

## Original Research Article

# Profile of articles addressed to dental pulp revascularization in PubMed database

Renata Grazziotin-Soares<sup>1</sup>  
Gabriela Bess Ferraz Blattes<sup>1</sup>  
Matheus Neves<sup>2</sup>

### Corresponding author:

Renata Grazziotin-Soares  
Departamento de Odontologia Conservadora – Área de Endodontia  
Faculdade de Odontologia – Universidade Federal do Rio Grande do Sul  
Rua Ramiro Barcelos, n. 2.492 – Santana  
CEP 90035-003 – Porto Alegre – RS – Brasil  
E-mail: renata.grazziotin@ufrgs.br

<sup>1</sup> Department of Conservative Dentistry, School of Dentistry, Federal University of Rio Grande do Sul – Porto Alegre – RS – Brazil.

<sup>2</sup> Department of Dentistry and Society, School of Dentistry, Lutheran University of Brazil – Canoas – RS – Brazil.

*Received for publication: January 12, 2015. Accepted for publication: February 28, 2015.*

### Keywords:

articles; endodontic;  
scientific publication;  
pulp revascularization.

## Abstract

**Introduction:** The study aimed to explore the profile of articles published on pulp revascularization by a bibliometric analysis. **Material and methods:** A search was conducted on the PubMed database and studies were independently categorized according to: (i) year of publication; (ii) country where the study was conducted; (iii) study design; (iv) main topic addressed; (v) main conclusion of the article; and (vi) clinical application/other results. Findings were reported descriptively. There was not restriction regarding to initial date and the established final date was December 2014. **Results:** 133 studies were found; but only 86 articles were included. The most of them was published recently (23.2% in 2014) and were conducted in 24 different countries. The most frequent study design was case report (37.2%), followed by narrative reviews (16.2%). The main topic addressed was the radiographic outcomes (38.3%) and tissue engineering (19.7%). Some of the articles point the clinical application of their results. **Conclusion:** Most of the publications highlight that the disinfection of the root canal (and the stimulation of residual stem cells) would induce formation of new hard tissue on the dentin wall and continue root development in length, improving the tooth survival. The number of publications on pulp revascularization has increased recently, but the majority of articles published are studies with low levels of evidence.

## Introduction

Nowadays, the revascularization therapy has gained a prominent role in the literature, which increasingly publications every year. This therapy is focused on necrotic permanent immature teeth and it can be considered an expectance to improve the quality of life of many individuals in the society.

The interruption of the root development in permanent teeth results from the pulp necrosis, which might be a consequence of a traumatic dental injury (where boys aged 8 – 12 are more susceptible). The root maturation of a central incisor, for example, occurs 3 or 4 years after the eruption of the teeth, *i.e.*, around the aged of 8-9. When the teeth present pulp necrosis at this specific period, the rhizogenesis might be interrupted. In the cases where the treatment is not performed, the patient might spend a long time of his/her life with the necrotic tooth without a diagnosis. Thus, the cases of permanent immature teeth is a challenging to the maintenance of the patient's health, and causes pain, chewing difficulties, undesirable esthetic effects and psychological disorders. Added to the implications to the patients, the treatment of permanent necrotic immature teeth also represents a challenging to the clinicians due to several factors associated with the conventional therapy generally used, the so called apexification technique [21].

The revascularization is an alternative therapy to the apexification. The new approach was initially reported by Rule and Winter [22], Iwaya *et al.* [16] and Banchs and Trope [1], and it involves disinfection of the root canal with sodium hypochlorite (NaOCl) and use of a triple antibiotic paste (ciprofloxacin, metronidazole and minocycline) as intra canal medication [15]. In a second appointment, bleeding inside the root canal should be achieved. The blood clot formed inside the root canal would act as a matrix for the migration of the progenitor cells from the apical papilla to the canal lumen [1]. Finally, the cervical portion of the canal should be sealed with MTA and a definitive restoration.

Considering that the pulp revascularization therapy is a relatively new approach in the literature and that clinicians should support their clinical decisions in the evidences currently available, it is essential to assemble and report the profile of articles published on pulp revascularization. The bibliometric analysis (to explore the profiles of articles) is used in the biomedical field aiming to collect data to development of policies (scientific and technologic) focused on the needs of investigators, health care administrators and institutions. In spite

of that, this type of study is still uncommon in endodontics, mainly to analyze articles addressed to pulp revascularization [20].

The aim of this study is to identify and explore the profile of articles regarding pulp revascularization available on PubMed/Medline database taking into consideration the date, location and other features from the study, such as: methodological design and main topic addressed.

## Material and methods

### Search strategy

It were included all articles addressed to pulp revascularization published in PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) which were searched after the using of the following Medical Subject Headings (MeSH terms) for the electronic search: dental pulp"[MeSH Terms] OR ("dental"[All Fields] AND "pulp"[All Fields]) OR "dental pulp"[All Fields] OR "pulp"[All Fields]) AND revascularization [All Fields]). There was not restriction regarding to initial date and the established final date was December 2014. At first, two investigators read all titles and abstracts aiming to collect the data. These data were organized in a Table. If the abstracts did not provide the required information, the full texts were accessed and reviewed. Articles were independently categorized according to the following aspects: (i) year of publication; (ii) country where the study was conducted; (iii) study design; (iv) main topic addressed; (v) main conclusion of the article; and (vi) clinical application/other results.

According to other authors [9, 12, 13] each study was classified into one of the following designs: systematic review, randomized clinical trial, quasi-experiment (lack of randomization or focus on secondary outcomes), cohort, case-control, cross-sectional, cost analysis, laboratory study (in vitro), laboratory study (animals), case report, case series, narrative review, bibliometric analysis, and opinion articles.

The main topic addressed was defined based on the main focus of the study, that is, the objective or research question that each study aimed to answer. The following topics were defined: tissues engineering; clinical and radiographic outcomes; radiographic outcomes; radiographic and histological outcomes; design and quality of the publications; cytotoxicity; definition, mechanisms and structure of the regenerated tissues; therapies for primary immature teeth; properties of the triple antibiotic paste; interview with clinicians; and study guide.

## Data analysis

Categories established for each variable were analyzed using Microsoft® Excel® for Mac 2011 Version 14.2.0 (120402) (2010 Microsoft Corporation) and were reported descriptively (frequency and percentages).

## Results

Our search strategy found 133 studies published from 1972 up to December 2014. Forty-seven articles (the most of them published before 2000's) were not related to the revascularization therapy, *i.e.*, they were addressed to other issues such as: regeneration of blood vessels after dental trauma, tooth re-implant, tooth auto-transplantation, bone regeneration, use of Laser Doppler to pulp diagnosis, healing, biocompatibility, and complete root canal filling with MTA. Besides that, two articles did not have the abstract available.

Among the 86 articles remaining, the majority of the studies have been published recently. Frequency and percentage of the articles published according to the year were as follows: 20 (23.2%) in 2014; 15 (17.4%) in 2013; 15 (17.4%) in 2012; 9 (10.4%) in 2011; 9 (10.4%) in 2010; 4 (4.6%) in 2009; 7 (8.1%) in 2008; 4 (4.6%) in 2007; 2 (2.3%) in 2004; and 1 (1.1%) in 2001. These studies were conducted in 24 different countries: United States (28); India (7); Korea (5); Turkey (5); Iran (4); China (4); Brazil (3); Canada (3); Australia (3); Japan (3); Thailand (3); Belgium (2); Israel (2); Kingdom of Saudi Arabia (2); Denmark (2); Egypt (2); Ireland (1); Italy (1); Switzerland (1); Spain (1); Argentina (1); Taiwan (1); Greece (1); Germany (1).

The scientific journals with more number of publications on pulp revascularization were: Journal of Endodontics (40 articles), Dental Traumatology (6 articles), Pediatric Dentistry (6 articles) and International Endodontic Journal (4 articles). Many other journals have published on the topic, such as: Indian Journal of Dental Research, Journal of Conservative Dentistry, Oral Surgery Oral Medicine, Oral Pathology, Oral Radiology & Endodontic, and Texas Dental Journal, Journal of Clinical Pediatric Dentistry, Dental Clinics of North America, Journal of Dental Research, International Journal of Pediatric Dentistry, Journal Canadian Dental Association, etc.

The most frequent study design was case report (32 publications, 37.2%), followed by narrative reviews (14 publications, 16.2%). Studies conducted in the laboratory also were present: studies with

animals (13 publications, 15.11%) and studies *in vitro* (10 publications, 11.6%). Besides, we found: 6 (6.9%) quasi-experiments; 6 (6.9%) case series; 2 (2.3%) cohorts; 1 (1.1%) bibliometric analysis and 1 (1.1%) cross-sectional. Among the studies that provide high evidence levels we found one systematic review (1.1%) and no clinical trials.

The main topic most frequently addressed was the radiographic outcomes from the revascularization therapy (38.3%) and the tissues engineering (19.7%). The clinical and radiographic outcomes analyzed together were addressed in 18.6%; only the clinical outcomes also were addressed in 5.8%; the definitions, mechanisms and structure of the regenerated tissues in 5.8%. The other topics with less number of publications were: therapies for immature teeth (3.4%); cytotoxicity (2.3%); properties of the triple antibiotic paste (1.1%); dentists' opinion (1.1%) and a study guide on revascularization therapy (1.1%).

The radiographic outcomes from the revascularization therapy were: progressive thickening of the root canal walls, root lengthening, apical closure as well as, formation of dentin bridge, and periapical healing. Those features were observed, in the majority of the cases, since 3 months up to 24 months after therapy. Longer periods of follow-up also were reported for instance: 48 months [18] and 5 years [17]. The clinical outcomes, reported after therapy, were: patients with their teeth asymptomatic and functional and no evidences of sinus tract.

Among the recent subjects investigated in the topic tissue engineering is the searching for autologous sources to generate mesenchymal stem cells, as well as, the investigation of substances to enhance angiogenesis and cellular proliferation aiming to promote neovascularization in the dental pulp tissue, for example, the biomolecules.

Notwithstanding the adequate radiographic and clinical outcomes from the revascularization therapy, a few studies have reported negative results. One of them, a case report published in the Journal of Endodontics [19], described that on the basis of histological and bacteriological observations, the failure of revascularized/revitalized tooth could be due to inadequate root canal disinfection without mechanical debridement. In 2013, Al-Kahtani published a case report about a 10-year-old male who suffered a fall injury and avulsed both his central incisors, when the revascularization process was not possible, due to patient compliance and geographic reasons. In this case the teeth were filled with mineral trioxide aggregate (MTA).

Another interesting report about the drawbacks from the revascularization therapy was published by Dabbagh *et al.* [8] where the following problems were reported: i) bluish discoloration of the crown; ii) failure to produce bleeding; and iii) collapse of the mineral trioxide aggregate (MTA) material into the canal.

Some of the articles point the clinical application of their results in both, a direct and indirect manner. The most of the publications highlight that the disinfection of the root canal (and the stimulation of residual stem cells) will induce formation of new hard tissue on the existing dentin wall and continue root development in length [25], improving the tooth survival. Clinically, as a negative point that can affect our patients, severe pulp canal calcification (obliteration) by hard tissue can occur. Such a formation might be a complication of internal replacement resorption or union between the intracanal hard tissue and the apical bone (ankylosis) in revascularized immature permanent necrotic teeth [3].

## Discussion

The results from this current study showed that the evidences available still may not consolidate the revascularization therapy as a standard to treat immature permanent teeth with apical periodontitis. Notwithstanding the benefits to the patients regarding to avoid a fragile tooth (in comparison with a tooth treated by apexification therapy); the outcomes from the revascularization therapy are still unpredictable [11].

This understanding comes from the low level of impact and the extremely new evidences published in the literature. More than a half of the studies have been publishing in the three last years (2014, 2013 and 2012) and they are mostly case reports (37.2%) and narrative reviews (16.2%). The low level of evidences generated by the case reports are justified by their conclusions that are not representative; in other words, they are based on an isolate case (or a few cases) then, their findings cannot be directly applied to the clinical scenario. Besides that, as stated by other authors, a causal relationship cannot be ensured and there is no control group for comparison [9, 12-14]. Although this statement, case reports on pulp revascularization are justifiable if they are able to report unusual and clinically relevant findings, such as, the complete formation of a mineralized tissue inside the canal, making impossible rehabilitates the teeth with a restoration retained by an intra-radicular post. In summary, we found a great amount of studies

with designs that provide low level of evidences [2]. Case reports and narrative reviews, added to case series and laboratorial studies (in vitro and animals) result in a percentage of 82.41% of low levels evidence studies.

Up to date no clinical trials were published and only one systematic review. It is understandable that well conducted clinical trials are still rare in this field because of many challenges faced by the researchers (need of financial support, achievement of consent and compliance to the treatment by the patient, longer periods to complete this type of study); but, at the same time, it is noticeable the lack of tradition in conducting clinical trials in the endodontic area.

It is interesting to note that the revascularization research is more consolidated in the North America, due to the majority of the studies were conducted in the United States. Consequently, these studies have been published in the Journal of Endodontics, published by the American Association of Endodontists. This periodic is the scientific journal that has the high level impact factor in endodontic field and the goal of many researchers who aim visibility (<http://www.jendodon.com/content/aims>). It is expect that over time, scientists, publishers, editors also will prioritize the revascularization issue in other media, for instance, journal focused in pediatric dentistry, dental traumatology and journals outside the United States, which could stimulate the development and implementation of health policies, as well as, improve the clinical practice, benefiting the population [12].

Regarding the main topic addressed, we found that the radiographic features of teeth treated by revascularization therapy are the main focus of the publications (38.3%). Several case reports have been demonstrated the regenerative potential of the therapy by means of the increasing in root length and in the thickness of the canal walls, as well as, the apical closure [2, 5-7, 10, 19, 25]. In this regard, these reports are important in an effort to disseminate the periods of time of follow up to observe the radiographic evidences that allow the conclusion concerning the success of the treatment, namely, average of 21 months post-therapy, in the 24 months [1]; or between 30 and 36 months [16]. Afterwards, the tissues engineering was the second topic most addressed (19.7%). This finding strongly reinforces the increasingly importance and visibility of the translational research, which starts in the basic science and has its conclusion in the practical application of the knowledge [26].

Studies published soon after the completion of this present bibliometric analysis have also focused on tissue engineering proving that the use of different types of scaffolds result in the novo ingrowth of pulp like-tissues, as well as, bone-like, cementum-like, and connective tissue into the pulp [4, 23, 24, 27]. In 2015, Torabinejad *et al.* [24] reported that when is used a platelet-rich-plasma or a blood clot as a scaffold; we found significantly more apical narrowing and hard tissue deposition in comparison to not using a scaffold. On the other hand, a recent histological study with dogs concluded that residual pulp tissue can remain into the canal after revascularization with immature teeth with artificially induced pulp infection, which can lead to the misinterpretation that true pulp regeneration has occurred [23].

Finally, our results prompt us to highlight that researchers, professors, lectures and clinicians should support their clinical decision making in the best available findings in the literature, *i.e.*, that findings which take into consideration not only the radiographic and histologic outcomes from the pulp revascularization therapy; but, mainly, that ones which correlate these outcomes with the consequent benefits to the patients, aiming to improve their quality of life.

## Conclusion

In conclusion, we showed that the number of publications on pulp revascularization has increased recently, but the majority of articles published are studies with low levels of evidence. Such a situation characterizes some uncertainty regarding the effectively of the revascularization therapy on the management of permanent immature necrotic teeth and does not provide sufficient scientific basis to apply this therapy as a first choice in the public health services to treat different populations.

## References

1. Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: new treatment protocol? *J Endod.* 2004 Apr;30(4):196-200.
2. Bose R, Nummikoski IP, Hargreaves K. A retrospective evaluation of radiographic outcomes in immature teeth with necrotic root canal systems treated with regenerative endodontic procedures. *J Endod.* 2009 Oct;35(10):1343-9.
3. Chen MY, Chen KL, Chen CA, Tayebaty F, Rosenberg PA, Lin LM. Responses of immature permanent teeth with infected necrotic pulp tissue and apical periodontitis/abscess to revascularization procedures. *Int Endod J.* 2012 Mar;45(3):294-305.
4. Chen YJ, Zhao YH, Zhao YJ, Liu NX, Lv X, Li Q *et al.* Potential dental pulp revascularization and odonto-/osteogenic capacity of a novel transplant combined with dental pulp stem cells and platelet-rich fibrin. *Cell Tissue Res.* 2015 Mar 24. [Epub ahead of print].
5. Chueh LH, Ho YC, Kuo TC, Lai WH, Chen YH, Chiang CP. Regenerative endodontic treatment for necrotic immature permanent teeth. *J Endod.* 2009 Feb;35(2):160-4.
6. Chueh LH, Huang GT. Immature teeth with periradicular periodontitis or abscess undergoing apexogenesis: a paradigm shift. *J Endod.* 2006 Dec;32(12):1205-13.
7. Cotti E, Mereu M, Lusso D. Regenerative treatment of an immature, traumatized tooth with apical periodontitis: report of a case. *J Endod.* 2008 May;34(5):611-6.
8. Dabbagh B, Alvaro E, Vu DD, Rizkallah J, Schwartz S. Clinical complications in the revascularization of immature necrotic permanent teeth. *Pediatr Dent.* 2012 Sep-Oct;34(5):414-7.
9. Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. *Ann Intern Med.* 2012 Jan 3;156(1 Pt 1):37-40.
10. Ding SJ, Kao CT, Chen CL, Shie MY, Huang TH. Evaluation of human osteosarcoma cell line genotoxicity effects of mineral trioxide aggregate and calcium silicate cements. *J Endod.* 2010 Jul;36(7):1158-62.
11. Diogenes AR, Ruparel NB, Teixeira FB, Hargreaves KM. Translational science in disinfection for regenerative endodontics. *J Endod.* 2014 Apr;40(4 Suppl):S52-7.
12. Feldens CA, Kramer PF, Feldens EG. Exploring the profile of articles on traumatic dental injuries in pediatric dental journals. *Dent Traumatol.* 2013 Jun;29(3):172-7.

13. Fletcher RH, Fletcher SW. *Clinical epidemiology: the essentials*. Baltimore: Lippincott Williams & Wilkins; 2005.
14. Greenhalgh T. *How to read a paper: the basics of evidence-based medicine*. 3. ed. Oxford: Blackwell Publishing; 2006.
15. Hoshino E, Kurihara-Ando N, Sato I, Uematsu H, Sato M, Kota K et al. In-vitro antibacterial susceptibility of bacteria taken from infected root dentine to a mixture of ciprofloxacin, metronidazole and minocycline. *Int Endod J*. 1996 Mar;29(2):125-30.
16. Iwaya SI, Ikawa M, Kubota M. Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. *Dent Traumatol*. 2001 Aug;17(4):185-7.
17. Jung IY, Lee SJ, Hargreaves KM. Biologically based treatment of immature permanent teeth with pulpal necrosis: a case series. *J Endod*. 2008 Jul;34(7):876-87.
18. Kim DS, Park HJ, Yeom JH, Seo JS, Ryu GJ, Park KH et al. Long-term follow-ups of revascularized immature necrotic teeth: three case reports. *Int J Oral Sci*. 2012 Jun;4(2):109-13.
19. Lin LM, Shimizu E, Gibbs JL, Loghin S, Ricucci D. Histologic and histobacteriologic observations of failed revascularization/revitalization therapy: a case report. *J Endod*. 2014 Feb;40(2):291-5.
20. Moreno-Hidalgo MC, Caleza-Jimenez C, Mendoza-Mendoza A, Iglesias-Linares A. Revascularization of immature permanent teeth with apical periodontitis. *Int Endod J*. 2014 Apr;47(4):321-31.
21. Rafter M. Apexification: a review. *Dent Traumatol*. 2005 Feb;21(1):1-8.
22. Rule DC, Winter GB. Root growth and apical repair subsequent to pulpal necrosis in children. *Br Dent J* 1966 Jun 21;120(12):586-90.
23. Saoud TM, Zaazou A, Nabil A, Moussa S, Aly HM, Okazaki K et al. Histological observations of pulpal replacement tissue in immature dog teeth after revascularization of infected pulps. *Dent Traumatol*. 2015 Jun;31(3):243-9.
24. Torabinejad M, Milan M, Shabahang S, Wright KR, Faras H. Histologic examination of teeth with necrotic pulps and periapical lesions treated with 2 scaffolds: an animal investigation. *J Endod*. 2015 Mar 6(15) [Epub ahead of print].
25. Wigler R, Kaufman AY, Lin S, Steinbock N, Hazan-Molina H, Torneck CD. Revascularization: a treatment for permanent teeth with necrotic pulp and incomplete root development. *J Endod* 2013 Mar;39(3):319-26.
26. Woolf SH. The meaning of translational research and why it matters. *JAMA* 2008 Jan 9;299(2):211-3.
27. Yang JW, Zhang YF, Wan CY, Sun ZY, Nie S, Jian SJ et al. Autophagy in SDF-1 $\alpha$ -mediated DPSC migration and pulp regeneration. *Biomaterials*. 2015 Mar;44:11-23.