West Kazakhstan Medical Journal
Volume 67, Issue 2, DOI 10.18502/wkmj.v67i2.17125
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Mini Review

Pulp Necrosis Treatment: Evaluating the Effectiveness of Stem Cell Therapy: A Minireview

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Abstract

Pulp necrosis, a prevalent condition in endodontics, poses significant challenges in preserving tooth vitality and function. Traditional treatment methods like root canal therapy often focus on managing symptoms and controlling the infection rather than promoting natural tissue regeneration. This article evaluates the effectiveness of stem cell therapy as an innovative approach to treating pulp necrosis. We review recent advancements and clinical trials that explore the regenerative potential of stem cells, including mesenchymal stem cells (MSCs), from various sources. The review highlights the underlying mechanisms of stem cell therapy, such as differentiation and angiogenesis, and compares these to conventional methods in terms of efficacy and patient outcomes. By examining the current state of research, challenges, and future directions, this article aims to provide a comprehensive understanding of how stem cell therapy could revolutionize the treatment of pulp necrosis and improve clinical practice.

Keywords: pulp necrosis, stem cell therapy, mesenchymal stem cells, regenerative endodontics, tooth vitality, angiogenesis

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Received: 7 September 2024
Accepted: 15 October 2024
Published: 2 June 2025

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1. Introduction

Pulp necrosis, also known as pulp death, is a condition characterized by the irreversible loss of vitality in the dental pulp, the soft tissue inside the tooth that contains nerves, blood vessels, and connective tissue [1]. This condition often arises due to severe dental caries, trauma, or repeated dental procedures that compromise the health of the pulp [2]. The prevalence of pulp necrosis is significant, with studies indicating that it affects a substantial proportion of the adult population [3]. According to epidemiological data, pulp necrosis can occur in up to 25% of patients undergoing endodontic treatment, making it a common and critical concern in dental practice [4].

Traditional treatment methods for pulp necrosis primarily involve endodontic therapy, commonly referred to as root canal therapy [5]. The procedure aims to remove the necrotic pulp tissue, disinfect the root canals, and fill them with a biocompatible material to prevent reinfection [6]. While root canal therapy is generally effective in resolving symptoms and preserving the tooth, it has limitations like potential complications related to canal anatomy, reinfection, and the inability to regenerate lost pulp tissue [7]. Despite advancements in endodontic techniques and materials, the challenge of achieving complete pulp regeneration remains a significant issue [8].

In recent years, stem cell therapy has emerged as a promising alternative to conventional treatments, particularly in regenerative medicine [9]. Stem cells are undifferentiated cells with the unique ability to differentiate into various cell types and regenerate damaged tissues [10], and restore the vitality and functionality of the dental pulp [11]. This concept aligns with the principles of regenerative endodontics, aiming to biologically restore the structural and functional integrity of the pulp tissue [12]. Stem cells derived from different sources, including dental pulp, dental follicle, and bone marrow, have demonstrated the potential to differentiate into odontoblast-like cells, produce dentin-like tissue, and promote vascularization within the pulp chamber [9, 13].

This regenerative potential addresses the limitations of traditional endodontic therapies by aiming to restore the natural pulp environment and its functions. Furthermore, stem cell-based approaches may offer improved clinical outcomes, reduce the risk of reinfection, and enhance long-term tooth survival [14].

As research continues to evolve, the integration of stem cell therapy into clinical practice presents an exciting opportunity to advance the treatment of pulp necrosis and improve patient outcomes. The subsequent sections of this article will delve into the specifics of stem cell therapy, review recent clinical studies, and explore the potential impact of this innovative approach on endodontic care.

2. Stem Cell Therapy for Pulp Necrosis

2.1. Types of stem cells used

Stem cell therapy for pulp necrosis primarily involves mesenchymal stem cells (MSCs), which are multipotent cells capable of differentiating into various cell types and contributing to tissue regeneration [11]. r Dental pulp stem cells (DPSCs) are isolated from the dental pulp of healthy, extracted teeth [15]. They possess the ability to differentiate into odontoblast-like cells, which are essential for forming dentin-like tissue [16]. DPSCs are advantageous due to their direct origin from the target tissue, which makes them highly suitable for pulp regeneration [17]. DPSCs are the most directly relevant to pulp regeneration, with strong potential for odontoblast differentiation and tissue formation [18]. However, their availability is limited to extracted teeth, which may not always be accessible or practical [15].

Dental follicle stem cells (DFSCs) are derived from the dental follicle, a tissue surrounding the developing tooth [19]. These stem cells have shown potential for differentiating into various cell types, including odontoblasts and cementoblasts [20]. Their advantage lies in their ability to contribute to the regeneration of both pulp and periodontal tissues, making them versatile [21, 22]. However, their isolation process can be more invasive, as it involves the extraction of developing teeth [7].

Bone marrow-derived stem cells (BMSCs) are obtained from the bone marrow and have been widely studied for their regenerative capabilities [23]. Although not specific to dental tissues, BMSCs can differentiate into odontoblast-like cells and support pulp regeneration through paracrine-signaling and cell-mediated mechanisms [24]. BMSCs are widely available and have extensive research backing their regenerative properties [25]. However, their differentiation potential into odontoblast-like cells is less specific compared to DPSCs [26].

Adipose-derived stem cells (ADSCs) are harvested from adipose tissue and have shown promise in regenerative applications due to their ease of procurement and multi-lineage differentiation potential [27]. They have been explored for pulp regeneration due to their ability to secrete growth factors and promote tissue repair [28]. ADSCs are advantageous due to their abundance and less invasive harvesting method [29]. Nevertheless, their differentiation into odontoblasts is less well-established compared to DPSCs [30].

2.2. Mechanisms of action

The regenerative processes involved in stem cell therapy for pulp necrosis are multifaceted and include differentiation, angiogenesis, anti-inflammatory effects, and cell-cell and cell-matrix interactions [31]. MSCs differentiate into odontoblast-like cells, which produce dentin-like tissue and support the restoration of the pulp's structural and functional properties [32]. MSCs secrete various cytokines and growth factors that modulate the inflammatory response within the pulp [33]. By reducing inflammation, stem cells create a more favorable environment for tissue regeneration [34]. In addition, they interact with surrounding cells

and the extracellular matrix, thereby promoting tissue repair [35] and contributing to the organization and structuring of newly formed pulp tissue [36]. This regenerative process is further supported by growth factors, signaling molecules, and microenvironmental cues that establish a conducive niche for pulp tissue development [37]. MSCs themselves can differentiate into specialized cells such as chondrocytes, osteocytes, and myocytes, directly contributing to the regeneration of cartilage, bone, and muscle tissues [60].

Key growth factors involved in pulp regeneration include:

Bone morphogenetic proteins (BMPs): These proteins play a critical role in the differentiation of MSCs into odontoblast-like cells [38]. BMP-2, for example, has been shown to enhance odontogenic differentiation by promoting the formation of dentin-like tissue and supporting pulp vitality [39].

Fibroblast growth factors (FGFs): FGFs, particularly FGF-2, contribute to the proliferation and differentiation of DPSCs [40, 41]. FGF signaling also supports the formation of new blood vessels (angiogenesis), which is essential for establishing a vascular supply within the regenerating pulp [42].

Vascular endothelial growth factor (VEGF): VEGF is another key growth factor that promotes angiogenesis within the pulp [43, 44]. This vascularization is critical for nutrient supply, oxygenation, and overall tissue survival and integration [45].

Signaling pathways that guide stem cell behavior in pulp necrosis therapy include:

Wnt signaling pathway: The Wnt/β-catenin pathway is known to regulate the proliferation and differentiation of stem cells into odontoblast-like cells [46]. Activation of Wnt signaling enhances the formation of dentin and supports tissue regeneration in the pulp [47].

Notch signaling pathway: This pathway influences cell fate determination and differentiation during tissue repair [48]. Notch signaling plays a role in the regulation of stem cell differentiation, helping to maintain the balance between stem cell self-renewal and differentiation (49).

Microenvironmental factors that influence stem cell activity during regeneration include:

Extracellular matrix (ECM): The ECM provides structural support and biochemical signals that guide stem cell behavior [50]. Components such as collagen and fibronectin interact with integrins on the surface of stem cells, promoting adhesion, migration, and differentiation [51].

Oxygen tension: Low oxygen levels (hypoxia) within the pulp tissue can influence stem cell differentiation [52]. Hypoxic conditions have been shown to enhance the osteogenic and odontogenic differentiation of DPSCs by activating hypoxia-inducible factors (HIFs) which play a role in tissue repair and regeneration [53]. These multifaceted actions underscore the potential of stem cells, particularly MSCs, as therapeutic tools in regenerative medicine (Figure **1**).

By integrating growth factors, signaling pathways, and microenvironmental elements, stem cell therapy can offer a more natural restoration of tooth vitality compared to conventional treatments. These processes are essential in guiding the differentiation of MCSs, enhancing tissue integration, and improving the clinical outcomes of regenerative endodontics.

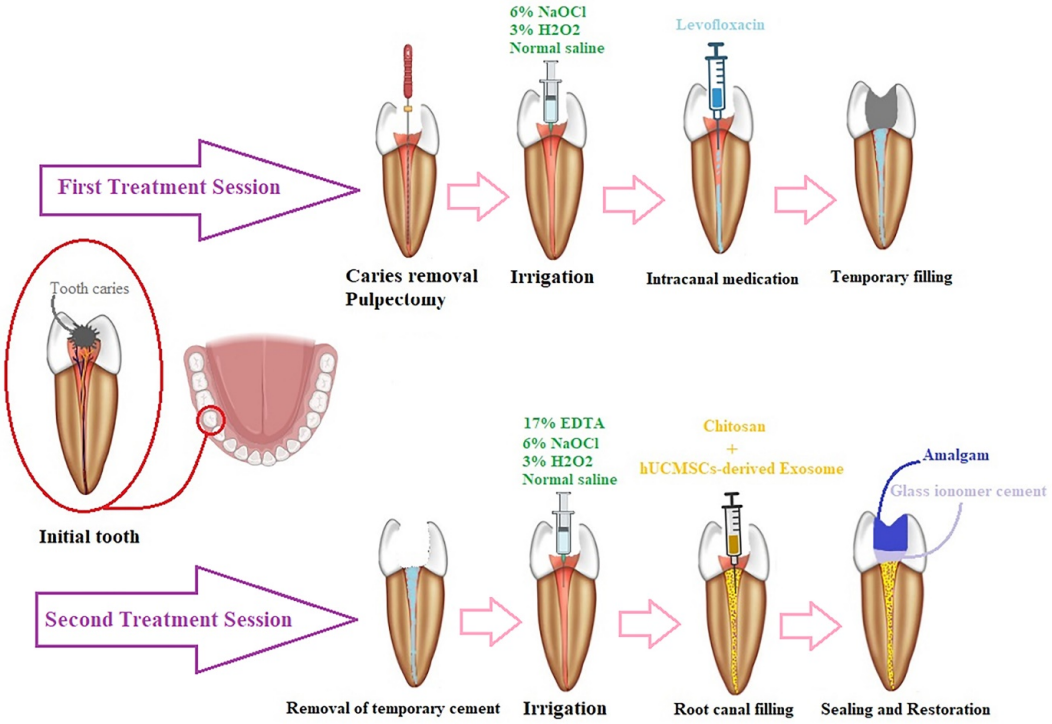

Figure 1: A schematic overview of the treatment process, detailing each step involved in the procedure. It shows the sequential stages of root canal preparation, the introduction of exosomes derived from human umbilical cord mesenchymal stromal/stem cells (hUCMSCs) combined with chitosan into the root canal, followed by the final cavity sealing using glass ionomer cement. Reproduced with permission from reference [61].

3. Review of Clinical Studies

Recent research has highlighted significant advancements in the use of stem cell therapy for pulp necrosis. Clinical trials and studies have explored various aspects of this innovative approach, revealing promising results (Table **1**).

4. Challenges and Future Directions

One of the primary technical challenges in stem cell therapy is the efficient and ethical sourcing of stem cells. Obtaining high-quality stem cells from sources such as dental pulp, dental follicle, or adipose tissue can be complex and resource-intensive. Additionally, maintaining stem cell viability and functionality during processing, storage, and transplantation requires meticulous handling and advanced techniques.

Furthermore, ensuring that stem cells differentiate into the appropriate cell types and integrate effectively with existing dental tissue is a significant biological challenge. Variability in differentiation outcomes, cell survival, and integration can impact the overall success of the therapy. Achieving consistent and predictable results remains an area of active research.

Table 1: Overview of clinical studies on stem cell therapy for pulp necrosis.

Stem Cell Type	Patient Population	Condition Treated	Methodology	Follow-up Period	Key Findings	References
DPSCs	36 patients, 26 incisors with dental trauma	Pulp necrosis	Autologous hDPSC aggregates implanted with extracellular matrix	1, 3, 6, 9, 12, and 24 months	3D regeneration of dental pulp, no significant side effects, no inflammation, root development continued, decrease in apical foramen width, increased root length, improved vascularization	[63]
Autologous DPSCs + GMP-grade G-CSF	5 adult patients with irreversible pulpitis	Irreversible pulpitis	DPSCs and G-CSF transplantation	4 weeks	Strong positive response to electric pulp testing in 4 patients, functional dentin formation confirmed in 3 patients, no adverse events or toxicity	[63]
DPSCs + L-PRF	1 patient with mature permanent tooth	Irreversible pulpitis	DPSCs + L-PRF transplanted into disinfected root canal	6 months, 3 years	Tooth responded to cold and electric pulp tests, vitality tests showed low blood perfusion, effective and safe therapy but limited by high costs and need for GMP-grade laboratory	[64]
Dental pulp from third molar	3 patients with single-rooted premolars	Pulp necrosis requiring RCT	Dental pulp autotransplantation	3, 6, 9, 12 months	Positive pulp vitality, regression of periapical lesions at 3 and 6 months, revascularization confirmed by Doppler imaging after 9–12 months. Promising, but requires larger clinical trials for validation	[65]

Although autologous stem cells (derived from the patient's own tissues) generally have a lower risk of immune rejection, the use of allogeneic (donor-derived) stem cells poses a risk of immunological complications. Addressing immune compatibility and minimizing adverse reactions are crucial for successful therapy.

Developing scalable and standardized protocols for stem cell isolation, processing, and application is essential for translating research findings into clinical practice. Variability in these processes can affect the reproducibility and effectiveness of treatments.

5. Conclusions

The evaluation of stem cell therapy for pulp necrosis reveals several key insights into its potential benefits and current limitations. Stem cell therapy, particularly using MSCs from dental pulp, dental follicle, or other sources, demonstrates a promising alternative to traditional root canal treatments. Recent clinical

trials and studies have shown that stem cell-based approaches can enhance pulp tissue regeneration, promote dentin formation, and improve clinical outcomes. Stem cell therapy for pulp necrosis represents a significant advancement in regenerative endodontics, offering the potential for improved outcomes and enhanced patient care. While challenges remain, ongoing research and innovation hold the promise of overcoming these obstacles and establishing stem cell therapy as a viable and effective treatment option in clinical practice.

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