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SYSTEMATIC REVIEW

Novel non-obturation based concept of regeneration

ABSTRACT

***Aim**: This systematic review aimed to evaluate the healing achieved through a novel SealBio technique and assess the inherent complications or failures caused during treatment of endodontic diseases.*
***Methodology**: The present review was conducted according to the PRISMA guidelines and was registered in PROSPERO (Registration number – CRD42020201943). The research question was formulated based on the PICO strategy. A comprehensive electronic literature search was conducted across PubMed/Medline, Google Scholar and Cochrane Database independently by two reviewers. Articles published on SealBio up to May 2024 were included. Based on the specified inclusion and exclusion criteria, the selected articles were subjected to quality assessment, and the risk of bias was conducted using the Cochrane risk of the bias assessment tool.*
***Results**: A total of 4 studies were included in the present systematic review and reported success rates with the SealBio technique around 97-100%. However, all included papers demonstrated a high overall risk of bias and some limitations.*
***Conclusion**: Based on the present study, SealBio technique did not furnished concrete evidence to replace the standard endodontic protocol. However, additional evidences provided by standardized and well conducted clinical trials with low risk of bias are needed.*

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Introduction

The endodontic procedure can be defined as a process where the complex root canal anatomy of teeth is treated in a simplified way. Endodontic success is attributed to three major factors: the complete disinfection of the root canal system, proper instrumentation and three-dimensional obturation (1). Ideally, an endodontic therapy aims at achieving the three-dimensional seal both coronally and apically after optimal shaping, cleaning, and disinfection of root canal space (2). Especially in cases of infected root canals, the combating strategies target microbial biofilm dislodgement which ultimately reduces the microbial colonies, although complete eradication of microbes is never achievable (3).

Endodontic literature has shown that outcome-based studies mainly categorize healing in terms of clinical resolution of symptoms and radiographic reduction of apical periodontitis if previously reported (4-6). The overestimation by periapical radiography and the questionable validity of peri-apical index (PAI) in detecting periapical lesions were considered serious limitations. A recent review discussed the fact that future studies should re-evaluate the outcomes through long-term longitudinal studies using CBCT-based criteria (7). Although endodontic therapy attempts to resolve the above-mentioned criteria by achieving adequate apical seal using sealer and gutta-percha, the ultimate goal would be to obtain a fibrous or cemental barrier at the root apex (8). Conventional endodontic treatment replaces the tissues with artificial materials resulting in a reparative process; however, endodontics' progression is towards regeneration rather than repair.

Considering the event of revascularisation conceptualized by Ostby in 1961 (9), few years later Rule & Winter (10) demonstrated the root development and apical barrier formation after pulpal necrosis. This concept of neurogenesis following a revascularization procedure gained significant interest in endodontics' regenerative aspect. It's seen that in immature permanent teeth, the periapex seems to harbour a variety of progenitor cells, which actively participate in the regeneration of tissues (11). Therefore, only an empty disinfected canal would not aid in tissues' growth from the periapex (12). Moreover, an intentional bleeding induced into the root canal space promotes a granulation tissue formation, creating a more favourable environment to allow self-renewal of stem cells and progeny, thereby providing a niche for future dental progeny (11).

Taking this scientific literature into consideration, a novel, non-obturation, regenerative treatment protocol "Seal Bio" was developed and a patent filed (US patent no: US, 9, 180, 072B2, Australian patent no: 2010355508) by N.Shah, A.Logani in 2009. It's based on the concept of revascularisation and depends on the claimed regenerative potential of the periarticular area near root apex. The release stimulated cells after bleeding induction should lead to a biological barrier at the root apex (2).

The basic technique of SealBio (2) includes the complete disinfection of root canal space following an optimal enlargement of root canals. Once the adequate disinfection is achieved, "Apical Clearing" is initiated, which includes the intentional over enlargement of apical diameter. Specifically, the apical third is enlarged with 2-4 file sizes larger than master apical file until the radiographic terminus without transporting the original canal path. Then, foramen widening is obtained using #25 or #30 k files. This process is claimed to clean the cemental part of the canal. Once the infection control is achieved and clinically symptom-free, intentional over instrumentation is done beyond the apex using the #20 K file to induce bleeding near the apical foramen. When a clot stabilizes the bleeding, an adequate coronal seal is given using a calcium sulfate-based material (Cavit). The benefit of this material was the achievement of good sealing (13) and more accessible removal during retreatment as compared to glass ionomer cement (GIC) or mineral trioxide aggregate (MTA) (2).

Although this new concept is gaining popularity and might change the endodontic treatment protocol, evidences have shown that outcome data are still lacking. Hence, this systematic review mainly aimed to evaluate the healing achieved through this technique and assess the inherent complications or failures caused during treatment of endodontic diseases with the following research question: "Is there any variation in the healing, failure or complications by employing the Seal Bio technique as an alternative to routine endodontic therapy?"

Methodology

The present review was conducted according to the PRISMA guidelines and was registered in PROSPERO (Centre for Reviews and Dissemination University of York; http://www.crd.york.ac.uk/PROSPERO) database with registration number CRD42020201943.
The PICOS was taken as
Population: teeth needing endodontic treatment;
ntervention/Comparison: teeth undergoing SealBio technique instead of conventional endodontic therapy;
Outcome: primary outcome was to assess the healing in terms of clinical and/or radiographic success, and the secondary outcome was to assess the inherent complications or failures.

Search Strategy
A comprehensive literature search was conducted on electronic databases as PubMed/Medline, Google Scholar, and Cochrane Database.
Articles published on SealBio up to May 2024 were included in the present review. Search was conducted with a combination of various Boolean operators which included key terms as the following; "Mature teeth", "Human teeth", "Irreversible pulpitis", "Apical periodontitis", "Conventional endodontic therapy", "SealBio", "Non-obturation technique", "Regeneration", "Healing", "Complications", "Failure". In addition, hand searching was done in the following journals; International Endodontic Journal, Journal of Endodontics, Restorative Dentistry and Endodontics, and European Endodontic Journal.

Inclusion criteria
The following inclusion criteria were used to select the studies:
- studies published in Peer-reviewed Journals;
- studies published in English language;
- studies reporting clinical trials: randomized clinical trials, comparative clinical trials, prospective clinical trial;
- studies reporting on use of SealBio technique assessing healing and complications/failures.

Exclusion criteria
The following exclusion criteria were used to select the studies:
- laboratory-based studies, case reports, case series or ex vivo studies;
- studies on animal samples;
- grey literature.

Study Selection
Screening and selection of studies was performed by two independent calibrated examiners (T.K.V & V.K.A) following the inclusion/exclusion criteria. After duplicates removal, papers were evaluated by title and abstract. Then, full texts of potentially relevant articles were obtained and data extracted. Reasons for studies exclusion were also reported. In case of disagreement, a consensus was reached after discussion with a third reviewer (M.M).

Data extraction and analysis
The qualitative assessments of included articles were undertaken independently during the data extraction process. For each studies the following information were reported: authors, year, study design, treatment groups and samples, patients age, gender, selected teeth, preoperative condition, sample size calculation, used anaesthetic and technique, isolation method, number of treatment visits, instrumentation system used (technique, taper, apical preparation size); type, concentration and volume of irrigants used and agitation systems; type of intracanal medicament;

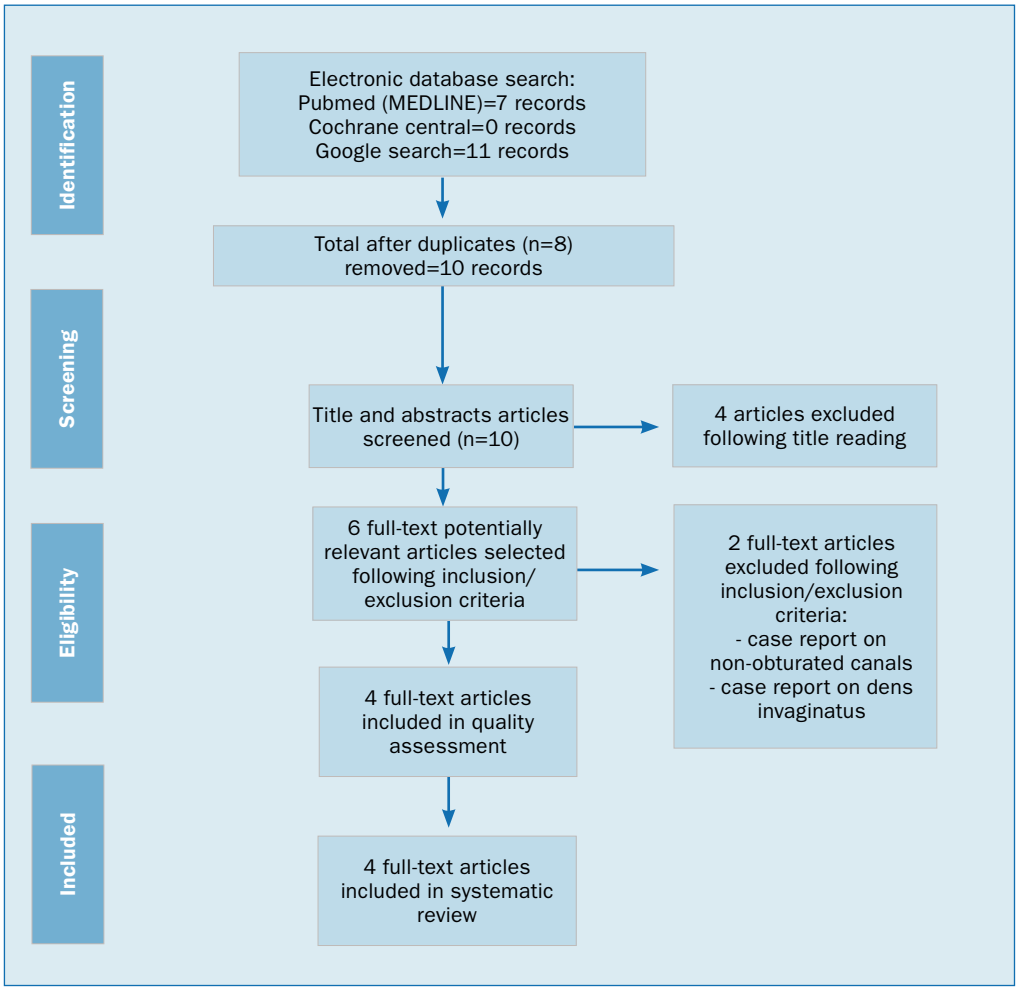

Figure 1
PRISMA flowchart study selection.

apical clearing protocol; foramen widening protocol, over instrumentation protocol; coronal seal, outcomes variables and their assessment, follow-up, drop-outs, success, failures/complications, conclusion. The risk of bias of included studies was assessed using the Cochrane Risk of Bias assessment tool based on major and minor assessment criteria. No additional analysis was performed, and only qualitative review was possible due to the heterogeneity of included studies.

Results

The search identified ten articles after the removal of duplicates. Then, four papers were excluded after title and abstract evaluation. The remaining six papers underwent full-text reading and according to eligibility criteria, four articles were included in the present systematic review and processed for quality assessment and data extraction (Figure 1).

Summary of included studies

Among the 4 included papers, (2, 16-18) three were prospective studies (2, 17, 18) and one was a retrospective based study (16). Three evaluated the SealBio technique in nonsurgical root canal treatment (2, 16, 18) whereas the remaining one assessed the success of SealBio technique in large periapical cysts managed by surgical fenestration followed by application of non-obturation technique for healing of surgical lesion (17).

Included studies have various heterogeneities ranging from study designs to the operator-based variants, such as instrumentation technique, choice of instrument, irrigation protocol, and selection of intra-

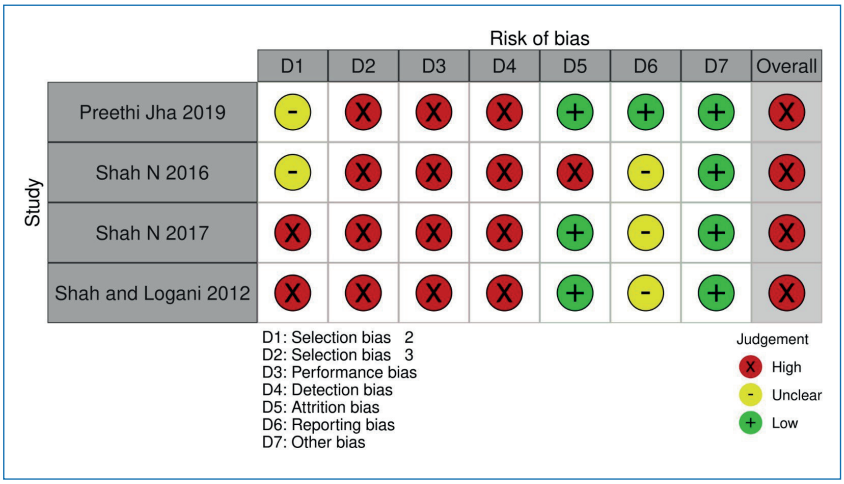

Figure 2
Risk of bias summary.

canal medicament and final irrigation activation. Although various factors were not similar, the actual SealBio technique, which included apical clearing protocol, foramen widening protocol, over instrumentation protocol for inducing bleeding, was almost identical in all included articles (Table 1). Coronal seal was obtained with only calcium sulfate-based cement (CAVIT) in almost all studies due to the easier removal during retreatment (if required) compared to MTA. On the other hand, the paper that involved a surgical design, used a double seal concept (17), namely a glass ionomer restoration was used on the top of the calcium sulfate. None of the included articles discussed data on the type of neither the irrigating needle used nor the gauge or depth of placement volume of irrigants (Table 1). The primary important factor missed in 3 of the included studies was the comparative group or control group (2 16, 17). Ideally, success or failure could not be evaluated using a single group. Only one study (18) included a comparative obturation and reported no differences between analysed groups.

When clinical success and failure rates among the included studies was analysed, a high heterogeneity with the assessed data and interpretation was observed. Only one study by Shah (16), had represented the data in terms of success and failure rates. Moreover, none of the selected articles discussed complications associated with the novel technique. Reasons of failure was only reported by Shah in 2016 (16).

Concerning clinical and radiographical evaluation criteria, they varied within different included studies. Most clinical criteria were more or less similar considering asymptomatic functional tooth with a resolution of sinus tract if reported before the treatment procedure as clinical success. With regard to radiographic criteria, 2 studies used PAI for radiographic evaluation (2, 18) and in few cases (n=3) CBCT was employed to measure the resolution of lesions (2). The study conducted by Shah in 2017 (17) reported no specification on the clinical or radiographic criteria used for assessments during follow-up.

The follow-up periods also varied among different included studies. Maximum follow-up period was up to 6 years in the study by Shah 2016 (16).

Figure 3
Risk of bias graph.

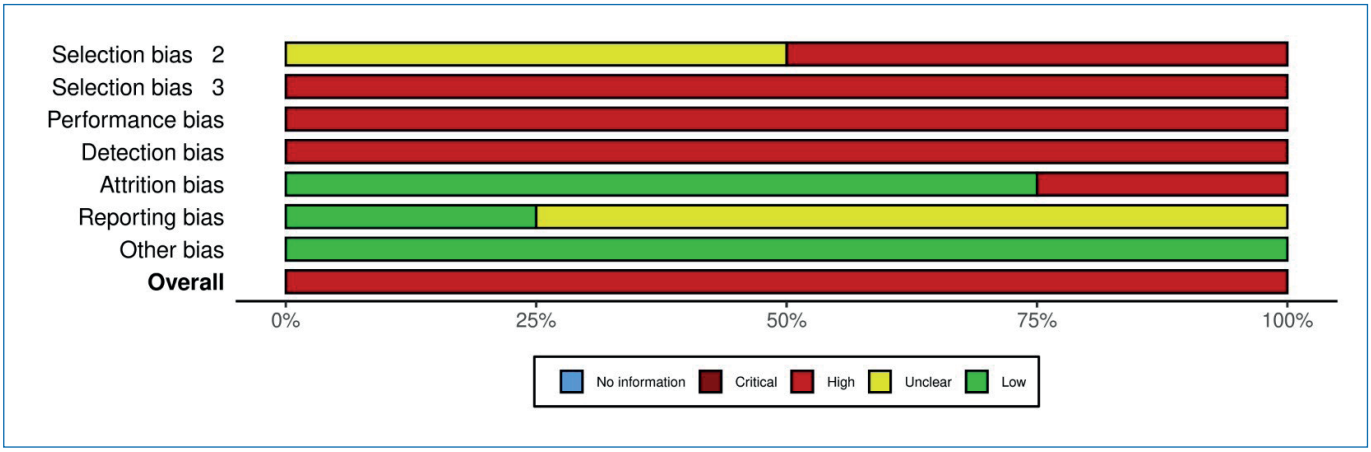

Table 1

Characteristics of included studies

	Shah & Logani 2012 (2), Prospective study	Shah N. 2016 (16), Retrospective study	Shah N. 2017 (17), Prospective study	Preeti Jha et al., 2019 (18), Prospective study
Treatment Groups and sample size	SealBio group (18 patients); No comparative or control group.	SealBio group (116 patients and 134 teeth); no comparative or control group.	Surgical curettage and SealBio group (5 patients); no comparative or control group.	SealBio group and obturation group.
Inclusion criteria: Patients age/gender, selected teeth, arch, preoperative condition, sample size calculation	15-76 years; both male and female; no specification on selected teeth and arch; teeth with pulp and periapical infection; sample size calculation not specified.	Age limit and gender not specified; no specification on selected teeth; either irreversible pulptis, acute or chronic apical periodontitis; sample size calculation not specified.	14-38 years; 4 males and 1 female patient; maxillary and mandibular anterior teeth were selected; radicular cyst cases; sample size calculation not specified.	Aged 9-15 years were selected; both male and female patients; no specification on teeth selected, arch; teeth with apical periodontitis with Ostravik's PAI score>=3 were included.
Treatment protocol (anaesthetic and technique; isolation method; number of treatment visits; instrumentation system (technique, taper, apical preparation size); type, concentration and volume of irrigants and agitation systems; intracanal medicament; apical clearing protocol; foramen widening protocol, over instrumentation protocol; coronal seal	Not specified the type of anaesthetic and method of administration; isolation; number of visits (one or two depending on infection); crown down technique: not specified used instrumentation system, taper and preparation size; irrigants: 2.5% sodium hypochlorite (no specification on volume, other irrigants and agitation technique); triple antibiotic paste as intracanal medicament; apical clearing: 2-4 file sizes larger than master apical file; foramen widening using 25-30 k files; over instrumentation using 20 k files beyond the apex; coronal restoration calcium sulphate based cement (Cavit) packed until cervical third of root canal.	Not specified the type of anaesthetic and method of administration; isolation; number of visits (one or two depending on infection); crown down technique: not specified used instrumentation system, taper and preparation size; irrigants: 2.5% sodium hypochlorite (no specification on volume, other irrigants and agitation technique); both triple antibiotic paste and calcium hydroxide intracanal medicament were used; apical clearing was done with 2-4 file sizes larger than master apical file; foramen widening using 25-30 k files; over instrumentation using 20 k files beyond the apex; coronal restoration calcium sulphate based cement (Cavit) packed until cervical third of root canal.	2% lignocaine hydrochloride (technique of administration varied depending on the arch and tooth); rubber dam isolation; no specification on number of treatment visits; hand k files, not specified instrumentation technique; 2% tapered preparations with no specifications on preparation sizes (it varied with cases); 1% sodium hypochlorite (no specification on other irrigants, volume of irrigant used, agitation method); calcium hydroxide paste as intracanal medicament; prior to the surgical fenestration, apical clearing was done with 2-4 file sizes larger than master apical file; foramen widening using 25-30 k files and access cavity was closed with cotton; after surgical curettage and closure of the site, cotton pellet was removed from the access cavity, canals were dried and over instrumentation using 20 k files beyond the apex; coronal restoration calcium sulphate based cement (Cavit) packed until cervical third of root canal followed by glass ionomer permanent restoration.	3% mepivacaine without adrenaline; rubber dam isolation; no specification on number of treatment visits; dentsply protaper universal files used for root canal preparation with no specified preparation technique; no specification on taper and apical preparation sizes; 2.5% sodium hypochlorite was used for irrigation using negative pressure EndoVac technique, 17% EDTA liquid was used as final irrigation solution; no specification on agitation systems used; triple antibiotic paste was used as an intracanal medicament; apical clearing was done with 2-4 file sizes larger than master apical file; foramen widening using 25-30 k files; over instrumentation using 20 k files beyond the apex; coronal restoration calcium sulphate based cement (Cavit) packed until cervical third of root canal.
Outcome variables and outcome assessments criteria (clinical and radiographic criteria).	Clinical and radiographic evaluations; no note on clinical methods; radiographic evaluation included both CBCT and IOPA based assessments; no specification on criteria used for IOPA based assessments; pre and post treatment CBCT was done for 3 cases (6 teeth) using single iCAT machine at 120kvp, 5mA, exposure time of 7 seconds and voxel size of 0.25; parameters evaluated included the lesion size, bone and cementum density in HU and assessment criteria followed was (CBCT-PAI index scoring).	Clinical and radiographic evaluations; clinical criteria included-asymptomatic and functional teeth, healed intraoral sinus or swelling if any presented prior to the treatment; radiographic evaluation included the complete healing or decrease in the size of radiolucency; in cases with normal periapex no lesion should develop subsequent to the treatment. No specification on index used nor the devices used for radiographic evaluation.	Clinical and radiographic evaluations; no specification on criteria used for clinical and radiographic assessments.	Clinical and radiographic evaluations; clinical criteria included: absence of clinical signs and symptoms (spontaneous pain, presence of sinus tract, swelling, mobility, periodontal probing depths greater than baseline measurement, sensitivity to percussion or palpation); radiographic evaluation included: assessments of change in apical bone densities at subsequent follow-up's and PAI index.
Follow-up period and drop-outs	6 months to 5 years; no drop-outs.	6 months to 6 years; 16 drop-outs.	No specification on follow-up periods. Only mentioned short follow ups (6-12 weeks).	6, 12 and 18 months of follow-up.
Success and failure of treated teeth (percentages); reasons for failures if specified; complications associated with the studied treatment (if specified).	All cases showed good healing response :success rate was 100% and failure rate was 0%. No the complications were reported.	Success rate: 97%, failure rate: 3%; reasons for failure: unsuccessful technique, endodontic cause, coronal leakage. No complications were reported.	No failures or complications were reported; success rates: 100%, failure rate: 0% within short follow-up period.	13 out of 15 cases completely healed and 2 out of 15 cases were healing with no persistent disease (success rates 100% and failure rate 0%); no complications were reported.
Conclusions	The novel treatment protocol showed to be favourable in resolving periapical infection, both clinically and radiographically.	SealBio was found to be successful non obturation and regeneration based endodontic treatment protocol.	SealBio combined with Surgical fenestration was found to be highly effective in healing large periapical cystic lesions.	Both groups showed favourable outcomes at the end of 18 months without any statistical significant difference.

CBCT: cone-beam computed tomography
HU: Hounsfield units
IOPA: Intra-Oral Periapical Radiograph
PAI. Peri-apical index

Table 2

Evidence level of selected articles

	Author & Year	Study Design	Level of Evidence
1	Shah & Logani 2012 (2)	Non-randomised clinical trial	Level 3
2	Shah 2016 (16)	Retrospective cohort study	Level 4
3	Shah 2017 (17)	Case control study	Level 4
4	Preeti Jha et al. 2019 (18)	Randomized clinical trial	Level 2

Qualitative analysis

The overall risk of bias was assessed and all the included studies showed high risk (Figure 2 and 3). There are many variables, which were unclear in the performed studies. The evidence level of included studies was also low except for Preethi Jha et al 2019 (18) namely a randomized clinical trial that included a comparative group of conventional root canal obturation and followed-up the groups for almost 18 months (Table 2).

Discussion

Most of the failures after endodontic treatment can be attributed to improper debridement (19, 20). In 1953, Grossman stated that the optimal concentration of the necrotic debris or toxic load is necessary to sustain or increase the periapical infection (21). Fabricius et al., on the other hand, stated that the permanent root canal filling has limited effect on endodontic treatment outcome unless and until the bacterial load was controlled, especially at the time of obturation (22). The concept of bacterial threshold was put forth by Siqueira & Rôças (23). They specified that any disease-causing species should reach a population density or load to cause direct tissue damage or modulate the host tissue response to infection. So, for a clinical successful procedure, the bacterial threshold has to be reduced below the cultivable levels (103-104 cells). Considering all these aspects, a novel regenerative non-obturation-based SealBio technique was introduced based on the concept of revascularisation.

The technique basically claims the benefit of utilizing the blood clots innate response formed at the apical area to allow the occurrence of healing. The present systematic review proves that the success rates using the SealBio technique were estimated to be around 97-100%. However, there are many limitations among the included studies, which hinder the generalized population's reliability. When these techniques have to be critically appraised, there were no data on the type of repaired tissue, both intra, and extra-radicular. Systematic reviews on histological assessments of failed revascularisation cases showed that the necrotized spaces were either replaced by the cementum or bone-like tissue or fibrous connective tissue (24). So, the hypothesis formulated as regeneration of the pulp-like tissue is not yet proven. Revascularization procedures are based on the utilization of various stem cells which reside in the periapical region, including the dental pulp stem cells (DPSC), periodontal ligament stem cells (SCPDL), bone marrow mesenchymal stem cells (BMMSC), and finally, the stem cells of the apical papilla (SCAP), that play a role in neurogenesis and the revascularization procedure (25, 26). None of the laboratory studies, either histological or molecular, has shown the presence of any of these cells at the terminus of the mature root apex. So, the concept of utilizing the native stem cells of inflamed periapex is not documented or proved yet.

Concerning the maintenance of results over time, one of main limitations of SealBio technique included the impossibility to predict its prognosis. The estimated success of conventional primary endodontic treatment ranges from 68-85% (4) and secondary endodontic treatment about 77% (5). On the contrary, the same success rate cannot be expected with SealBio technique as proved by varied reported outcomes. The other important factor that has to be discussed is the generation or propagation of cracks (incomplete or complete) caused by the enlargement of the apical foramen (27), even though a recent study by Pradeep et al. (28) showed no evident crack formed in vivo. However,

this aspect has to be clarified. Moreover, although some authors discussed that post and core restoration could be performed after a Bio Seal procedure (2) there are many concerns about blindly restoring an open space with a post and guarantee a long-term success. Ideally, performing post and core restorations in the teeth that underwent SealBio technique is still a controversial topic, which has to be critically analysed.

The major disadvantage of the abovementioned technique is tooth status estimation. Ideally, there is no vital pulp nor tissue that may respond to vitality test. Therefore, the prediction of pulpal status is not quantifiable. Furthermore, deposition of calcific material in the open root canal spaces after revascularization procedures have been reported (29-31), and it should be considered that deposition rate or the type of formed deposition are not predictable due to unexpected response to treatment procedure.

In conclusion, the limitations are more as compared to benefits. Therefore, when risks have to be addressed, the limited data are insufficient to prove that SealBio treatment strategy is superior or similar when compared with the present high standard of endodontic therapy.

Conclusion

Prospective research has to be performed with the aim to analyze various molecular insights of healing response after SealBio technique. In addition, histological studies have to confirm the type and rate of tissue deposition. The role of stem cell within disinfected root canal space should also be analysed and investigated at a vast level to modify the present regenerative treatment protocol. Although the present review concludes the success rates of 97-100% with SealBio technique in surgical and nonsurgical endodontics, the literature is scarce with the low evidence-based studies. Therefore, the present technique did not furnish concrete evidence to replace the standard endodontic protocol.

Clinical Relevance

The present review provides an insight into the success of the SealBio technique for endodontic treatment and its potential to be considered as a valid alternative to traditional endodontic treatment.

Conflict of Interest

None.

Acknowledgements

None.

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