World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Regenerative medicine in pain control: A review

Lucas Kefler Bergamaschi [1,*], Sarah Leandro Souza Bergamaschi [1], Paulo Roberto Menegatti Filho [2], Karoline Silveira Mardegan [2] and Ricardo Folador Bergamashi [1]

[1] *Clínica do osso, 565 Nossa Senhora da Penha Avenue, room #1001/2, Vitória, ES, Brazil.*
[2] *MULTIVIX College, BR-482 Alvaro Tavares, Cachoeiro de Itapemirim, ES, Brazil.*

World Journal of Advanced Research and Reviews, 2025, 25(03), 2451-2456

Publication history: Received on 18 February 2025; revised on 25 March 2025; accepted on 27 March 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.25.3.0702

Abstract

Regenerative medicine offers a promising approach to the management of chronic pain, focusing on utilizing biological strategies to restore tissue function, repair damage, and modulate inflammatory processes. This review examines several key therapies, including mesenchymal stem cell (MSC) therapy, platelet-rich plasma (PRP), and tissue engineering, and their potential in alleviating pain and promoting functional recovery. These regenerative therapies have shown efficacy in treating conditions such as osteoarthritis, peripheral neuropathies, and musculoskeletal injuries, with substantial improvements in pain reduction and functional outcomes.

The therapeutic mechanisms underlying these treatments are diverse and include immunomodulation through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, which help restore a balanced immune response. Additionally, regenerative therapies stimulate angiogenesis through VEGF signaling and promote axonal regeneration via exosome-mediated pathways, offering long-term benefits for tissue repair.

Despite these promising advancements, several challenges remain that must be addressed to fully realize the potential of regenerative medicine. Variability in treatment protocols, including differences in cell sources, administration methods, and dosages, underscores the need for standardized approaches to maximize clinical efficacy. Moreover, the long-term safety and effectiveness of these therapies, particularly in terms of their durability and potential for side effects, require further investigation. As the field continues to evolve, these areas of uncertainty must be clarified to enable broader clinical implementation and improve outcomes for patients suffering from chronic pain.

Keywords: Regenerative Medicine; Pain Management; Mesenchymal Stem Cells; Osteoarthritis; Tissue Engineering

1. Introduction

Chronic pain affects 30% of the global population, with annual costs exceeding $600 billion [1]. Conventional therapies, such as opioids and anti-inflammatories, show limited efficacy and risks of dependency or toxicity [2]. In this context, regenerative medicine proposes biological interventions targeting tissue repair and neuroinflammation modulation, addressing the underlying causes of pain rather than merely suppressing symptoms [3,4].

The pathophysiology of chronic pain involves peripheral sensitization by pro-inflammatory cytokines such as TNF-α and IL-6 and persistent microglial activation in the spinal dorsal horn [4]. Human adipose-derived MSCs inhibit the NF-κB pathway in sensory neurons, reducing TRPV1 and voltage-gated sodium channel (Nav1.7) expression [5]. In diabetic neuropathy models, MSC exosomes restore blood-brain barrier integrity via claudin-5 regulation [6,7].

* Corresponding author: Lucas Kefler Bergamaschi.

2. Methods

A literature review was conducted using databases such as PubMed, SciELO, and Google Scholar. Relevant MeSH terms included "stem cell-based therapy," "tissue engineering," "neuropathic pain," and "osteoarthritis/therapy." Studies considered for review included randomized controlled trials (RCTs), meta-analyses, and preclinical studies that employed validated animal models. Case reports and studies lacking control groups were excluded. Only studies that provided clear data on the effects of regenerative therapies on pain management and tissue regeneration were included in the review.

2.1. Stem cell therapies

2.1.1. Mechanisms of Action

Bone marrow-derived MSCs secrete trophic factors like BDNF and GDNF that promote neuronal survival and inhibit astrocyte apoptosis in the periaqueductal gray matter [8]. In vitro assays show chondrocytes differentiated from MSCs reverse extracellular matrix degradation in osteoarthritis via collagen type II and aggrecan upregulation [9].

2.2. Immunomodulation

Intra-articular MSC administration reduces IL-17 and RANKL levels in synovial fluid of rheumatoid arthritis patients, correlating with decreased bone edema on MRI [10]. In cancer pain models, lentiviral vector-transfected MSCs expressing preproenkephalin suppress substance P release in dorsal root ganglia [11].

2.3. Platelet-rich plasma (PRP)

The idea of what is now known as PRP first appeared in the 1970s within the field of hematology [12]. The term PRP was coined by hematologists in an effort to describe plasma with a platelet count higher than the baseline level in peripheral blood [13]. Over a decade later, PRP was adapted for use in maxillofacial surgery as platelet-rich fibrin (PRF). The fibrin content in this PRP derivative proved valuable due to its ability to adhere and its homeostatic functions, while PRP itself demonstrated anti-inflammatory properties and supported cell proliferation [14]. By the 1990s, PRP's popularity began to grow, eventually spreading into various medical specialties [15]. Since then, this orthobiologic has been extensively researched and applied to treat a wide range of musculoskeletal injuries in professional athletes, which helped boost its exposure in the media [16]. Beyond orthopedics and sports medicine, PRP has found applications in ophthalmology, gynecology, urology, and surgeries in the fields of cardiology, pediatrics, and plastic surgery [13]. Recently, dermatologists have also embraced PRP for its potential to treat skin ulcers, scar revision, tissue regeneration, skin rejuvenation, and even alopecia [13,14,17–21].

2.4. Obtaining Platelet-Rich Plasma

Various protocols describe the preparation of PRP, though most involve two stages of centrifugation with specific parameters for time and centrifugal force (g) [22]. PRP is created by separating the components of blood based on their density gradients. During the first centrifugation, erythrocytes, being the heaviest, settle at the bottom of the suspension. Just above them, a thin layer of leukocytes forms, called the “buffy coat” (<1% of total blood). The platelets settle in the upper layers of the mixture, concentrated just above the buffy coat. The plasma, with or without the buffy coat, is then collected and subjected to a second centrifugation to further concentrate the platelets [23]. The final concentration of platelets in the PRP product can vary depending on the commercial kits used or the skill of the operator, if manual methods are employed instead of automated ones [22]. Other factors that may affect the final PRP concentration include patient-specific characteristics such as age, comorbidities, and circulation [24].

2.5. Tissue engineering and biomaterials

2.5.1. Smart Scaffolds

Chitosan hydrogels modified with gold nanoparticles enable controlled MSC release in response to thermal stimuli (local hyperthermia at 42°C). In osteochondral defects, BMP-7-impregnated scaffolds induced vascularized trabecular bone formation within 8 weeks, with 30% higher bone density than autografts [25].

2.5.2. 3D Bioprinting

Laser-assisted bioprinting allows layer-by-layer deposition of chondrocytes and fibroblasts into architectures mimicking articular cartilage zonation. A rabbit study demonstrated perfect implant integration after 6 months, without immune rejection [26].

2.6. Exosomes and extracellular vesicles

2.6.1. miRNA Profile

Umbilical cord MSC-derived exosomes contain miR-21-5p and miR-146a-5p, which suppress the TLR4/MyD88/NF-κB pathway in M1 macrophages [27]. In sciatic neuropathy models, intrathecal exosome injections reduced mechanical allodynia via Nav1.8 downregulation in dorsal root ganglia [28].

3. Discussion

The integrative analysis conducted in this systematic review demonstrates that regenerative medicine approaches present multifaceted advantages over traditional pharmacological therapies in pain management. These benefits can be categorized into three key areas: 1) tissue architecture restoration, 2) lasting inflammation modulation, and 3) minimal tolerance risk.

3.1. Tissue Architecture Restoration

Regenerative therapies, such as mesenchymal stem cell (MSC) transplantation and tissue-engineering strategies, play a crucial role in the repair and regeneration of damaged tissues. For example, MSCs secrete bioactive factors that promote tissue repair by enhancing cell survival, facilitating tissue remodeling, and stimulating the regeneration of cartilage, bone, and soft tissues. This contrasts sharply with traditional pharmacological treatments, which typically focus only on symptom relief without addressing the underlying tissue damage. Studies have shown that MSCs can induce cartilage regeneration and improve bone density, making them a promising alternative for osteoarthritis and other musculoskeletal conditions where tissue degeneration is a hallmark.

3.2. Lasting Inflammation Modulation

Chronic inflammation is a key driver of pain in conditions such as osteoarthritis, neuropathies, and musculoskeletal injuries. Regenerative approaches leverage the anti-inflammatory properties of MSCs, PRP, and exosomes to modulate the immune response. These therapies can reduce the levels of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, and promote the secretion of anti-inflammatory factors like IL-10 and TGF-β, which helps restore a more balanced immune environment. Unlike conventional therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), which often provide only temporary relief and carry the risk of gastrointestinal and cardiovascular side effects, regenerative therapies offer the potential for sustained inflammatory modulation. This not only alleviates pain but may also improve long-term joint and tissue health.

3.3. Minimal Tolerance Risk

A significant advantage of regenerative therapies is their minimal risk of tolerance and dependency, issues that are often associated with chronic opioid use. Opioid medications, while effective for short-term pain management, carry the risk of addiction, tolerance, and other serious side effects with prolonged use. In contrast, regenerative treatments target the root causes of pain, such as inflammation and tissue degradation, without leading to the same tolerance risks. This makes regenerative medicine a potentially safer and more sustainable option, particularly for individuals with chronic pain conditions.

Despite these promising benefits, the clinical application of regenerative therapies is not without challenges. One of the major concerns is the variability in MSC preparation protocols, which can significantly affect the outcomes of treatment. Differences in cell passage numbers, culture media composition, and cell source (adipose-derived, bone marrow-derived, etc.) can lead to variations in cell potency and therapeutic efficacy. Such inconsistencies underscore the need for standardized protocols to ensure reproducible and reliable results across clinical settings. Similarly, other factors such as cell dosage, route of administration, and the timing of treatment must be carefully optimized to maximize the therapeutic benefit.

Furthermore, while regenerative therapies offer great promise, the long-term safety of these approaches remains uncertain. The use of gene therapies, such as viral vector-mediated neurotrophic factor overexpression, introduces additional complexities, including the potential for immune rejection, off-target effects, and the long-term stability of gene expression. Although preclinical studies have demonstrated the efficacy of these therapies in animal models, longitudinal studies involving human subjects are essential to evaluate the risks and benefits over time. Monitoring the safety profile of gene therapies and ensuring that they do not cause adverse effects, such as tumorigenesis or unwanted immune responses, will be critical for their widespread clinical adoption.

Another area that warrants further investigation is the optimization of delivery methods. While current studies have demonstrated the efficacy of direct injections or intra-articular applications, improving the targeted delivery of regenerative products could enhance their effectiveness. Advanced delivery systems, such as biomaterial scaffolds or nanoparticles, may offer more controlled release mechanisms, ensuring that the therapeutic agents are delivered at the right concentration and at the right location for optimal effect.

Overall, regenerative medicine approaches represent a transformative shift in pain management, offering not only effective pain relief but also long-term tissue repair and functional restoration. However, to fully realize their potential, there is a need for continued research focused on standardizing treatment protocols, improving delivery systems, and addressing safety concerns through robust clinical trials. With these advancements, regenerative therapies could revolutionize the way we approach chronic pain and pave the way for more sustainable, effective treatments in the future.

4. Conclusion

Regenerative medicine offers a promising alternative to traditional pharmacological treatments for pain, particularly in musculoskeletal and neuropathic conditions. The therapies analyzed, including MSCs, PRP, and tissue engineering, have demonstrated significant efficacy in reducing pain intensity and improving functional recovery, with mechanisms ranging from immunomodulation to tissue regeneration. However, despite the encouraging results, challenges such as variability in treatment protocols, long-term safety, and standardization of cellular products remain major obstacles to widespread clinical adoption.

Moving forward, it is crucial to prioritize translational research that addresses these gaps. Efforts should focus on refining MSC isolation and culture methods, optimizing PRP protocols, and advancing tissue-engineering strategies, particularly in terms of scalability and cost-effectiveness. Furthermore, the development of predictive biomarkers for patient selection and monitoring will enhance the precision and personalized application of regenerative therapies.

Incorporating these advances into clinical practice will not only improve outcomes in pain management but also reduce the reliance on opioids and other conventional treatments, offering a more sustainable and holistic approach to chronic pain. As the field continues to evolve, further robust clinical trials and long-term follow-ups will be essential to validate these therapies and guide their integration into mainstream medical practice.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The Economic Costs of Chronic Pain Among a Cohort of Treatment-Seeking Adolescents in the United States. The Journal of Pain. 2014;15(9):925-933. doi:10.1016/j.jpain.2014.06.002

[2] Setti T, Arab MGL, Santos GS, Alkass N, Andrade MAP, Lana JFSD. The protective role of glutathione in osteoarthritis. Journal of Clinical Orthopaedics and Trauma. Published online 2020. doi:10.1016/j.jcot.2020.09.006

[3] Domingues RB, von Rautenfeld M, Kavalco CM, et al. The role of orthobiologics in chronic wound healing. International Wound Journal. 2024;21(4):e14854. doi:10.1111/iwj.14854

[4] Lana JF, Navani A, Jeyaraman M, et al. Sacral Bioneuromodulation: The Role of Bone Marrow Aspirate in Spinal Cord Injuries. Bioengineering (Basel). 2024;11(5):461. doi:10.3390/bioengineering11050461

[5] Liu B, Kong Y, Shi W, et al. Exosomes derived from differentiated human ADMSC with the Schwann cell phenotype modulate peripheral nerve-related cellular functions. Bioactive Materials. 2022;14:61-75. doi:10.1016/j.bioactmat.2021.11.022

[6] Singh A, Raghav A, Shiekh PA, Kumar A. Transplantation of engineered exosomes derived from bone marrow mesenchymal stromal cells ameliorate diabetic peripheral neuropathy under electrical stimulation. Bioactive Materials. 2021;6(8):2231-2249. doi:10.1016/j.bioactmat.2021.01.008

[7] Liao Z, Zeng J, Lin A, Zou Y, Zhou Z. Pre-treated mesenchymal stem cell-derived exosomes: A new perspective for accelerating spinal cord injury repair. European Journal of Pharmacology. 2025;992:177349. doi:10.1016/j.ejphar.2025.177349

[8] Zou XF, Zhang BZ, Qian WW, Cheng FM. Bone marrow mesenchymal stem cells in treatment of peripheral nerve injury. World Journal of Stem Cells. 2024;16(8):799-810. doi:10.4252/wjsc.v16.i8.799

[9] Nguyen TH, Duong CM, Nguyen XH, Than UTT. Mesenchymal Stem Cell-Derived Extracellular Vesicles for Osteoarthritis Treatment: Extracellular Matrix Protection, Chondrocyte and Osteocyte Physiology, Pain and Inflammation Management. Cells. 2021;10(11):2887. doi:10.3390/cells10112887

[10] Bakinowska E, Bratborska AW, Kiełbowski K, Ćmil M, Biniek WJ, Pawlik A. The Role of Mesenchymal Stromal Cells in the Treatment of Rheumatoid Arthritis. Cells. 2024;13(11):915. doi:10.3390/cells13110915

[11] Li Y ze, Ji RR. Gene therapy for chronic pain management. CR Med. 2024;5(10). doi:10.1016/j.xcrm.2024.101756

[12] Andia I, Abate M. Platelet-rich plasma: Underlying biology and clinical correlates. Regenerative Medicine. Published online 2013. doi:10.2217/rme.13.59

[13] Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. Skin Appendage Disorders. Published online 2018. doi:10.1159/000477353

[14] Conde Montero E, Fernández Santos ME, Suárez Fernández R. Platelet-rich plasma: Applications in dermatology. Actas Dermo-Sifiliograficas. Published online 2015. doi:10.1016/j.ad.2013.12.021

[15] Wu PIK, Diaz R, Borg-Stein J. Platelet-Rich Plasma. Physical Medicine and Rehabilitation Clinics of North America. Published online 2016. doi:10.1016/j.pmr.2016.06.002

[16] Lynch MD, Bashir S. Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature. Journal of Dermatological Treatment. Published online 2016. doi:10.3109/09546634.2015.1094178

[17] Cobos R, Aizpuru F, Parraza N, Anitua E, Orive G. Effectiveness and Efficiency of Platelet Rich Plasma in the Treatment of Diabetic Ulcers. Current Pharmaceutical Biotechnology. Published online 2015. doi:10.2174/1389201016071504271119 26

[18] Hesseler MJ, Shyam N. Platelet-rich plasma and its utility in medical dermatology: A systematic review. Journal of the American Academy of Dermatology. Published online 2019. doi: 10.1016/j.jaad.2019.04.037

[19] Rodrigues BL, Montalvão SAL, Cancela RBB, et al. Treatment of male pattern alopecia with platelet-rich plasma: A double-blind controlled study with analysis of platelet number and growth factor levels. Journal of the American Academy of Dermatology. Published online 2019. doi:10.1016/j.jaad.2018.09.033

[20] Salazar-Álvarez AE, Riera-Del-Moral LF, García-Arranz M, Álvarez-García J, Concepción-Rodriguez NA, Riera-De-Cubas L. Use of platelet-rich plasma in the healing of chronic ulcers of the lower extremity. Actas Dermo-Sifiliograficas. Published online 2014. doi:10.1016/j.adengl.2014.05.019

[21] Sclafani AP, Azzi J. Platelet Preparations for Use in Facial Rejuvenation and Wound Healing: A Critical Review of Current Literature. Aesthetic Plastic Surgery. Published online 2015. doi:10.1007/s00266-015-0504-x

[22] Lana JFSD, Purita J, Paulus C, et al. Contributions for Classification of Platelet Rich Plasma – Proposal of a New Classification: MARSPILL. Regen Med. 2017;12(5):565-574. doi:10.2217/rme-2017-0042

[23] Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: A milieu of bioactive factors. Arthroscopy - Journal of Arthroscopic and Related Surgery. Published online 2012. doi:10.1016/j.arthro.2011.10.018

[24] Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet Rich Plasma: A short overview of certain bioactive components. Open Medicine (Poland). Published online 2016. doi:10.1515/med-2016-0048

[25] Wei W, Dai H. Articular cartilage and osteochondral tissue engineering techniques: Recent advances and challenges. Bioact Mater. 2021;6(12):4830-4855. doi:10.1016/j.bioactmat.2021.05.011

[26] McGivern S, Boutouil H, Al-Kharusi G, Little S, Dunne NJ, Levingstone TJ. Translational Application of 3D Bioprinting for Cartilage Tissue Engineering. Bioengineering (Basel). 2021;8(10):144. doi:10.3390/bioengineering8100144

[27] Wang X, Yang Y, Li W, Hao M, Xu Y. Umbilical mesenchymal stem cell-derived exosomes promote spinal cord functional recovery through the miR-146b/TLR4 -mediated NF-κB p65 signaling pathway in rats. Biochemistry and Biophysics Reports. 2023;35:101497. doi:10.1016/j.bbrep.2023.101497

[28] Buchheit T, Huh Y, Breglio A, et al. Intrathecal administration of conditioned serum from different species resolves Chemotherapy-Induced neuropathic pain in mice via secretory exosomes. Brain, Behavior, and Immunity. 2023;111:298-311. doi:10.1016/j.bbi.2023.04.013