

Regenerative endodontic treatment performed with platelet-rich plasma presents better periapical healing than only induced blot clot: a systematic review

Tratamento endodôntico regenerativo realizado com plasma rico em plaquetas apresenta melhor cicatrização periapical do que apenas indução de coágulo: uma revisão sistemática

El tratamiento endodóntico regenerativo realizado con plasma rico en plaquetas presenta una mejor cicatrización periapical que solo el coágulo de transferencia inducido: una revisión sistemática

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Abstract

This study comprehensively reviewed two different treatments for regenerative endodontic: platelet-rich plasma and induced blot clot, in regarding to periapical healing. Two investigators performed a systematic review. MEDLINE/PubMed, Cochrane Library and Scopus supplied relevant data from studies published until December 2020 to answer the PICO question. Primary outcome was periapical healing. Eight randomized clinical trials fulfilled eligibility criteria. Primary outcome indicated that platelet-rich plasma results in similar or better periapical healing compared to blot clot group. The reported failures were related to blot clot group due to incomplete radiographic parameters, pain and reinfection; however, few cases of unsucces were reported to platelet-rich plasma group. Only two studies observed better results to blot clot group in relation to increase of radiographic area and partial pulp canal obliteration. This review showed that procedures using platelet-rich plasma were successful in treating permanent teeth with root development.

Keywords: Regenerative endodontics; Platelet-rich plasma; Regenerative medicine; Tooth apex.

Resumo

Este estudo revisou de forma abrangente dois diferentes tratamentos endodônticos regenerativos: com plasma rico em plaquetas e coágulo induzido no que diz respeito à cicatrização periapical. Dois investigadores realizaram uma revisão sistemática. MEDLINE / PubMed, Cochrane Library e Scopus forneceram dados relevantes de estudos publicados até dezembro de 2020 para responder à pergunta PICO. O desfecho primário foi a cura periapical. Oito ensaios clínicos randomizados preencheram os critérios de elegibilidade. O desfecho primário indicou que o plasma rico em plaquetas resulta em cicatrização periapical semelhante ou melhor em comparação com o grupo coágulo induzido. As falhas relatadas foram relacionadas ao grupo coágulo induzido devido a parâmetros radiográficos incompletos, dor e reinfeção; no entanto, poucos casos de insucesso foram relatados ao grupo plasma rico em plaquetas. Apenas dois estudos observaram melhores resultados para o grupo coágulo induzido em relação ao aumento da área radiográfica e obliteração parcial do canal pulpar. Esta revisão mostrou que procedimentos com plasma rico em plaquetas tiveram sucesso no tratamento de dentes permanentes necróticos com desenvolvimento radicular incompleto.

Palavras-chave: Endodontia regenerativa; Plasma rico em plaquetas; Medicina regenerativa; Ápice dentário.

Resumen

Este estudio revisó exhaustivamente dos tratamientos diferentes para la endodoncia regenerativa: plasma rico en plaquetas y coágulo de transferencia inducido, en lo que respecta a la curación periapical. Dos investigadores realizaron una revisión sistemática. MEDLINE / PubMed, Cochrane Library y Scopus proporcionaron datos relevantes de estudios publicados hasta diciembre de 2020 para responder a la pregunta PICO. El resultado primario fue la curación periapical. Ocho ensayos clínicos aleatorizados cumplieron los criterios de elegibilidad. El resultado primario indicó que el plasma rico en plaquetas produce una cicatrización periapical similar o mejor en comparación con el grupo de coágulos de transferencia. Los fracasos informados se relacionaron con el grupo de coágulos de transferencia debido a parámetros radiográficos incompletos, dolor y reinfección; sin embargo, se informaron pocos casos de fracaso al grupo plasma rico en plaquetas. Sólo dos estudios observaron mejores resultados con el grupo de coágulos de transferencia en relación con el aumento del área radiográfica y la obliteración parcial del canal pulpar. Esta revisión mostró que los procedimientos que utilizan plasma rico en plaquetas tuvieron éxito en el tratamiento de dientes permanentes con desarrollo radicular.

Palabras clave: Endodoncia regenerativa; Plasma rico en plaquetas; Medicina regenerativa; Ápice del diente.

1. Introduction

Immature permanent teeth have been characterized, histologically, by no formation of the apical dentin coated with cementum (Leonardo, 2005). Radiographically, it is not possible to see the root closure - root development does not reach Nolla stage 10, the foraminal opening may have a larger diameter than the diameter of the canal in the middle and cervical third and the root walls are thin and fragile (Leonardo, 2005). Thus, the conventional mechanical preparation becomes unfeasible to be performed, needing other therapeutic alternatives, making this treatment a challenge for endodontic practice (Leonardo, 2005).

Currently, regenerative endodontics has been shown to be effective in the treatment of immature permanent teeth. Such therapy may be defined as a biologically based procedure designed to replace damaged structures, including dentin, root structure and pulp tooth complex cells (Murray et al., 2007). The most well-known and successful approach to regenerative therapy in endodontics is revascularization (Murray et al., 2007; Shah et al., 2008). This procedure is performed to restore the vitality of a dental element, to stimulate the apical closure, to increase the thickening of fragile dentinal walls and to lengthen the underdeveloped root (Jadhav et al., 2012).

The traditional method of regenerative endodontic treatment for immature permanent teeth is conducted under local anesthesia without vasoconstrictor, access to the root canal and abundant irrigation with sodium hypochlorite (Metlerska et al., 2019). Due to the reduced dentin thickness, the canal is not subjected to any type of instrumentation, but disinfection with chemical solution (Bezgin et al., 2015). To achieve the disinfection process, the root canal is filled with a tri-antibiotic paste for an average period of 3 weeks (Bezgin et al., 2014). In the second session, the tri-antibiotic paste is removed and a manual file or a needle is used to evoke bleeding and a clot to form in the root canal (Jadhav et al., 2012). The root canal is sealed with a synthetic material (for example MTA) and radiographic monitoring is carried out periodically (Metlerska et al., 2019).

Recent research on new proposals for endodontic regenerative treatments has shown interesting results when using platelet concentrate, called platelet-rich plasma (PRP) (Jadhav et al., 2012; Bezgin et al., 2015; Narang et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; Rizk et al., 2019; Ulusoy et al., 2019; ElSheshtawy et al., 2020). PRP contains growth factors, stimulates collagen production, recruits other cells to the injury site, produces anti-inflammatory agents, initiates vascular growth, induces cell differentiation and improves the healing of soft and hard tissue wounds (Sachdeva et al., 2015). For the use of PRP in revascularization, the patient's venous blood is collected, centrifuged and blood free of erythrocytes and leukocytes is inserted into the root canal up to 3 mm from the cement-enamel junction (Dohan et al., 2006). As in traditional regenerative treatment, the root canal is sealed with a synthetic material and radiographic monitoring is carried out periodically (Metlerska et al., 2019).

In 2019, Metlerska and colleagues conducted a systematic review with studies in humans and the answer to the PICO question "Is the use of platelet concentrates effective in regenerative endodontics?" was those procedures using autologous

platelet concentrates contribute to the success of treating immature permanent teeth, especially when there are problems with bleeding, but the level of evidence is weak. Furthermore, they have observed that autologous platelet concentrates can lead to development of the root and protect the tooth from extraction. However, in 2019 and 2020 new randomized clinical trials have been published driving the need of a new systematic review (Rizk et al., 2019; Ulusoy et al., 2019; ElSheshtawy et al., 2020). Therefore, the purpose of this systematic review was to assess the outcomes of periapical healing after regenerative endodontic treatment with induced blot clot and with PRP. Null hypothesis was that both platelet-rich plasma and induced blot clot present similar periapical healing in regenerative endodontic treatment.

2. Methodology

Protocol and registration

This article was designed according to the Cochrane criteria (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0) (Higgins and Green, 2011; Koche et al., 2011; Ludke and Andre, 2013; Estrela, 2018; Pereira et al., 2018; Yin, 2015) for elaborating a systematic review and meta-analysis and adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009). The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO – 233444).

Eligibility criteria

The inclusion criteria were: (1) randomized controlled trials, (2) studies that evaluated periapical healing in patients who were submitted to regenerative endodontic treatment, (3) studies that used platelet-rich plasma compared to induced blot clot in regenerative endodontic treatment, and (4) studies published in English language with available abstracts. Exclusion criteria included any articles that failed to meet the inclusion criteria and studies that evaluated platelet-rich fibrin.

A specific clinical question was structured according to the PICO approach: The addressed focus question was: does regenerative endodontic treatment performed with platelet-rich plasma presents better results than only induced blot clot? In this process, (P) represents patients submitted to regenerative endodontic treatment that were treated with (I) platelet-rich plasma, (C) compared to induced blot clot; and, (O) the periapical healing as outcome.

Information Sources

An electronic search in the PubMed/MEDLINE, Cochrane Library and Scopus databases was conducted until August 2020. Furthermore, a manual search was conducted to identify gray literature (<http://www.opengrey.eu>) and registered trials not yet published until 2020 from the following journals: Journal of Endodontics, International Endodontic Journal, Journal of Dental Research, Journal of Dentistry and Clinical Oral Investigations.

Search

Two independent researchers (M.F.K. and L.S.M.) performed the electronic search at the selected databases. The search terms used were: (1) platelet-rich plasma and regenerative endodontic treatment, (2) platelet-rich plasma and revascularization, (3) platelet-rich plasma and revitalization, (4) platelet-rich plasma and regenerative endodontic treatment and induced blot clot, (5) platelet-rich plasma and revascularization and induced blot clot, (6) platelet-rich plasma and revitalization and induced blot clot, (7) platelet-rich plasma and regenerative endodontic treatment and randomized clinical trial, (8) platelet-rich plasma and revascularization and randomized clinical trial, (9) platelet-rich plasma and revitalization and randomized clinical trial, (10) platelet-rich plasma and regenerative endodontic treatment and induced blot clot and randomized clinical trial, (11) platelet-rich plasma and revascularization and induced blot clot and randomized clinical trial, (12) platelet-rich plasma and revitalization and

induced blot clot and randomized clinical trial.

Study Selection

Two researchers (M.F.K. and L.S.M.) independently selected the studies according to their titles and abstracts and categorized them as included or excluded. Any disagreements were settled through discussion and consensus with a third researcher (C.M.M.). After that both investigators read the articles selected for inclusion and a manual search was performed on the reference list.

Data collection process and data items

Subsequently, the full-text of the obtained articles was analyzed. The analysis of these selected articles was used to answer the PICO questions. The researchers (M.F.K and L.S.M) collected relevant information from the articles, including author, year, study type, number of patient and teeth sample size, gender, age average, methods for diagnosis, pulp diagnosis, anesthesia, the use of rubber dam, the working length, the instrumentation technique and irrigating protocol, the use of intracanal medication protocol, the scaffolds for platelet-rich plasma, the platelet-rich plasma group initial sample size and the drop-out, the scaffolds for induced blot clot, the induced blot clot plasma group initial sample size and the drop-out, the final restoration, the follow up protocol, the periapical healing and cases of unsuccess, the complete apical closure, the increase of radiographic root area, the discoloration, the presence of partial pulp canal obliteration, positive vitality testing, wall thickening and root length. Then, a third researcher (C.M.M.) checked all of the collected information. A fourth researcher (V.E.S.B.) settled any disagreement between the investigators through discussion until a consensus was obtained. Duplicate subject publications within separate unique studies were not reported twice.

Risk of Bias

The risk of bias assessment in the included studies was evaluated using the Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials (Higgins and Green, 2011). The assessment criteria are a domain-based evaluation in which critical assessments are made separately for different domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (Higgins and Green, 2011). For each domain the risk of bias was graded as high, low or unclear based on criteria described in the Cochrane Handbook for Systematic reviews of Interventions 5.1.0 (Table 1) (Bezgin et al., 2015).

Table 1. Risk of bias among the studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other bias
Jadhav et al. 2012	+	?	?	+	+	+	?
Bezgin et al. 2015	+	?	?	+	+	+	?
Narang et al 2015	+	?	?	+	?	?	-
Alagl et al. 2017	+	?	?	+	+	+	?
Shivashankar et al. 2017	+	?	?	+	+	+	?
Rizk et al. 2019	+	+	-	+	+	+	+
Ulusoy et al. 2020	+	+	-	+	+	+	?
EISheshtaw et al. 2020	+	+	-	+	+	+	-

Key: + Low risk of bias
? Unclear risk of bias
- High risk of bias
Source: Authors.

3. Results and Discussion

Study selection

A total of 220 articles were retrieved, of which only 8 fulfilled eligibility criteria (inter-reader agreement, Kappa = 1 for PubMed/Medline and Kappa = 1 for Cochrane Library) (Figure 1). All the studies selected were randomized clinical trials and compared the outcomes of periapical healing after regenerative endodontic treatment using blot clot and PRP (Jadhav et al., 2012; Bezgin et al., 2015; Narang et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; Ulusoy et al., 2019; Rizk et al., 2019; EISheshtawy et al., 2020). The risk of bias assessment of the included studies is described in Table 1. Extracted data are summarized in Table 2 and Table 3.

Table 2. Articles included in the systematic review

Author	Initial Patients / Teeth Sample Size	Final Patients / Teeth Sample Size	Gender	Age range / average	Methods for diagnosis	Pulp diagnosis	Anesthesia	Isolation with rubber dam	Working length	Instrumentation	Irrigating protocol	Intracanal medication protocol	Scaffolds for PRP	PRP Group: Initial Sample Size / Sample Size After Drop-Out	Scaffolds for BC	BC Group / Initial Sample Size / Sample Size After Drop-Out	Final restoration
1 Jadhav et al.	n = 20 / n = 20	n = 20 / n = 20	Both	15-28 / 21,5	Clinical examination, periapical radiograph and pulp vitality test	Nonvital, immature anterior teeth with or without periapical lesions	Local anesthetic solution without adrenaline	Access opening under rubber dam	Established radiographically by placing a large file in the canal	Minimal mechanical instrumentation with an ISO #60 H-file	20 mL 2.5% NaOCl	Triple antibiotic paste	About 8 mL blood drawn by venipuncture of the antecubital vein was collected in a sterile glass tube coated with an anticoagulant; this was centrifuged at 2,400 rpm for 10 minutes to separate PRP and platelet-poor plasma (PPP) from the red blood cell fraction; PRP + PPP was transferred to another tube and again centrifuged at 3,600 rpm for 15 minutes to PRP precipitate at the bottom of the glass tube. It was mixed with 1 mL 10% calcium chloride. A revascularization was performed according to described to blot clot and, before the formation of a clot, PRP soaked on a 1x1 mm ² of sterile collagen sponge was introduced into the root canal with cotton pliers and carried to the apical portion with a size 30 finger plugger.	n = 10 / n = 10	A fresh, sterile 23-G needle was used to evoke bleeding in the root canal. Then, a dry cotton pellet was inserted 3-4 mm into the canal and held there for 5-7 minutes to allow blood clot formation.	n = 10 / n = 10	Between sections: IRM; Final restoration: resin-modified glass ionomer cement
2 Bezgin et al.	n = 20 / n = 22	n = 19 / n = 20	Both	7-13 / 9,95	Clinical examination, periapical radiograph, electric pulp and cold stimulation tests	Nonvital, immature single-rooted teeth with or without periapical lesions	Local anesthetic solution without adrenaline	Access opening under rubber dam	Established radiographically by placing an ISO #20 k-file in the canal	Canals were not instrumented	20 mL 2.5% NaOCl, 20 mL sterile saline and 10 mL 0.12% chlorhexidine	Triple antibiotic paste	PRP was prepared according to Dohan et al 2006. Coagulation was achieved by combining PRP with equal volumes of sterile saline solution containing 10% calcium chloride and sterile bovine thrombin (100 U/mL)	n = 11 / n = 10	An ISO #20 k-file was used to evoke bleeding in the root canal. Then, the teeth was allowed 10 min to form the blot clot.	n = 11 / n = 10	Between sections: IRM; Final restoration: white MTA, reinforced glass ionomer cement and composite resin

3	Narang et al.	n= 10 / n = 10	n= 10 / n = 10	Both	Unclear	Clinical examination, periapical radiograph, palpation, percussion, electric pulp and cold stimulation tests	Nonvital, immature teeth with or without periapical lesions	Local anesthetic solution for BC Group	Access opening under rubber dam	Unclear	Minimal mechanical instrumentation	2.5% NaOCl	Triple antibiotic paste	Venous blood was collected in a sterile glass tube coated with an anticoagulant; this was centrifuged at 2,400 rpm for 10 minutes to separate PRP and platelet-poor plasma (PPP) from the red blood cell fraction; PRP + PPP was transferred to another tube and again centrifuged at 3,600 rpm for 15 minutes to PRP precipitate at the bottom of the glass tube. It was mixed with 1 mL 10% calcium chloride. The PRP with collagen was introduced as scaffolds and pushed toward the apical area using endodontic pluggers.	n = 5 / n = 5	A fresh, sterile 23-G needle was used to evoke bleeding in the root canal. Then, a dry cotton pellet was inserted 3–4 mm into the canal and held there for 5–7 minutes to allow blood clot formation.	n = 5 / n = 5	Between sections: IRM; Final restoration: resin-modified glass ionomer cement and composite resin
4	Alagl et al.	n = 16 / n = 32	n = 15 / n = 30	Both	Unclear	Clinical examination, periapical radiograph, electric pulp and cold stimulation tests	Nonvital, immature teeth with or without periapical lesions	Local anesthetic solution for BC Group	Access opening under rubber dam	Established radiographically by placing an ISO #20 k-file in the canal	Canals were not instrumented	20 mL 2.5% NaOCl, 20 mL sterile saline and 10 mL 0.12% chlorhexidine	Triple antibiotic paste	PRP was prepared according to the description by Dohan et al. 2006. PRP was combined with equal volumes of sterile saline solution containing 10% calcium chloride and sterile bovine thrombin (100 U/mL) to achieve coagulation. The PRP was then injected into the root canal up to the level of the CEJ.	n = 16 / n = 15	An ISO #20 k-file was used to evoke bleeding in the root canal. Then, the teeth was allowed 10 min to form the blot clot.	n = 16 / n = 15	Between sections: reinforced zinc oxide–eugenol cement; Final restoration: white MTA, reinforced glass ionomer cement and composite resin
5	Shivashankar et al.	n = 40 / n = 40	n = 34 / n = 34	Both	6-20 / 20	Periapical radiograph elucidating wide apical foramen and thin dentinal walls.	Nonvital, immature teeth with or without periapical lesions	Unclear	Access opening under rubber dam	Unclear	Minimal mechanical instrumentation	5.25% NaOCl	Triple antibiotic paste	Unclear	n = 20 / n = 19	Unclear	n = 20 / n = 15	Between sections: IRM; Final restoration: white MTA, reinforced glass ionomer cement and composite resin

6	Rizk et al.	n = 15 / n = 30	n = 13 / n = 26	Both	8 - 14 / 11	Clinical and periapical radiograph.	Nonvital, immature teeth with or without periapical lesions	Local anesthetic solution without adrenaline	Access opening under rubber dam	Established radiographically by placing an ISO #40-90 k-file in the canal	Canals were not instrumented	20 mL 2% NaOCl, 20 mL EDTA and 10 mL sterile saline to remove intracanal medication	Triple antibiotic paste	4,5 mL of venous blood was collected in a sterile glass tube coated with an anticoagulant; this was centrifuged at 2,400 rpm for 10 minutes to separate PRP and platelet-poor plasma (PPP) from the red blood cell fraction; PRP + PPP was transferred to another tube and again centrifuged at 3,600 rpm for 15 minutes to PRP precipitate at the bottom of the glass tube. It was mixed with 1 mL 10% calcium chloride. The PRP with collagen was introduced as scaffolds and pushed toward the apical area using endodontic pluggers.	n = 15 / n = 13	An ISO #40 Hedstrom file was used to evoke bleeding in the root canal. The canal was allowed to fill with blood until 2 mm below the CEJ to wait for blood clot formation for 10-15 minutes. A collagen matrix was placed on top of the blood clot. An ISO #15 k-file was used to evoke bleeding in the root canal. The canal was allowed to fill with blood until 3 mm below the CEJ to wait for blood clot formation for 10 minutes.	n = 15 / n = 13	Between sections: Coltosol; Final restoration: MTA, glass ionomer material and composite resin
7	Ulusoy et al.	n = 77 / n = 88	n = 65 / n = 73	Both	8 - 11 / 9,5	Clinical examination, periapical radiograph, electric pulp and cold stimulation tests	Nonvital, immature anterior teeth with or without periapical lesions	Local anesthetic solution without adrenaline	Access opening under rubber dam	Unclear	Canals were not instrumented	20 mL 1,25% NaOCl, 20 mL EDTA and 10 mL sterile saline to remove intracanal medication	Triple antibiotic paste	20 mL blood was drawn from the patient's right arm and placed in the test tube containing 15 mL citrate solution for PRP preparation. Citrated blood was centrifuged in a standard laboratory centrifuge for 15 minutes at 1250 rpm to obtain PRP without erythrocytes and leukocytes. The PRP sample was placed into the canal space to a level 3 mm below the cemento-enamel junction using sterile 27-G needle tips	n = 22 / n = 18	An ISO #15 k-file was used to evoke bleeding in the root canal. The canal was allowed to fill with blood until 3 mm below the CEJ to wait for blood clot formation for 10 minutes.	n = 22 / n = 21	Between sections: conventional glass ionomer cement; Final restoration: white MTA, glass ionomer cement and composite resin

8	ElSheshtaw et al.	n = 31 / n = unclear	n = 28 / n = 31	Both	Unclear / 12,66	Clinical, periapical radiograph and CBCT.	Nonvital, immature anterior teeth with or without periapical lesions, 1mm of apical foramen width	Local anesthetic solution with and without adrenaline, for PRP and BC Groups respectively	Access opening under rubber dam	Established using a Root ZX-II apex locator and confirmed radiographically.	Minimal mechanical instrumentation	20 mL 1,25% NaOCl, 20 mL EDTA and 20 mL sterile saline followed by 10 mL of 17% EDTA solution and 10 mL sterile saline to remove intracanal medication	Triple antibiotic paste	PRP was prepared according to Dohan et al. (2006). The concentrated platelet-rich plasma was prepared and introduced inside dry root canals using a sterile 30 G syringe. Collagen plug was placed over in order to restrict apical placement of the bioactive material.	Unclear / 14	An pre-curved ISO #15 k-file was used to evoke bleeding in the root canal. The canal was allowed to fill with blood until 3 mm below the CEJ to wait for blood clot formation for 10 minutes. Collagen plug was placed over in order to restrict apical placement of the bioactive material.	Unclear / 17	Between sections: Coltosol; Temporary restoration: MTA and Coltoson; Final restoration: reinforced glass ionomer and composite resin.
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Source: Authors.

Table 3. Summary of each study according to aim of the study and outcome.

Author, Year	Follow up protocol	Periapical healing	Unsuccessful	Apical closure	Increase of radiographic root area	Discoloration	Partial pulp canal obliteration	Positive vitality testing	Wall thickening	Root length
Jadhav et al., 2012	Clinical and radiographical evaluation at 6 and 12 months; Scores: satisfactory, good and excellent.	PRP Group: 100% presented periapical healing; 10% satisfactory; 40% good; 50% excellent. BC Group: 100% presented periapical healing; 30% satisfactory; 70% good.		PRP Group: 100% presented complete apical closure; 0% satisfactory; 30% good; 70% excellent. BC Group: 100% presented complete apical closure; 50% Satisfactory; 30% good; 20% excellent.					PRP Group: 20% satisfactory; 50% good; 30% excellent. BC Group: 70% satisfactory; 30% good; 0% excellent.	PRP Group: 10% satisfactory; 50% good; 40% excellent. BC Group: 40% satisfactory; 60% good; 0% excellent.
Bezgin et al., 2015	Clinical and radiographical evaluation at 3, 6, 9, 12, 15 and 18 months. Scores: unsuccessful, satisfactory, good and excellent.	PRP Group: 100% presented periapical healing. BC Group: 88,9% presented periapical healing.	PRP Group: 0% of unsuccessful; BC Group: 10% of unsuccessful.	PRP Group: 70% presented complete apical closure. BC Group: 60% presented complete apical closure.	PRP Group: presented a mean of 9.86% increase of radiographic root area. BC Group: presented a mean of 12.6% increase of radiographic root area.	No discoloration was observed.	PRP Group: 40% partial pulp canal obliteration was observed; BC Group: 40% partial pulp canal obliteration was observed.	PRP Group: 50% presented positive vitality testing; BC Group: 20% presented positive vitality testing.		
Narang et al., 2015	Clinical and radiographical evaluation at 6 and 18 months; Scores: none, fair, good and excellent. Clinical and radiographical evaluation at 3, 6, 9 and 12 months. Pulp vitality was evaluated thru electric pulp and cold stimulation tests. CBCT were performed to analyze lesion size, periapical healing, and apical closure.	PRP Group: 20% fair; 80% good periapical healing. BC Group: 40% fair; 60% good; 0% excellent periapical healing.		PRP Group: 40% fair; 60% good apical closure. BC Group: 33,3% fair; 66,7% good apical closure.					PRP Group: 80% fair; 20% good wall thickening. BC Group: 50% fair; 50% good wall thickening.	PRP Group: 60% fair; 40% good root length. BC Group: 60% fair; 40% good root length.
Alagl et al., 2017		PRP Group: 100% presented periapical healing. BC Group: 100% presented periapical healing.		PRP Group: 92,9% presented apical closure; BC Group: 53,3% presented apical closure.				PRP Group: 85,7% presented positive vitality testing; BC Group: 40% presented positive vitality testing.		PRP Group presented high measurement of root length compared to BC Group

Shivashankar et al., 2017	<p>Clinical and radiographical evaluation at 3, 6, 9 and 12 months. Scores for periapical index: 1 - Normal periapical structures; 2 - Small changes in bone structure; 3 - Changes in bone structure with some mineral loss; 4 - Periodontitis with well defined radiolucent area; 5 - Severe periodontitis with exacerbating features. Scores for root lengthening and lateral wall thickening: Satisfactory - if there was increase in a single increment of Schei's ruler; Good - if there was increase in two or more increments of Schei's ruler. Types of apical responses: Type 1 - Increased thickening of the canal walls and continued root maturation; Type 2 - No significant continuation of root development with root apex becoming blunt and closed; Type 3 - Continued root development with the apical foramen remaining open; Type 4 - Severe calcification (Obliteration) of the canal space; Type 5 - A hard tissue barrier formed in the canal between the coronal MTA plug and the root apex</p> <p>Clinical and radiographical evaluation at 3, 6, 9 and 12 months. It was evaluated the percentage of increased root length, root thickness and bone</p>	<p>PRP Group: 90% presented clinical success and 75% presented radiographic success; Mean periapical index score after 12 months 1.32±0.478. BC Group: 100% presented clinical success and 80% presented radiographic success; Mean of periapical index score after 12 months 2.07±0.594.</p>	<p>PRP Group: 10% of clinical and radiographical unsuccessful and 15% of incomplete radiographical success; BC Group: 20% of incomplete radiographical success.</p>	<p>PRP Group: 63,2% continued root development with the apical foramen remaining open; BC Group: 53,3% continued root development with the apical foramen remaining open..</p>	<p>BC Group showed a higher crown discoloration than PRP Group.</p>	<p>PRP Group: 15,8% presented positive vitality testing; BC Group: 13,3% presented positive vitality testing.</p>	<p>PRP Group: 26,3% good; 57,9% satisfactory; 15,8% no change. BC Group: 20% good; 73,3% satisfactory; 6,7% no change.</p>	<p>PRP Group: 26,3% good; 47,4% satisfactory; 26,3% no change. BC Group: 26,7% good; 60% satisfactory; 13,3% no change.</p>
Rizk et al., 2019	<p>Clinical and radiographical evaluation at 3, 6, 9 and 12 months. It was evaluated the percentage of increased root length, root thickness and bone</p>	<p>PRP Group presented high measurement of bone density compared to BC Group in all experimental times.</p>	<p>PRP Group presented low measurement of apical diameter compared to BC Group in all experimental times.</p>	<p>BC Group showed a higher crown discoloration than PRP Group.</p>	<p>No positive pulp vitality test was observed for all groups in at the end of 12 months.</p>	<p>PRP Group presented high measurement of wall thickening compared to BC Group in 6, 9 and 12 months.</p>	<p>PRP Group presented high measurement of root length compared to BC Group in all experimental times</p>	

<p>Ulusoy et al., 2020</p>	<p>density and the decrease of apical diameter. Pulp vitality was evaluated thru electric pulp, cold and heat stimulation tests.</p> <p>Clinical and radiographical evaluation at 3, 6, 9, 12, 18, 24 months. Radiographical scores: 0 - Failure, persistence of clinical and radiographic findings; 1 - resolution of disease, absence of swelling, drainage, and pain along with radiographic evidence of osseous healing; no evidence of increased root dimensions; 2: score 1 + radiographic root development and a positive response to cold testing and electric pulp testing. Pulp vitality was evaluated thru electric pulp and cold stimulation tests. Clinical, radiographical and CBCT evaluation at 3, 6, 9 and 12 months. Clinical: tooth colour, tenderness to percussion, presence of swellings/sinus tracts, tooth mobility, and pulp vitality thru electric pulp, cold and hot stimulation tests. Radiographical: root length, root dentinal thickness, apical foramen width and total radiographic root area. CBCT: periapical area diameters (PAD) scores 0: PAD ≤ 0.5 mm; 1: PAD of >0.5 to 1 mm; 2: PAD of >1 to 2 mm; 3: PAD of >2 to 4 mm; 4: PAD of >4 to 8 mm.</p>	<p>All teeth showed similar and high success scores regarding to periapical healing.</p>	<p>BC group: 4,8% of unsuccessful due signs and symptoms including spontaneous pain and extreme sensitivity to percussion at 14 months.</p>	<p>PRP Group: 66,7% presented apical closure; BC Group: 76,2% presented apical closure.</p>	<p>PRP Group: there was an increase in radiographic root area by 9,5%; BC Group: there was an increase in radiographic root area by 15,8%.</p>		<p>PRP Group: there was a decrease in radiographic canal area by 13,8%; BC Group: there was a decrease in radiographic canal area by 32,8%.</p>	<p>PRP Group: 72,2% presented positive vitality testing; BC Group: 95,2% presented positive vitality testing.</p>	<p>PRP Group: there was an increase in root width by 19%; BC Group: there was an increase in root width by 14,9%.</p>	<p>PRP Group: there was an increase in root length by 4,7%; BC Group: there was an increase in root length by 7,2%.</p>
<p>ElSheshtaw et al., 2020</p>		<p>PRP Group: 88% presented success. BC Group: 85,7% presented success.</p>	<p>PRP Group: 12% presented unsuccess due reinfection. BC Group: 14,3% presented unsuccess due reinfection.</p>	<p>Periapical radiograph and CBCT methods revealed apical closure in both groups</p>	<p>Periapical radiograph and CBCT methods revealed an increase in radiographic root area in both groups</p>	<p>PRP Group: 78,6% presented discolouration. BC Group: 82,4% presented discolouration.</p>		<p>No change in pulp sensibility was observed throughout the study period with a 100% lack of response.</p>	<p>Periapical radiograph and CBCT methods revealed an increase in dentinal root widths in both groups.</p>	<p>Periapical radiograph and CBCT methods revealed an increase in root lengths in both groups.</p>

Source: Authors.

For the first selection, one article was selected and subsequently excluded. Adel Ragab et al., 2019 evaluated the effect of platelet rich fibrin (PRF) during revitalization of necrotic immature permanent anterior teeth, however there was no PRP group.

Study characteristics

A total of 204 patients, regardless of gender, with an average age of 14.1 years had 244 teeth treated endodontically thru regenerative. From this, 104 teeth were treated with PRP and 106 teeth were treated with blot clot.

All cases treated were diagnosed with pulp necrosis with the presence or absence of periapical lesion. The methods or diagnosis used were clinical examination, periapical radiograph and pulp vitality test (electric pulp and cold stimulation) and only in one research CBCT was used (ElSheshtawy et al., 2020).

Regenerative endodontic treatment was performed in two visits and triple antibiotic paste was used between sections in all cases. The temporary restoration between sections was IRM® (Jadhav et al., 2012; Bezgin et al., 2015; Narang et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017). Coltisol® (Rizk et al., 2019; ElSheshtawy et al., 2020) and glass ionomer cement (Ulusoy et al., 2019).

Four studies performed minimal mechanical instrumentation and the canals were not instrumented in the remained studies. Sodium hypochlorite (NaOCl) was the irrigant of choice in all 8 articles, with concentrations ranging from 1.25 to 5.25%. Bezgin et al. (2015) and Alagl et al. (2017) associated the irrigation with chlorhexidine. Rizk et al. (2019), Ulusoy et al. (2020) and ElSheshtaw et al. (2020) used EDTA to remove the smear layer after the use of tri antibiotic paste.

For achieve the scaffolds for PRP, all researchers followed the protocol of Dohan et al. in 2006. And the blot clot was obtained through evoke bleeding from periapices and only ElSheshtaw et al. (2020) placed a collagen over the blot clot.

The final restoration was MTA, reinforced glass ionomer cement and composite resin (Bezgin et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; Rizk et al., 2019; Ulusoy et al., 2019; ElSheshtawy et al., 2020) only resin-modified glass ionomer cement 4 or its association with composite resin (Narang et al., 2015).

The follow up was completed mostly evaluating the periapical healing and apical closure. It was observed that the periapical healing was similar or superior for PRP group compared to blot clot group. The reported failures were related to blot clot group due to incomplete radiographic parameters, pain and reinfection; however, few cases of unsuccess was reported to PRP group. Two studies (Ulusoy et al., 2019; Narang et al., 2015) observed better results to blot clot group, ElSheshtaw et al. 2020 observed similar results to both groups and most research points to a better result with the use of blot clot.

Some studies observed better results to blot clot group in relation to increase of radiographic area (Bezgin et al., 2015; Ulusoy et al., 2019) and partial pulp canal obliteration¹⁰. However, studies that evaluated discoloration pointed to better results to PRP Group (ElSheshtawy et al., 2020; Rizk et al., 2019). On the other hand, controversial results are observed or aspects positive vitality test, wall thickening and root length.

4. Discussion

The findings of the present systematic review deny the null hypothesis since the performance of the regenerative treatment with PRP was better when compared to regeneration with the stimulation of the blood clot. The main results show that periapical health with complete root formation (apical closure) was greater in most studies with the induction of PRP in the regenerative process than blood clot (Jadhav et al., 2012; Bezgin et al., 2015; Narang et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; ElSheshtawy et al., 2020). Furthermore, some studies have shown that the teeth treated with a blood clot had a lower success rate (Bezgin et al., 2015; Shivashankar et al., 2017; Ulusoy et al., 2019; ElSheshtawy et al., 2020). Not all studies have

shown results regarding pulp vitality, however, in spite of those who evaluated after regenerative process, most demonstrated that the use of PRP was clinically better (Bezgin et al., 2015; Shivashankar et al., 2017; Rizk et al., 2019).

Treatment of immature permanent teeth is a challenge for clinicians and its success can be analyzed through thickening and lengthening of the root wall and closure of the apical foramen. Osteoblasts/odontoblasts, adipocytes, and neuronal-like cells provided by periodontal ligament, with or without scaffold of PRP will develop the root and the apex. Adequate length with a sufficient thickness of the root canal leads to a greater resistance to masticatory forces, thus preventing possible fractures.

However, great disinfection is primordial in the process (Jadhav et al., 2012). Sodium hypochlorite (NaOCl) is most commonly used. NaOCl presents the characteristic of dissolve organic matter and in high concentrations, the substance may denature growth factors, besides affects stem cell attachment, survival, and the differentiation. The American Association of Endodontists (AAE) recommend using a 1.5% concentration of NaOCl in regenerative treatments. Nonetheless, it was observed that in cases treated in the present research different concentrations were used, ranging from 1.25 to 5.25%. Chlorhexidine was also used as complement to disinfection; however, its use is discouraged due to its cytotoxic to stem cells from human apical papilla.

In all cases, a tri antibiotic paste was used. Several combinations of antibiotics have been shown to be able to decontaminate the channels, but the mixture of metronidazole, monocycline and ciprofloxacin was the most used in the studies of our review (Jadhav et al., 2012; Bezgin et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; Ulusoy et al., 2019; Rizk et al., 2019). The main disadvantage in using this paste is the discoloration, which - for aesthetic reasons - can put in check the maintenance and longevity of the tooth. Kim et al. (2010) reported that there was coronary discoloration after the use of monocycline in the antibiotic paste introduced into the root canal during the regenerative process. In order to prevent, Dabbagh et al. (2012) proposed the replacement of monocycline by cefaclor, obtaining favorable clinical results, both from the periapical repair process and from coronary discoloration. In the present systematic review, only one study used cefaclor instead of monocycline, and they found results that corroborates with previous published research (Bezgin et al., 2015).

Discoloration was also evaluated comparing the treatment performed. Regenerative endodontics using the blood clot was better in terms of increasing the radiographic area and partial obliteration of the canal (Bezgin et al., 2015; Ulusoy et al., 2019). On the other hand, the group that used PRP had advantages related to coronary discoloration and periapical healing (Bezgin et al., 2015; Rizk et al., 2019; ElSheshtawy et al., 2020).

The blood clot is a traditional method for regenerative treatment. The blood clot acts as a scaffold, and the growth factors inside recruit stem cells, most likely from periapical papilla. An ideal blood clot is necessary to achieve the success; however, incomplete bleeding inhibits suitable clot formation and sometimes it happens. The use of anesthetics with vasoconstrictor impairs the formation of clots, so some studies guide the use of these substances free of vasoconstrictor (Jadhav et al., 2012; ElSheshtawy et al., 2020).

All studies of this systematic review predicted the use of rubber dam to avoid bacterial contamination in the canal, thus improving the prognosis of the treatment. In addition, all studies carried out exclusively chemical or mechanical minimally invasive preparation for disinfecting the root canal with sodium hypochlorite, avoiding conventional mechanical preparation, thus preventing wear and weakening of the dentinal wall (Jadhav et al., 2012; Bezgin et al., 2015; Narang et al., 2015; Alagl et al., 2017; Shivashankar et al., 2017; Ulusoy et al., 2019; Rizk et al., 2019; ElSheshtawy et al., 2020).

The role of scaffolding materials is to fix, proliferate, migrate, and organize the spatial population of cells required for structural and functional term replacement of the target tissue. The latest research concerns the use of platelet concentrates and the most popular platelet concentrates are platelet-rich plasma (PRP). The use of PRP has been suggested as an adequate matrix for the stimulation of the endodontic regenerative process, due to the presence of alpha granules in the platelets, which are

considered reservoirs of growth factors and pro inflammatory cells (Narang et al., 2015; Adel Ragab et al., 2019; ElSheshtawy et al., 2020). In addition, PRP acts as a reservoir of biochemical assets that are released slowly and continuously over a period of 7 to 14 days, increasing the proliferation of various types of cells, in addition to stimulating cell differentiation and angiogenesis (Adel Ragab et al., 2019).

5. Conclusion

This review showed that procedures using PRP were successful in treating permanent teeth with root development. According to good properties, the promising results of the treatment of endodontic revascularization are understood using a matrix with PRP, in order to maintain the integrity and periapical healing, in addition to the longevity of the element in the oral cavity. However, it is necessary future researches regarding to randomized clinical trials to consolidate the therapy.

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