SYSTEMATIC REVIEW

Induced Periapical Bleeding in Regeneration of Immature Permanent Teeth with Necrosis: A Systematic Review

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Abstract

Background and objectives: Regenerative treatment of immature teeth leads to continued root maturation thereby restores the physiologically functional pulp-dentin complex. The present systematic review is conducted to evaluate the efficacy of regenerative endodontic treatment by induced periapical bleeding (IPB) in the regeneration of immature necrosed permanent teeth with an open apex.

Materials and methods: This review was conducted in adherence to PRISMA standards and was registered in PROSPERO with registration number CRD42018091574. We graded the methodological quality of the studies using Cochrane's tool of risk of bias in nonrandomized studies–of interventions (ROBINS-I).

Results: In total, 200 studies were identified for screening, and nine studies were eligible. The quality assessment rated one study as strong, three studies (33.3%) as fair, and five studies (55.6%) as poor. The number of study participants ranged from 17 to 118 (total $n = 394$), with a mean of 43.8. Four studies showed 100% clinical success with IPB. The radiographic success ranged from 60 to 100%.

Conclusion: All of the included studies showed IPB treatment resulted in increased root length, progressive thickening of the dentinal walls, and narrowing of the canal space. Induced periapical bleeding is the best treatment of choice for immature permanent teeth with pulpal necrosis.

Keywords: Immature permanent teeth, Necrosis pulp, Regenerative endodontic treatment, Systematic review.

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Introduction

Immature permanent teeth become non-vital because of infection, dental trauma, operative procedures, or congenital abnormalities.[1] Current endodontic treatment involves the replacement of infected or damaged pulp with exogenous material like calcium hydroxide (CH) or mineral trioxide aggregate (MTA).[1–3] Despite its satisfactory clinical efficacy in pain elimination and infection control, they only seek to seal the space of the root canal system without restoring its original function. Therefore, it may lead to tooth fractures and reinfection of teeth.[4,5] To overcome these limitations, new treatment paradigm is evolved in treatment of immature permanent teeth with necrotic pulp, which is oriented towards preservation and tissue regeneration with better understanding of biological mechanisms, the use of mesenchymal stem cells (MSCs).[6–8] Induced periapical bleeding (IPB) is a regenerative treatment based on the concept that endogenous stem cells which are introduced in root canal space by lacerating the surrounding periapical tissues lead to continued root maturation, thereby increasing root length and root wall thickness and proper apical closure thereby restores the physiologically functional pulp-dentin complex.[9,10]

Recently many human clinical studies were conducted to show the effectiveness of IPB treatment for immature permanent teeth with necrosed pulp.[11–28] The present systematic review is conducted to evaluate the quantitative effects of the IPB treatment for immature necrosed permanent teeth with an open apex.

Materials and Methods

This review was planned, conducted, and reported in adherence to PRISMA standards of quality for reporting systematic reviews and meta-analyses.[29] IRB approval was not required. The present review was registered in PROSPERO with registration number CRD42018091574.

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Conflict of interest:

Questions

We sought to examine the quantitative effects of the IPB on the healing pattern of immature permanent teeth with necrosed pulp compared to the teeth treated with other endodontic treatment procedures.

Study Eligibility

We included studies published in the English language only that investigated the effects of the IPB on the healing pattern of immature permanent teeth with necrosed pulp in humans. Papers were excluded at this stage if they were editorial letter, case report, case series, *in vitro*, animal studies, the regenerative endodontic procedure used for other purposes. The research question of the present systematic review was defined according to the PICO format as:

Population/Patients (P): Subjects with immature permanent teeth with necrosed pulp treated by IPB (MeSH-pulp treatment, endodontic treatment, pulpal therapy, permanent, teeth, dentition, pulpectomy, immature).

Intervention (I): IPB regenerative endodontic treatment in humans only (MeSH–Regenerative, revascularization, bleeding, IPB, revitalization, induced, periapical).
Comparison (C): Treatment of immature permanent teeth with necrotic pulp by other endodontic treatment.
Outcome (O): Clinical or radiographical success with IPB regenerative endodontic treatment.

Study Identification

Various research databases were searched which include, Medline (PubMed, Ebsco, OVID Medline), Embase, (pharmacological literature, European studies), Cochrane library (Trails, Cochrane review), Web of Knowledge (Social science, conference abstract), SCOPUS (scientific web pages, conference abstracts), CINAHL (Nursing and allied health), PsycInfo (Psychology and psychiatry), ERIC (Education) using key terms focused on the specific search strategy. For gray literature following databases were searched: Open Grey, National Library of Medicine, Google scholar, Social science research, For thesis (EthOS, DART-Europe), Institutional repositories (OpenDOAR, e-publications@RCSI Lenus, Bielefeld Base, RIAN). No beginning date was used, and the last date of the search was February 25, 2018. We searched for additional studies in the reference lists of all articles included.

Study Selection and Assessment of Study Quality

We screened all titles and abstracts independently and in duplicate for inclusion. In the event of a disagreement or insufficient information in the abstract, we independently and in duplicate reviewed the full text of potential articles. The inter-rater agreement for study inclusion, as assessed using an intra-class correlation coefficient, was 0.88. Conflicts were resolved by consensus discussion between the two reviewers. The quality of the selected studies was assessed using the Risk of Bias tool (ROB) according to the Cochrane Handbook for Systematic Reviews of Interventions.[30] The selected studies were assessed using the following criteria: random sequence generation, allocation concealment, selective reporting of outcomes, blinding of participants, personnel and outcome assessment, incomplete outcome data (reporting of dropouts), and other bias (bias due to problems not covered elsewhere in the table). Cochrane ROB tool is converted to Agency for Healthcare Research and Quality (AHRQ) standards (Good, Fair, and Poor): good quality when all criteria met (i.e., low for each domain), fair quality if one criterion not met (i.e., high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results and poor quality if two or more criteria listed as high or unclear risk of bias or one criterion not met (i.e., high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results.

Data Extraction and Data Synthesis

Two reviewers did data extraction independently for the included studies using a data extraction sheet, and any discrepancies were resolved by discussion and consensus. The following data were extracted from each included study: first author, publication year, study type, study quality, sample size, treated teeth, total teeth, follow-up period, method of regenerative treatment, outcome assessed, and the authors' conclusion.

Results

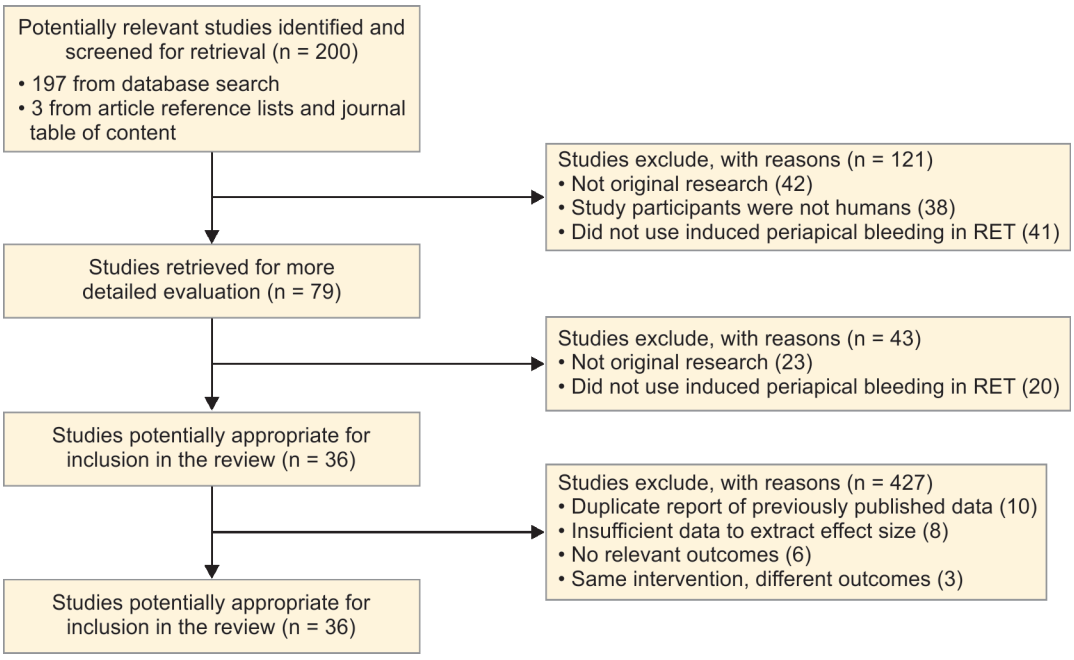
Trail Flow

Using our search strategy, we identified 197 articles with an additional three identified from our review of references and journal indices. From these, we identified nine articles for inclusion in the present systematic review (Flowchart 1).

Study Characteristics and Study Quality

The number of study participants ranged from 17 to 118 (total $n = 394$), with a mean of 43.8. Out of nine studies included in the

Flowchart 1: Study selection flow diagram



review, four studies used controls and five studies assessed the efficacy of IPB endodontic regenerative treatment on immature necrotic pulp without controls (Table 1). The follow-up period varied from 12 to 30 months (Table 2). In all of the included studies, sodium hypochlorite (1.5% to 5.25%) was used as canal irrigating agent followed by application of triple antibiotic paste. Bleeding was induced by lacerating the periapical tissues using K file (Table 3). Table 4 shows the results of the included studies. Lin et al., Li et al., Ashiry et al., and Saoud et al. showed 100% clinical success with IPB. The radiographic success with induced periapical regeneration was ranged from 60 to 100%.

The quality assessment rated one study as strong, three studies (33.3%) as fair, and five studies (55.6%) as poor (Table 5).

Discussion

Recent treatment approaches to pulpal infection or injury to immature permanent teeth include the traditional root canal treatment with the use of improvised synthetic materials, which provide better pulpal seal compared to calcium hydroxide or biological approach based on the molecular and cellular basis for pulpal regeneration.[2,3,11–28] The present systematic review was conducted to analyze the efficacy of IPB endodontic regeneration treatment on necrosed immature permanent teeth in humans. Nine studies were included in the present review.[3,12,15–19,21,22]

Canal Disinfection in Regeneration of Pulp

In all of the included studies, sodium hypochlorite was used as a pulp irrigating agent, followed by the application of triple antibiotic paste for dried canals. A critical step in regenerative therapy is complete eradication of the root canal microbes using copious irrigation, placement of antibiotic pastes, and minimal instrumentation. Disinfection of pulp canal plays an important role in revascularization of immature necrotic pulp by IPB.[31]

Method of Regenerative Procedure

In all of the included studies, bleeding was induced into the root canals by lacerating the periapical tissues and a blood clot was allowed to form and act as a scaffold. Bleeding, in turn, delivers stem cells from the periapical area to the root canal system, and the fibrin scaffold of the blood clot entraps stem cells which are capable of initiating regeneration of necrosed pulp tissue. In all of the included studies, the coronal seal was done with MTA which in turn provided the excellent coronal sealing of pulp canal and marginal adaptation.[6–9]

Clinical and Radiographic Outcome

All of the included studies showed IPB regenerative treatment resulted in increased root length, progressive thickening of the dentinal walls, and narrowing of the canal space. The blood clot inside the sterile root canal acts as a matrix onto which vital periapical stem cells were seeded to reestablish pulp vascularity. These dental periapical stem cells have tissue regeneration potential and proliferated into the newly formed blood clot matrix, differentiate into odontoblasts, and deposit tertiary or tubular dentin. Because of its apical location, the apical papilla has a collateral circulation that enables it to survive during the process of pulp necrosis.[6–9] Lin et al.[3] compared IPB with calcium hydroxide apexification and showed a significant increase in root length, canal wall thickness, and closure of apical foramen with RET group compared to controls. Nagy et al.[22] compared IPB alone

Table 1: Descriptive characteristics of included studies

Author	*Study design, study group*	*Sample size*	*Male to female number*	*Mean or range of age in years*	*Tooth type*	*Number of teeth*
Chan/2017	P, IPB	22	12/10	9.2 years	Central and lateral incisor, premolar and molar	28
Lin/2017	RCT, G1 = IPB G2 = A	118	NA	10.5 years	Central incisor and premolar	118 (G1 = 80, G2 = 38)
Li/2017	P, IPB	20	9/11	10.6 years	1st and 2nd Man molar	20
Shivashankar/2017	RCT, G1 = IPB, G2 = PRF, G3 = PRP	60 (20 in each group)	32/28	6–28 years	Anterior teeth	20 in each group
Ashiry /2016	P, IPB	20	NA	NA	Incisor or premolar	20
Estefan/2016	P, IPB G1–Yn, G2–Yw, G3–On, G4–Ow	40	23/17	9–18 years	Max-anterior	40
Saoud/2014	P, IPB	17	12/5	11.3 years	Anterior teeth	20
Nagy/2014	P, G1 = IPB, G2 = IPB with FGF, G3 = MTA	36 (12 patients/group)	19/17	9–13 years	Max anterior teeth	36 (12/group)
Jeeruphan/2012	R, G1 = IPB, G2 = A with $Ca(OH)_2$, G3 = A with MTA	61 (G1 = 20, G2 = 22, G3 = 19)	36/25	G1 = 12.9 years G2 = 10.5 years, G3 = 14.6 years	Max and Mand incisor and premolar	61 (G1 = 20, G2 = 22, G3 = 19)

RCT, randomized controlled trail; G1, group I; G2, group II; G3, group III; G4, group IV; Yn, 9–13 years of age with apical diameter 0.5–1 mm; Yw, 9–13 years of age with apical diameter ≥ 1 mm, On–14–18 years of age with apical diameter 0.5–1 mm y–years; Ow, 14–18 years of age with apical diameter ≥ 1 mm; PRF, platelet rich fibrin; PRP, platelet rich plasma; IPB, induced periapical bleeding; A, apexification; MTA, mineral trioxide aggregate; FGF, injectable hydrogel scaffold impregnated with basic fibroblast growth factor; Man, mandibular; Max, Maxillary

Table 2: Inclusion criteria, follow-up time, outcome assessment, and author's conclusion

Author	*Inclusion criteria*	*Follow-up time*	*Outcome assessment method*	*Statistical analysis*	*p value for each time interval*	*Authors conclusion*
Chan	Necrotic pulp with open apex	30 m	C–lack of sign and symptoms R (CBCT)–PAH, IRL, ICT, AF	ANOVA and Mann–Whitney *U* test	$p < 0.001$ for PAH, IRL, ICT and AF	Successful revascularization
Lin	Necrotic pulp with open apex (>1 mm)	12 m	C–lack of sign and symptoms R (CBCT)–PAH, IRL, ICT, AF	*t*-test	$p < 0.001$ for IRL and ICT, $p = 0.03$ for AF	Successful revascularization in IPB
Li	Necrotic pulp with open apex	12 m	C–lack of sign and symptoms R–PAH, IRL, ICT, AF	McNemar's test	PAH $p < 0.05$ compared to baseline	Successful revascularization
Shivashankar	Necrotic pulp with open apex (≥1 mm), PAR–>10 mm	12 m	C–lack of sign and symptoms R–PAH, IRL, ICT, AF	ANOVA	ANOVA at 6 month $p = 0.015$, at 12 m $p = 0.016$	PRP better in periapical healing compared to IPB and PRF
Ashiry	Necrotic pulp with open apex	24 m	C–lack of sign and symptoms R–PAH, IRL, ICT	NA	NA	Successful revascularization
Estefan	Necrotic pulp with open apex (0.5–≥1 mm)	12 m	C–lack of sign and symptoms R–IRL, ICT, AF	Two way ANOVA	$p < 0.001$ for IRL, ICT and AF	Younger age with apical diameter 0.5 mm better revascularization
Saoud	Necrotic pulp with open apex	12 m	C–lack of sign and symptoms R–PAH, IRL, ICT, AF	Repeated measures ANOVA and McNemar's test	Repeated measures ANOVA $p <$ 0.0001 for IRL, ICT and AF	Successful revascularization
Nagy	Necrotic pulp with open apex	18 m	C–lack of sign and symptoms R–PAH, IRL, ICT, AF	ANOVA	$p < 0.0001$ for IRL and AF	IPB alone good for revascularization
Jeeruphan	Necrotic pulp with open apex	G1 = 21.1 m, G2 = 27.3 m, G3 = 14.2 m	C–lack of sign and symptoms R–PAH, IRL, ICT, AF	Kruskal–Wallis ANOVA and Mann–Whitney *U* test	$p < 0.0001$ for IRL, ICT and AF in IPB compared to controls	Successful revascularization in IPB

C, clinical; R, radiographic; PAH, evidence of periapical healing (if a periapical lesion was present); CBCT, cone beamed computed tomography; PAR, periapical radiolucency; IRL, increased root length; ICT, increased root canal wall thickness; AF, apical foramen diameter; PRF, platelet rich fibrin; PRP, platelet rich plasma; IPB, induced periapical bleeding; ANOVA, analysis of variance

Table 3: Root canal irrigating agent, antibiotic treatment used, regeneration procedure of included studies

Author	*Canal irrigating agent*	*Antibiotic treatment of canal*	*Regenerative treatment, apical tissue*	*Medicament over blood clot*	*Follow-up periods*	*Total subjects at final follow-up*
Chan	5.25% NaOCL	TA–metronidazole–500 mg, ciprofloxacin–500 mg, cefaclor–100 mg	After 2–6 weeks ATB using file, 1–2 mm below apical tissue bleeding to the 3 mm below CEJ	MTA	1, 2, 3, 6, 9, 12, 18, 24, and 30 m	22
Lin	20 mL of 1.5% NaOCL, 0.9% saline, 17% EDTA	TA (1 : 1 : 1 weight)–metronidazole, ciprofloxacin, clindamycin	After 3 weeks ATB using 25 K-file bleeding to the 3–4 mm below CEJ	ACB and MTA	3, 6, 9, and 12 m	103
Li	2.5% NaOCL	NA	After 2 weeks, ATB using 15 K-file bleeding to the 2–3 mm below CEJ	MTA	3, 6, 9, and 12 m	20
Shivashankar	5.25% NaOCl	TA (1:1:1 weight)–metronidazole–400 mg, ciprofloxacin–200 mg, minocycline–100 mg	After 3 weeks, ATB using K-file 2 mm below apical foramen bleeding to the of level CEJ	MTA	3, 6, 9, and 12 m	54
Ashiry	10 mL 2.5% NaOCl with a 27-g syringe for 2 min	TA–metronidazole, ciprofloxacin, minocycline–250 mg each, using L, 2 mm short of root apex	After 2 weeks, ATB using 20 K-file at a level 3 mm below CEJ	MTA followed by Cavit seal	2 weeks, 6, 12, and 24 m	16
Estefan	10 mL 2.6% NaOCl	TA–metronidazole–500 mg, ciprofloxacin–250 mg, doxycycline–100 mg	After 3 weeks, ATB using 50 K-file at 2 mm below apical opening bleeding to the level of CEJ	MTA	3, 6, 9, and 12 m	35
Saoud	2.5% NaOCl	TA (1:1:1 weight)–metronidazole–500 mg, ciprofloxacin–200 mg, minocycline–100 mg	After 2 weeks, ATB using precurved K-file, 2 mm below apical foramen bleeding to the of level CEJ	MTA	1, 3, 6, 9, and 12 m	20
Nagy	10 mL 2.6% NaOCl	TA (1:1:1 weight)–metronidazole–500 mg, ciprofloxacin–200 mg, doxycycline–100 mg	ATB using 80 K-file, 2 mm below apical foramen bleeding to the of level CEJ	MTA	3, 6, 12, and 18 m	29
Jeeruphan	2.5% NaOCl	TA (1:1:1 weight)–metronidazole–500 mg, ciprofloxacin–200 mg, minocycline–100 mg	ATB using K-file or endo spreader, 2 mm below apical foramen bleeding to the of level CEJ	MTA	21.1 m	61

g, gauge; NaOCL, sodium hypochlorite; TA, triple antibiotic dressing paste; L, lentulo-spiral; ATB, apical tissue bleeding; ACB, absorbable collagen barrier; PPI, positive pressure irrigation; CEJ, cementoenmel junction; MTA, mineral trioxide aggregate; m, month

Table 4: Outcome of included studies

		Clinical outcomes in a number of teeth or mean score ± SD			*Radiographic outcomes in a number of teeth or mean score ± SD*				*Main study outcome in percentage*	
Author		*Spontaneous pain or pain initiated by stimuli*	*Signs of S, TTP, and M*	*Signs of DR or RC*	*PAH*	*IRL*	*ICT*	*AF*	*Clinical success*	*Radiographic success*
Chan		2	2	2	21	22	18	22	92.8	96.4
Lin	G1 (IPB)	0	0	0		1.6 ± 1.4	0.2 ± 0.2	1.5 ± 0.9	100	81
	G2 (A)	0	0	0		0.6 ± 1.06	0.08 ± 0.2	1.8 ± 0.6	100	26
Li		0	0	0	18	11	19	8	100	90
Shivashanker	G1 (IPB)	0	0	0	12	12	12	12	80	60
	G2 (PRF)	2	2	2	15	15	15	15	100	100
	G3 (PRP)	0	0	0	19	19	19	19	100	100
Ashiry		0	0	0	16	16	16	NA	100	100
Estefan	G1-Yn	0	0	0	NA	1.09± 0.5	0.5 ± 0.2	0.4 ± 0.2	100	100
	G2-Yw	0	0	0	NA	1.3 ±1.08	0.6 ± 0.4	1.1 ± 0.5	88.9	88.9
	G3-On	0	0	0	NA	0.4 ± 0.2	0.1 ± 0.1	0.1± 0.09	88.9	88.9
	G4-Ow	0	0	0	NA	0.4 ± 0.3	0.4 ± 0.2	0.7 ± 0.4	100	100
Saoud		0	0	0	20	20	20	11	100	79
Nagy	G1 (IPB)	1	1	1	12.7 ± 5.5	1.2 ± 0.5	0.3 ± 0.1	0.8 ± 0.3	90	90
	G2 (IPB with FGF)	2	2	2	12.2 ± 6	1.3 ± 0.5	0.2 ± 0.09	0.9 ± 0.2	80	80
	G3 (MTA)	0	0	0	14.6 ± 7	0 ± 0	0 ± 0	0 ± 0	100	100
Jeeruphan	IPB	0	0	0	20	20	20	20	100	100
	$Ca(OH)_2$	5	5	5	17	0	0	0	77.3	77.3
	MTA	1	1	1	18	0	0	0	94.7	94.7

G1, group I; G2, group II; G3, group III; G4, group IV, Yn, 9–13 years of age with apical diameter 0.5–1 mm; Yw, 9–13 years of age with apical diameter ≥1 mm; On, 14–18 years of age with apical diameter 0.5–1 mm y–years; Ow, 14–18 years of age with apical diameter ≥1 mm; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; IPB, induced periapical bleeding; S, sinus formation; TTP, tenderness to percussion; M, mobility; DR, defective restoration; PAH, evidence of periapical healing (if a periapical lesion was present); IRL, increased root length; ICT, increased root canal wall thickness; A, apexification; AF, apical foramen diameter

Table 5: Risk of bias tool for included studies

	Risk of bias tool						
Author/year	*RSG*	*AC*	*BPPO*	*IOD*	*SOR*	*OSB*	*AHRQ rating*
Chan/2017	Low	Low	High	Low	Low	Low	Fair
Lin/2017	High	Low	High	Low	Low	Low	Poor
Li/2017	High	Unclear	Low	High	Unclear	Low	Poor
Shivashankar/2017	Low	Low	Low	Low	Low	Low	Good
Ashiry/2016	High	High	Low	High	High	Unclear	Poor
Estefan/2016	High	High	Low	High	Low	Unclear	Poor
Saoud/2014	High	Unclear	Low	Low	Low	Low	Fair
Nagy/2014	High	Unclear	Low	Low	Low	Low	Fair
Jeeruphan/2012	High	Low	Unclear	Low	High	Low	Poor

RSG, random sequence generation; AC, allocation concealment; BPPO, blinding of participants, personnel and outcome assessors; IOD, incomplete outcome data; SOR, selective outcome reporting; OSB, other sources of bias; AHRQ, agency for healthcare research and quality

and IPB with fibroblast growth factors (FGFs) with MTA. The result showed significant radiographic changes in IPB and IPB with the FGF group compared to MTA.

Study Limitations

The limitation of the present review was, due to heterogeneity across the studies, we could not do the meta-analysis of included studies. The heterogeneity was caused by variation in the *in vivo* models, such as follow-up period, type of teeth included, age of the study participants. Therefore, no forest plots or funnel plots were constructed. Due to the disparate nature of the studies, only simple descriptive and stratified comparisons are reported. The quality assessment rated only one study as good, three as fair, and four as poor. The present results point to the need for high-quality randomized controlled trials in further research and the need for alternative methods to perform "*in vitro*" researches on the effects of pulp regenerations in customized models.

Conclusion

All of the included studies showed IPB regenerative endodontic treatment resulted in increased root length, progressive thickening of the dentinal walls, and narrowing of the canal space. Induced periapical bleeding is the best treatment of choice for immature permanent teeth with pulpal necrosis.

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