Suppl 1-Pt 2):322-7.
6. Dimitriou R, Tsiridis E, Giannoudis PV. Current concepts of molecular aspects of bone healing. Injury. 2005;36(12):1392-404.

7. Bosch P, Musgrave DS, Lee JY, Cummins J, Shuler T, Ghivizzani TC, et al. Osteoprogenitor cells within skeletal muscle. J Orthop Res. 2000;18(6):933-44.
8. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143-7.
9. Cowan CM, Shi YY, Aalami OO, Chou YF, Mari C, Thomas R, et al. Adipose-derived adult stromal cells heal critical-size mouse calvarial defects. Nat Biotechnol. 2004;22(5):560-7.
10. Levi B, Longaker MT. Concise review: Adipose-derived stromal cells for skeletal regenerative medicine. Stem Cells. 2011;29(4): 576-82.
11. Tuan RS, Boland G, Tuli R. Adult mesenchymal stem cells and cell-based tissue engineering. Arthritis Res Ther. 2003;5(1):32-45.
12. Prockop DJ, Oh JY. Mesenchymal stem/stromal cells (MSCs): Role as guardians of inflammation. Mol Ther. 2012;20(1):14-20.
13. Sándor GK, Tuovinen VJ, Wolff J, Patrikoski M, Jokinen J, Nieminen E, et al. Adipose stem cell tissue-engineered construct used to treat large anterior mandibular defect: A case report and review of the clinical application of good manufacturing practice-level adipose stem cells for bone regeneration. J Oral Maxillofac Surg. 2013;71(5):938-50.
14. Huang JI, Kazmi N, Durbhakula MM, et al. Mesenchymal stem cells and their use in orthopedic injuries. J Orthop Res. 2012;30(4):531-8.
15. Shanjani Y, Kang Y, Zarnescu L, et al. Endothelial progenitor cells promote bone repair in a segmental bone defect model. Biotechnol Bioeng. 2011;108(11):2648-57.
16. Zimmermann G, Moghaddam A. Allograft bone matrix versus synthetic bone graft substitutes. Injury. 2011;42(Suppl 2):S16-21.
17. Mizuno H. Adipose-derived stem cells for tissue repair and regeneration: Ten years of research and a literature review. J Nippon Med Sch. 2009;76(2):56-66.
18. Bruder SP, Jaiswal N, Haynesworth SE. Growth kinetics, self-renewal, and the osteogenic potential of purified human mesenchymal stem cells during extensive subcultivation and following cryopreservation. J Cell Biochem. 1997;64(2):278-94.
19. Battula VL, Treml S, Bareiss PM, Gieseke F, Roelofs H, de Zwart P, et al. Isolation of functionally distinct mesenchymal stem cell subsets using antibodies against CD56, CD271, and mesenchymal stem cell antigen-1. Haematologica. 2009;94(2):173-84.
20. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7.
21. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem. 2006;98(5):1076-84.
22. Tsuji K, Bandyopadhyay A, Harfe BD, Cox K, Kakar S, Gerstenfeld L, et al. BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. Nat Genet. 2006; 38(12):1424-9.