

Dental Pulpal Tissue Regeneration, Pulpal Vitality Testing, and Healing of Apical Lesions Following Stem Cell Transplant: A Systematic Review and Meta-Analysis

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Abstract

Objective: To analyze data obtained from animal and human studies using stem cells. **Material and Methods:** Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, Cochrane Library, Embase, Information Sciences Institute (ISI), as well as Google Scholar were utilized and searched as available electronic databases to perform a systematic literature review of articles published between 2010 and 2019. The Endnote X9 for Windows was also employed to manage electronic titles and abstracts of the selected studies. Searches were conducted using keywords of “pulpal OR pulpal tissue OR pulpal vitality”, “regeneration”, “apical healing”, “stem cells OR progenitor cells”, and “mediated pulpal tissue”. Consequently, 189 titles and abstracts endowed with potential relevance were discovered based on searches into manual and electronic sources. Ultimately, a total of six articles met the inclusion criteria in the present systematic review and meta-analysis. **Results:** Out of the six articles identified and selected, five studies were categorized as animal experiments and one article was nominated as a human clinical trial. The greatest bias risks were accordingly observed in the majority of animal examinations, but articles related to humans revealed decreased risks of bias, while the human clinical trial showed some concerns. **Conclusion:** Promising parameters testing functional pulp regeneration could be represented through stem cell transplants.

Keywords: Endodontics; Dental Pulp; Dental Pulp Test; Stem Cells.

Introduction

The main goals of mechanical preparation of root canals are to remove vital or necrotic pulp tissues, to eliminate infected dentin, and to provide space for disinfecting agents along with filling materials [1]. As stated by researchers, regenerative medicine is among one of the increasingly growing fields associated with the creation of living functional tissues for repairing or replacing functions of tissues or organs missed as a result of various diseases, aging, lesions, or even congenital defects [2].

There have been many attempts for a long time to induce regeneration of tissues in pulp space. Actually, biodegradable synthetic materials of polyglycolic acid (PGA) seeded with pulp cells have been used to explore pulp tissue regeneration. Outputs have further specified the formation of pulp-like tissues in in-vivo and in-vitro models [3]. Even though a large number of research studies have tested stem cell-mediated regenerative endodontics with the help of animal models, outputs obtained through human clinical trials are recently available [4].

Current research has made use of a greater and more various series of findings that can clinically represent relevant dimensions of regeneration with higher similarities in comparison with previous ones [5,6]. Given the use of dental stem cells in regenerating and repairing teeth as well as their differentiation potentials, such mesenchymal stem cells (MSCs) can be promising for tooth repair.

Thus, developing the regeneration of dental tissues can denote an appropriate but demanding objective for treating dental stem cells [7]. As a whole, data obtained from human and animal investigations on stem cells were collected to meet the objectives of the present systematic review and meta-analysis.

Material and Methods

Search Strategy

Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, Cochrane Library, Embase, Information Sciences Institute (ISI), and Google Scholar were utilized as electronic databases for a systematic literature review of articles published between 2010 and 2019. Therefore, the Endnote X9 for Windows was applied to manage electronic titles and abstracts. Searches were also conducted using keywords of “pulpal OR pulpal tissue OR pulpal vitality” “regeneration”, “apical healing”, “stem cells OR progenitor cells”, and “mediated pulpal tissue”.

Exclusion and Inclusion Criteria

The following inclusion criteria were implemented in this systematic review and meta-analysis: Animal or human studies; Use of intra-pulpal regeneration models; Adoption of oral-pulpal regeneration models; Stem cell transplant as pellet; Stem cell transplant as a carrier; No stem cell transplant in control groups; and Randomized controlled studies and controlled clinical trials. The following exclusion criteria were also met: Control groups with an active cellular transplant.

Quality Evaluation of Selected Articles

The methodological quality of human examinations was assessed using the risk of bias method recommended by the Cochrane Collaboration. The Guide for the Care and Use of Laboratory Animals was also utilized for animal studies [8,9].

Data Extraction and Analysis Procedure

Baseline and outcome information were independently abstracted; then, study designs were extracted. Afterwards, heterogeneity of the randomized clinical trials (RCTs) and meta-analysis (95% confidence interval and weighted mean difference) was evaluated and forest plots were drawn using the Comprehensive Meta-Analysis Stata (version 14).

Results

A total of 189 research titles and abstracts with potential relevance were consequently found based on searches into manual and electronic sources. However, 76 studies were excluded with regard to their titles and abstracts during the initial phase of article selection. Then, 94 full-text articles obtained from the remaining 113 studies were assessed completely within the second phase because the given articles could not meet the inclusion criteria. Ultimately, six articles, in accordance with the inclusion criteria, were used for this systematic review and meta-analysis (Figure 1 and Tables 1 and 2).

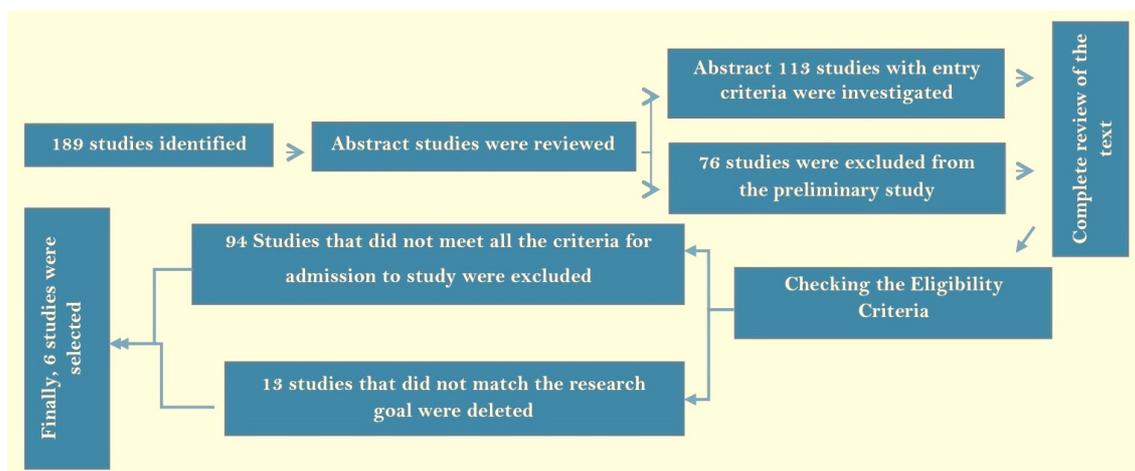


Figure 1. Study attrition diagram.

According to the research design, two articles were randomly allocated to each control and treatment group in order to fulfill animal examinations [10,11]. All the studies had parallel-group designs except one, conducted on dogs [12]. Studies had also utilized minipigs in their transplant models and dogs as experimental models except one [11]. Two studies had also addressed the transplant of allogeneic stem cells in experimental deficiencies [10,11] and three studies had transplanted autogenous cells [12-14]. One study had been limited to human clinical trials [4]. The risk of bias in animal examinations had also increased. In addition, risks of selection, function, and detection bias had enhanced (Table 3) and the overall estimated bias risks had been followed by a number of issues for the human clinical trial (Table 4). According to Figure 2, pulp regeneration is higher in the experimental group compared with that in the control one. All the studies had also found dental pulp stem cells (DPSCs) considerably better for regenerating pulp in comparison with experimental groups. Furthermore, findings about healing of apical lesions had revealed that DPSCs were superior to controls.

Table 1. Selected studies to enter systematic review and meta-analysis.

Study/Year	No. Teeth	Animal or Human Model	Blind Random	Design	Stem Cells' Source	Defects	Scaffold/ Carrier	Group	
								Test	Control
El Ashiry et al. (2018) [12]	36	12 Dogs	Randomly	Split	DPSCs; Autologous	Pulps from crown and root	Chitosan Hydrogel Scaffold	DPSCs + growth factors + scaffold	Growth factors + scaffold
Xuan et al. (2018) [4]	26	40 Patients	Randomly	Parallel	Human Deciduous	-----	-----	hDPSCc	Apexification (CaOH)
Jia et al. (2016) [13]	18	2 Dogs	Randomly	Parallel	Canine DPSCs; Autologous	Pulp chamber until root	Absorbable Gelatin Sponge	1. Canine DPSCs (cDPSCs) 2. SCG group SIM + cDPSCs + gelatin sponge	1. The mineral trioxide aggregate 2. Absorbable gelatin sponge
Iohara et al. (2014) [14]	16	4 Dogs	Randomly	Parallel	MDPSCs; Autologous	Whole pulp removed, apical foramen enlarged to 0.5 mm	Atelocoll Agen Scaffold	young MDPSCs with G-CSF	Aged MDPSCs with G-CSF
Iohara et al. (2013) [10]	72	18 Dogs	Randomly	Parallel	DPSCs; Allogenic	Whole pulp removed, apical foramen enlarged to 0.6 mm	Atelo Collagen; Collagen	1. DPSCs/G-CSF /atelo-collagen 2. DPSCs 3. G-CSF	1. Total pulp cells/ G-CSF 2. Total pulp cells 3. Collagen
Zheng et al. (2012) [11]	56	7 Mini Pigs	Randomly	Parallel	SHEDs; Allogenic	Pulp chamber defects (3-4 mm diameter)	β -TCP Scaffolds	1. DPSCs/ β -TCP	1. Ca(OH) ₂ 2. β -TCP

Table 2. Outcome of pulp tissue regeneration, apical healing and pulp vitality.

Study	Pulp Tissue Regeneration (Mean ± SD)		Apical Healing N (%)		Pulp Vitality	
	Test	Control	Test	Control	Test	Control
El Ashiry et al. [12]	Not reported	Not reported	12 (83.33%)	(83.33%)	Radicular Walls - N (%)	
					12 (91.67%)	12 (25.0%)
					Root Lengthening - N (%)	
					12 (75.0%)	12 (16.67%)
					Apical Closure - N (%)	
					12 (75.0%)	12 (16.67%)
Xuan et al. [4]	Not reported	Not reported	Not reported	Not reported	Root Lengthening (Mean ± SD)	
					10.69 ± 1.32 mm	9.99 ± 0.82 mm
					Apical Closure (Mean ± SD)	
					3.17 ± 0.69 mm	3.54 ± 0.44 mm
					Laser Doppler (Mean ± SD)	
					2.81 ± 0.41	3.01 ± 0.44
Jia et al. [13]	Soft Tissue Regeneration		Not reported	Not reported	Not reported	Not reported
	76.8 ± 4.3	47.3 ± 2.5				
Iohara et al. [14]	Soft Tissue Regeneration		Not reported	Not reported	Not reported	Not reported
	60 ± 3.0	9.6 ± 2.9				
Iohara et al. [10]	Soft Tissue Regeneration		Not reported	Not reported	Not reported	Not reported
	13.5 ± 5.5	9.6 ± 2.9				
	Vascularization					
	3.1 ± 0.2	1.8 ± 0.3				
	Neural Regeneration					
1.5 ± 0.2	0.1 ± 0.1					
Zheng et al. [11]	Dentine Regeneration		Not reported	Not reported	Not reported	Not reported
	81.4 ± 7.3	34.6 ± 4.5				

Table 3. Risk of bias of animal studies by SYRCLE guideline.

Risk of Bias	Animal Studies				
	Iohara et al. [10]	Zheng et al. [11]	El Ashiry et al. [12]	Jia et al. [13]	Iohara et al. [14]
Selection Bias					
Sequence	Yes	Yes	No	No	No
Baseline	Yes	Yes	Yes	Yes	Yes
Allocation	Unclear	No	No	No	No
Performance Bias					
Random	Unclear	Unclear	Unclear	Unclear	Unclear
Blinding	No	No	No	No	No
Detection Bias					
Random Outcome	No	Yes	No	No	No
Blinding	No	No	No	No	No
Attrition Bias	Unclear	Unclear	Unclear	Unclear	Unclear
Reporting Bias	Unclear	Unclear	Unclear	Unclear	Unclear
Other Bias	No	No	No	No	No

Table 4. Risk of bias of human trial with Cochrane Risk of Bias Tool for RCTs.

Risk of Bias	Human Trial Xuan et al. [4]
Randomization Process	Low
Deviation from the Intended Intervention	Effect of Assignment Adhering to Intervention Low
Missing Outcome Data	SC
Measuring of the Outcome	Low
Selection of the Reported Result	Low
Overall Risk of Bias	SC

SC: Some concerns.

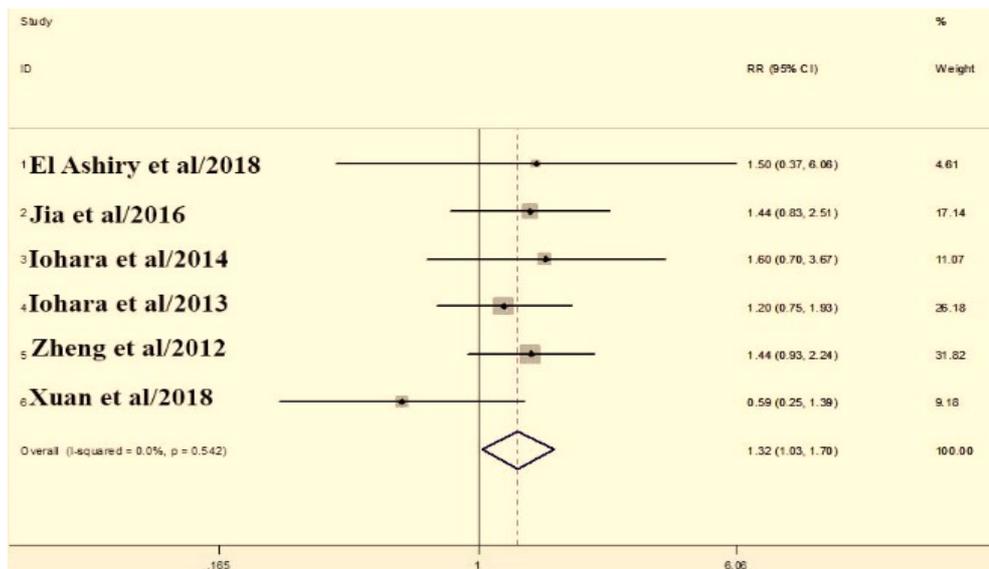


Figure 2. Forest plots showed heterogeneity chi-squared of the strength of the recommendation regarding the effect of stem/progenitor cells' transplantation on pulpal tissue regeneration. Test of RR=1 : z= 2.18; p = 0.029. Risk of Bias: very serious; Strength of Quality: Very Low; Magnitude of the Effect: Large.

Discussion

Studies conducted in this area demonstrated multiple forms of stem cells, such as pluripotent and mature stem cells. In fact, it is assumed that pluripotent stem cells, including induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are among emerging instruments in regenerative medicine. However, it is necessary to resolve numerous issues, e.g., safety and ethical problems prior to the utilization of these tools in clinical settings [15].

It should be noted that researchers have mostly examined MSCs derived from bone marrow and utilized mature stem cells clinically [16]. Moreover, recent research studies have discovered that dental pulp is one of the potent sources of alternative candidate stem cells to be used in clinical settings because of its increased capability for rapid growth and proliferation that is also useful for cellular therapies in diverse utilizations. Additionally, it is possible to obtain dental pulp safely and conveniently from inessential teeth with no considerable unhealthful conditions or ethical problems [16-19].

It is also noteworthy that transplant of DPSCs has been done into human mandibles in clinical settings, demonstrating regeneration of compact bone in spite of uncommon alveolar spongy bone. Nonetheless, no publications were found about the safety of transplant of DPSCs in none of the diseases in clinical settings. A previous study also indicated that no tumor had been formed by mesenchymal dental pulp stem cells (MDPSCs) separated from humans and dogs with regard to good manufacturing practice (GMP) condition as they had been transplanted into NOD scid gamma (NOD/SCID) mice or KSN nude mice [20].

In addition, it is possible to use DPSCs in diverse areas including tissue engineering and regenerative medicine as a result of their increased capability for proliferation and multilineage differentiated capability [21]. Therefore, this can be one of the options for iPSC to solve issues related to reprogramming and epigenetic alterations [22]. Moreover, it is notable that treating dental stem cells would adopt multi-directional differentiation characters for reconstructing normal cell functions or repair of diseased ones [23-25].

In this review of pulp regeneration, publication biases and allusiveness characteristics were also reported, although the data were scattered and partly incompatible. Besides, human examinations considered in this review exhibited lower risks of bias. This systematic review also demonstrated a potential for regenerating stem cell-mediated pulpal tissue, due to discovered heterogeneity and numerous limitations outlined before. Finally, it should be mentioned that, based on the five animal examinations and one human clinical trial with heterogeneous research approaches, the potential of stem cell transplant would be one of the therapeutic approaches for achieving functional dental pulp regeneration.

Conclusion

Promising parameters testing functional pulp regeneration can be represented by transplanting stem cells that include vascular and neural regeneration. Therefore, the given parameters should be designed and evenly utilized in high-quality and rigorously programmed examinations for providing similar and valid documents at the earliest opportunity. In fact, further research must utilize procedure assessment, e.g., its usability and patient's admission, and reveal economic dimensions with the help of suitable outcomes.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

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