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TITLE OF THE THESIS

"A comparison between the sealing ability of mineral trioxide aggregate and different root-end filling materials used in endodontic microsurgery" – A systematic review

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List of symbols and acronyms

RCT- Root canal treatment

CBCT – Cone beam computerized tomography

EDTA - Ethylenediaminetetraacetic acid

MTA- Mineral trioxide aggregate

Super-EBA – Super ethoxy benzoic acid

ZOE – Zinc oxide eugenol

IRM – Intermediate restorative material

Abstract

Background:

Periapical surgery is a procedure performed in a tooth with persistent periapical lesions, either after a failed primary endodontic root canal treatment or after a failed non-surgical root canal retreatment. For a successful clinical outcome, a correct apical seal needs to be achieved and this is highly influenced by the material chosen. Mineral trioxide aggregate has long been considered the gold-standard material but as it faces some disadvantages newer materials have been introduced which overcomes these obstacles. Some of these materials includes Biodentine, Super-EBA and glass-ionomer cements.

Objective:

The main objective of the present systematic review was to evaluate the sealing capacity of root-end filling materials used in periapical surgery.

Furthermore, MTA is compared to different root-end filling materials in regard to their sealing capacity by measuring the leakage produced with a dye solution.

Material and methods:

An electronic search was conducted by one independent examiner on Medline and Scopus. The search was made in accordance with the PICO-question "In extracted human teeth treated with apicoectomy, what root-end filling material offers the higher sealing quality measured with a dye solution in comparison to MTA?". Studies with a sample size less than 10 teeth and studies which did not indicate the sample size and root-canal filling material were excluded.

To assess the risk of bias, the OHAT (National Toxicology Program Office of Health Assessment and Translation) risk of bias rating tool was used.

Results:

Following an analysis of 69 studies, 9 articles were included in the study. The studies comparing Biodentine to MTA showed that Biodentine had a similar sealing quality to MTA and no statistical difference could be found between the two materials.

All the studies that included Amalgam would show that to be the material with highest leakage.

Conclusion

Based on the results from this systematic review, MTA maintains as the material offering the highest sealing, although Biodentine shows very promising results that could be superior to MTA. More long-term in vivo studies should be performed with Biodentine.

Keywords: "Apicoectomy", "Endodontic microsurgery", "MTA", "Sealing", "Retrograde obturation"

1. Introduction

1.1 Endodontic treatments

Endodontic treatments comprise a variety of dental treatments dealing with the pulpal tissue for instance vital pulp therapies, root canal treatments (RCT), non-surgical retreatments and endodontic surgery (1). The principal objective is to remove or prevent bacterial infiltration in the root canal system through different techniques and materials (2). A RCT is required when the inside of a tooth becomes infected without the possibility to repair itself or, if left untreated, necrotic (3). The main goals of the preparation of conducts are to clean and disinfect the conducts while shaping them for finally sealing the system using a biocompatible material (4).

In the event of a persistent periapical lesion with no signs of healing after an initial RCT the clinician is faced with the following treatment options; nonsurgical retreatment, surgical retreatment or extraction with the possibility of placing an implant (5).

Non-surgical root canal retreatment is composed by the cleaning and shaping of the previously obturated root canals for re-obturation. The old root canal filling material is removed using different endodontic instruments (6).

1.2 Endodontic microsurgery

When a non-surgical retreatment has been unsuccessful or after a failed primary endodontic treatment, a surgical approach may be indicated. With a surgical procedure both the intracanal and extra-canal infection can be managed through the resection of the apical portion of the root (7).

The primary indication for an endodontic surgery includes persistency of an apical infection with or without symptoms in a previously root-canaled tooth where either a non-surgical approach has failed or could not be attempted, in cases where a biopsy is implied due to a suspicious lesion, correcting an iatrogenic mistake such as instrumentation fracture or other patient related factors (8).

A non-healing periapical lesion can be diagnosed through radiographs in which a radiolucent area around the apex is maintained 4 years after treatment. Generally, this is done with a periapical radiograph, or a cone-beam computed tomography (CBCT) in which a three-dimensional image of the structures will appear (9).

1.2.1 Traditional vs modern endodontic surgery

Root-end surgery can be divided into traditional endodontic surgery and modern endodontic surgery, also called endodontic microsurgery. When performing a modern endodontic microsurgery an operating microscope is used permitting the surgeon to precisely visualize the surgical area at a high magnification (10).

In a traditional root-end surgery root-end preparation is conducted using a small round bur. Modern endodontic surgery uses a magnification device in combination with an ultrasonic instrument for root-preparation and micro-instruments for root-resection. As each tooth has its own distinct anatomy and features, the availability of ultrasonic devices with tips of different shapes and angulations has made it possible to prepare with a greater accuracy, as opposed to the use of burs (11).

1.2.2 Anesthesia

Anesthesia and hemostasis are two linked aspects in surgical endodontics regarding patient comfort during surgical intervention and through the control of hemorrhage of the surgical site. The conventional technique consists of a regional anesthesia such as a nerve block followed by a local infiltration (12) .

1.2.3 Flap design

Once the anesthetic effect is achieved the flap design will be made. It is an important surgical step as it will influence the visibility, accessibility, reposition, suturing and the postoperative care of the surgical site (9). Overall, vertical and horizontal incisions are combined to obtain an appropriate flap (13). By making the incisions straight and parallel, rather than angled, the blood supply to the submucosa and attached gingiva can be maintained. At the same time, less fibers and vessels are damaged from transection leading to less hemorrhage. For a complete bone exposure, a full thickness or mucoperiosteal flap is required (14).

The full thickness incisions can be divided into complete and incomplete with the complete flaps including: sulcular or horizontal, triangular, rectangular and trapezoidal flaps. The incomplete flaps are constituted by semilunar, submarginal Ochsenbein-Luebke or scalloped and vertical flaps (15). In the complete flap no preservation of the marginal interdental tissue is made, it is completely included in the incision. In the incomplete flap they are however conserved which have been seen to prevent loss of papilla height (14).

1.2.4 Tissue retraction, bone removal and apical curettage

With the use of an elevator or retractor rested towards the cortical bone, the flap elevation will be carried out using light pressure while intermittingly irrigating with physiological sterile saline (8,13). Following the flap elevation, depending on the extend of the periapical lesion, we will have intact cortical bone or scarce to no cortical bone left overlying the lesion. If there is scarce cortical bone left, with the use of sharp excavator the remaining thin bone can be removed. In the event of a periapical lesion in which the cortical bone has been completely perforated, the location of the affected root-end will be done easily. In case of an intact full thickness cortical bone, its removal and access to the root- end area is realized using predominantly a round bur combined with a cooled sterile saline irrigation to prevent overheating and subsequently delayed bone healing or bone necrosis (8,13,14).

The greater part of periapical lesions arises from the pulp and are classified as either a cyst or granuloma which essentially are inflamed lesion produced as a response to irritation caused by microorganisms. For a complete healing of the tooth and apical area, it is essential to remove the diseased tissue. Generally, this is achieved with a bone or periapical curette. Beginning at the lateral border, the soft-tissue lesion is gently detached from the bony surface. Once this is achieved, the curette will be used by means of scraping the bony crypt off of any residual reactive tissue (8,13).

1.2.5 Surgical hemostasia

It is critical to obtain control of bleeding on the surgical site during a periapical surgery as the presence of excessive bleeding will lead to longer operating time, difficult vision and contamination of the filling material.

Numerous hemostatic agents are available each holding their own benefits and disadvantages (16). The materials diverse from each other in sense of their mechanism of action, efficacy to control bleeding and systematic effects (17). Some of the more common and most efficient hemostatic agents include calcium sulfate, collagen-based materials, epinephrine and ferric sulphate (16).

1.2.6 Root-end resection

The next step of the surgical procedures includes the apical root resection in which part of the root apex is cut and removed. It is a crucial step because once the cut is made it cannot be undone (12).

Different instruments and techniques have been suggested for root- resection with the main goal to leave the apical surface smooth and regular without any irregularities which could be irritative and possibly induce resorption during the healing stages. The use of fissured burs on high-speed handpiece have been considered the method of choice as it tends to leave the surface with these ideal characteristics (18).

Laser is avnew technique that has been employed for both root resection as well as root-preparation. Some of its advantages over burs are that it is sterile, does not produce vibrations possible leading to micro-fractures and it has anti-inflammatory properties (19).

1.2.7 Cutting length and angle

The amount of root-apex removed needs to leave the tooth in a condition in which the stability and integrity is not compromised. Many clinical studies have demonstrated that by removing 3mm of the root length, up to 93% of lateral canals and 98% of apical ramifications will be eliminated. Essentially this is the goal, as the extra conducts and canals are possible sites for bacteria to stay and maintain the infection (10,12).

The angle in which the apical root resection is done influences the outcome of the surgery. An inappropriate angle cut due to restricted visibility could lead to the inappropriate placement of filling material and a deficient root sealing (20). In the past the standard cutting angle has been 45 degrees (21). However, nowadays with the use of microscope a perpendicular cut along the longitudinal axis of the tooth has been achievable and is preferred over the conventional technique. With 0 degrees cut we are reducing the overall number of exposed dentinal tubules which is believed to distribute the apical forces more evenly and decrease the extension of apical fractures (13,14).

1.2.8 Periapical cavity preparation

As mentioned earlier, the periapical cavity preparation has traditionally been performed with a round bur. In modern endodontic surgery the root end cavity preparation is done using ultrasonic instruments which are available in different tips specifically developed for this purpose (14). The tip of the device is placed in the center of the canal space to remove the old restoration material until a full depth of 3 mm is attained (12) . There are many advantages using ultrasonic instruments for the preparation such as reduced production of smear layer and deeper and more uniform cavity preparation. The principal disadvantage is the potentially higher risk of generating root fracture due to the vibrations produced (13).

1.2.9 Ideal root-end filling material

The principal objective with root-end surgery is to achieve a proper sealing of the root apex to prevent recontamination inside the canal system and the choice of root-end filling material highly impacts the outcome.

The ideal root-end filling material should carry certain characteristics for instance it needs to be biocompatible, radiopaque, prevent microleakage and offer high marginal seal, adhere to the root surface and exert antimicrobial action (22).

The conventional filling material has been amalgam, but it has been completely substituted by other materials due to its high cytotoxic risk, reduced sealing ability and gingival discoloration (23). The gold standard material in endodontic treatments as well as endodontic microsurgery for the past two decades has become a material called mineral trioxide aggregate (MTA) (24). It carries many beneficial characteristics particularly a high sealing ability and biocompatibility which are two important properties for a root-end filling material. MTA cements have the ability to stimulate the formation of hard tissue and thanks to its high pH is antimicrobial (25). Its main setbacks are the long setting time, sensitive handling and high cost (26).

Apart from Amalgam and MTA, a large variety of restorative and endodontic materials are available to be used for root-end fillings. These include ethoxy benzoic acid (EBA), super EBA, glass ionomer cement (GIC), intermediate restorative material (IRM) composite resin, zinc oxide eugenol (ZOE) and most recently biodentine (27).

The different properties and their suitability as a root-end filling material has been examined through sealing or leakage assessment, cytotoxicity and marginal adaptation (28).

The aim of a root-end filling material is to provide a sealing of the conduct to inhibit the passage of bacteria and its toxins in the radicular space. Orthograde materials are not placed in a manner that they are in direct contact with vital periapical tissue. However, this is the case for retrograde or root-end filling materials and it is therefore important they hold certain properties as to generate desired healing response in these tissues (27).

There are several techniques utilized for the evaluation of apical sealing such as radioisotopes, dye and bacterial penetration and fluid filtration techniques (28).

Dye penetration technique is the most frequently used technique for assessing the sealing quality of root canal sealers (29). It is a simple and affordable method which uses different organic dyers as markers to measure penetration in extracted human teeth. Once a RCT has been performed on the extracted tooth, it will be stored a certain time as to make sure that the filling material is completely set. Then, the complete tooth surface, apart from the area around the apex, is coated with a material like paraffin or nail polish to avoid dye contamination by penetration through the root surface. The tooth will then be immersed in in the dye solution for varied time durations, generally at 37 degrees Celsius. Once the immersion period as passed, the tooth is removed from dye solution, washed and dried. For the evaluation of dye penetration different methods are suggested. Generally, a longitudinally section of the tooth is made in which the dye penetration is measured. Perpendicular sections are also used in which several sections are made and evaluated.

The most common dye solutions used include Indian
ink, Pelikan ink, Rhodamine B dye, aniline dye and methylene blue dye (30)

2. Rationale, hypothesis and objectives

2.1 Rationale

With the rise of dental implant treatments in the last decade, other conservative treatments options to save a tooth is many times overlooked. As opposed to an intent to save the tooth, the extraction and placement of an implant is usually selected.

When performing an endodontic retreatment on the anterior sector of the mouth it is important to not compromise the esthetics as this part of the mouth clearly has a higher esthetic demand, compared to the posterior teeth. By placing an implant, we will potentially reduce the esthetics as an implant can never replicate a natural tooth. It is therefore indicated to perform an endodontic surgery instead.

One of the most important factors for a successful endodontic surgery is a high sealing of the apex, preventing the bacterial dissemination inside the root canals or maintenance of a bacterial infection. The main clinical factors to achieve plugging of the root apex lies in the material and surgical technique used.

The present systematic review will compare how well root-filling materials can create an apical sealing compared to the gold standard material MTA by measuring the leakage with a dye solution.

The review can help clinicians choose the most appropriate material when preparing to perform a periapical surgery.

2.2 Hypothesis

The new sealing materials used in endodontic microsurgery provide a higher sealing capacity compared to the gold standard material MTA.

2.3 Objective

General objective:

The general objective of the following study is to analyze the different root-end filling materials used in endodontic microsurgery.

Specific objectives:

- Evaluate the sealing-ability of the root-end filling materials and compare them to MTA using a dye solution for measuring how deep the penetration of the material is.
- Determine what material offers higher sealing quality.

The objective around this study has been prepared from a PICO (patient/population, intervention, comparison, intervention) question formulated in the following way:

"In extracted human anterior teeth treated with apicoectomy (P), what root-end filling material (I) offers higher sealing quality measured with a dye solution (O) in comparison to MTA (C)?

3. Methods and materials

For the preparation of this systematic review, the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews) was used (31).

3.1 Eligibility

The selection of the studies used were based on the following inclusion and exclusion criteria's:

Inclusion criteria

- **Patient (P):** Human anterior extracted teeth with a single root being treated with apicoectomy.
- **Intervention (I):** Root-end filling materials
- **Comparison (C):** MTA gold standard
- **Outcome (O):** Sealing quality in relation to the sealing material using dye solution measurement
- **Study design:** In-vitro studies

In-vitro studies performing apicoectomy in extracted human single rooted teeth comparing MTA to different root-end filling materials were included. Furthermore, their sealing ability was evaluated using dye solution measurement.

Exclusion criteria

- Animal studies
- Clinical cases and case reports
- Sample size less than 10 teeth
- Studies published before 2000
- Studies which did not indicate type of tooth, sample size or root-end filling material

Studies conducted on animals have been excluded as it may not offer valid results in humans. In addition, clinical cases and case reports were excluded due to potential risk of bias. If the study had a sample size of less than 10 teeth it was considered low and therefore not of interest. Studies published before 2000 were not included in the review. Lastly, studies in which the type of tooth, sample size and filling material were not indicated was not included.

3.2 Search strategy

An electronic literature search was conducted on the databases Scopus and Medline. The search was based on in vitro studies evaluating the sealing quality in extracted human teeth using dye solution measurement.

The search in the databases was made in accordance with a PICO question as followed: In extracted human anterior teeth treated with apicoectomy (P), what root-end filling material (I) offers the higher sealing quality measured with a dye solution (O), in comparison to MTA (C)?

After the PICO question was formed, the search terms were created (Table 1.) and organized within each section. These terms were then correlated between each other using Boolean operators. The Boolean operator OR was applied to retrieve records including either one or both terms, synonyms. The Boolean operator AND was applied to combine the different sections (Diagram 1).

Table 1. *The electronic database search was conducted as follow:*

Database	Keywords	Date	Number of hits
Medline	((MH "Apicoectomy") OR ("periapical surgery") OR ("root-end surgery") OR ("Endodontic microsurgery")) AND (("root-end filling material")) OR (MH "Retrograde Obturation")) AND (("MTA") OR ("mineral trioxide aggregate")) AND (("sealing") OR ("micro-leakage") OR ("sealing ability") OR ("apical seal") OR ("dye") OR ("dye penetration") OR ("dye measurement") OR ("dye solution"))	March 22, 2022	31
Scopus	(("Apicoectomy") OR ("Periapical surgery") OR ("Root-end surgery") OR ("Endodontic microsurgery")) AND (("Root-end filling material") OR ("Retrograde obturation")) AND (("MTA") OR ("Mineral Trioxide aggregate")) AND (("Sealing") OR ("Micro-leakage") OR ("Sealing ability") OR ("Apical seal") OR ("Dye") OR ("Dye penetration") OR ("Dye measurement") OR ("Dye solution"))	March 22, 2022	37

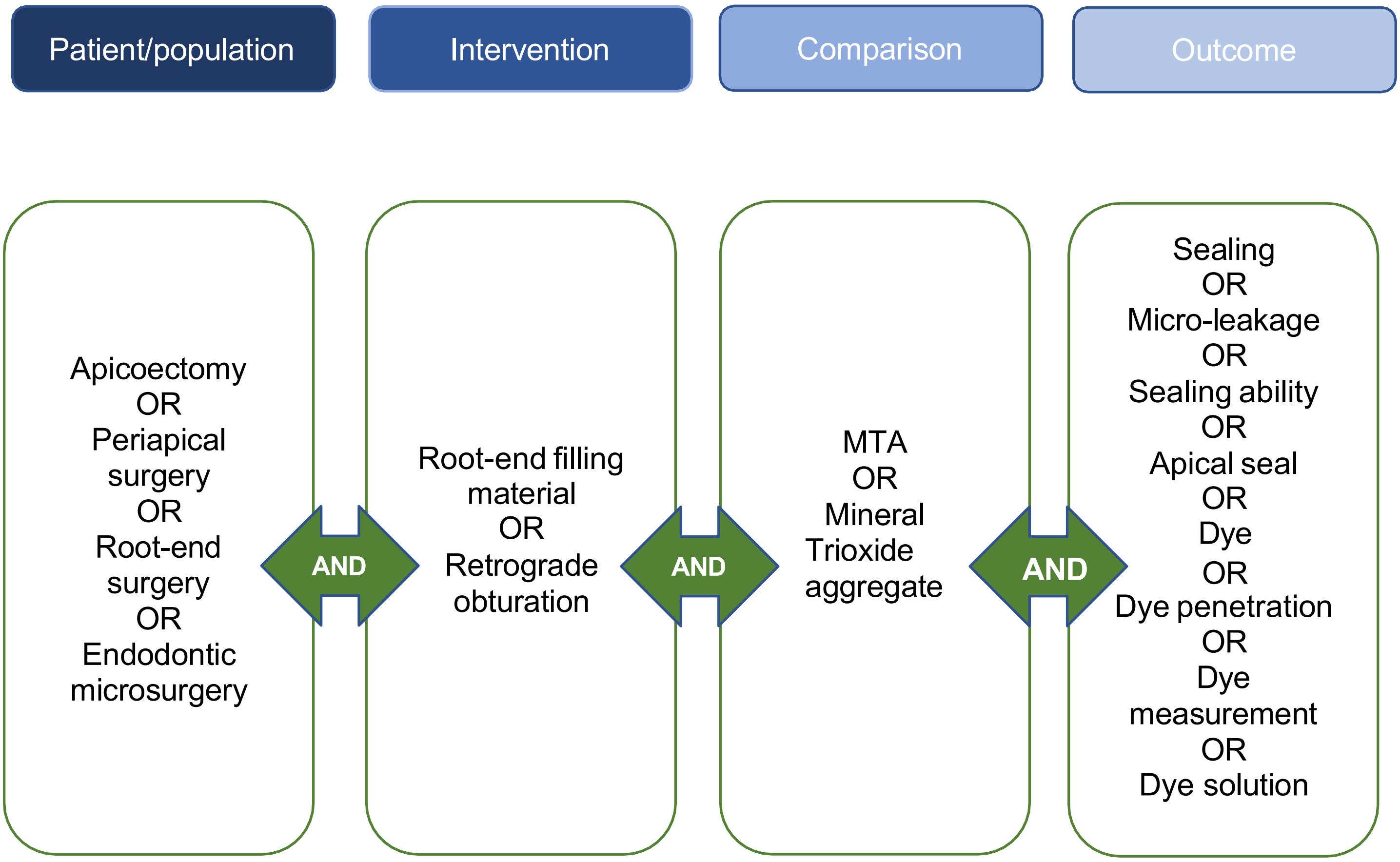


Diagram 1. *The search terms were sorted in each part of the PICO question and correlated using Boolean operators*

Ultimately, the search strategy was organized accordingly:
((MH "Apicoectomy") OR ("periapical surgery") OR ("root-end surgery") OR ("Endodontic microsurgery")) AND (("root-end filling material")) OR (MH "Retrograde Obturation")) AND (("MTA") OR ("mineral trioxide aggregate")) AND (("sealing") OR (“micro-leakage") OR ("sealing ability") OR ("apical seal") OR ("dye") OR ("dye penetration") OR ("dye measurement") OR ("dye solution")).

To find the most precise results in our field of interest, a combination of keywords and the following MeSH terms were used: *apicoectomy and retrograde obturation.*

3.3 Study selection

Restriction was set to include articles published from 2000 until day of search. No restriction was set regarding language. The search was conducted in March 2022 with the intention of finding all the latest publication in our field of interest and include them in the review.

The studies were individually screened by one reviewer in accordance with the inclusion and exclusion criteria.

Each study was assessed by their title and abstract and any irrelevant study and duplications were removed. For studies in which the title or the abstract did not provide sufficient information full articles were acquired in order to take a final decision.

Ultimately, full text of the selected articles was read and the reason for rejecting the excluded studies were listed.

3.4 Data extraction and list of variables

After a comprehensive reading of the included studies, factors present in all the articles providing adequate information regarding the objectives of the study were obtained. These variables were then summarized in tables.

The factors evaluated in each of the studies were: author, year of publication, sample size, root-end filling material, apical resection technique, periapical cavity preparation technique, leakage analyzing method and results.

3.5 Quality of the evidence assessment

All included studies in this systematic review were in-vitro studies. A standard tool to assess the risk of bias in in-vitro studies does not exists. The OHAT (National Toxicology Program Office of Health Assessment and Translation) risk of bias rating tool developed a tool used for human and animal studies in which the same questions used for experimental animal studies can be implemented in in-vitro studies.

The tool consists of 11 risk-of-bias questions in which each question can be applied to 1-6 study design types. Each question then has possible answers: definitely low risk of bias, probably low risk of bias, probably high risk of bias and definitely high risk of bias. These questions are sorted to cover 6 types of bias: selection, cofounding, performance, attrition/exclusion, detection and selective reporting.

Of the 11 questions used in this tool, 9 questions can be applied in experimental animal studies (32).

4. Results

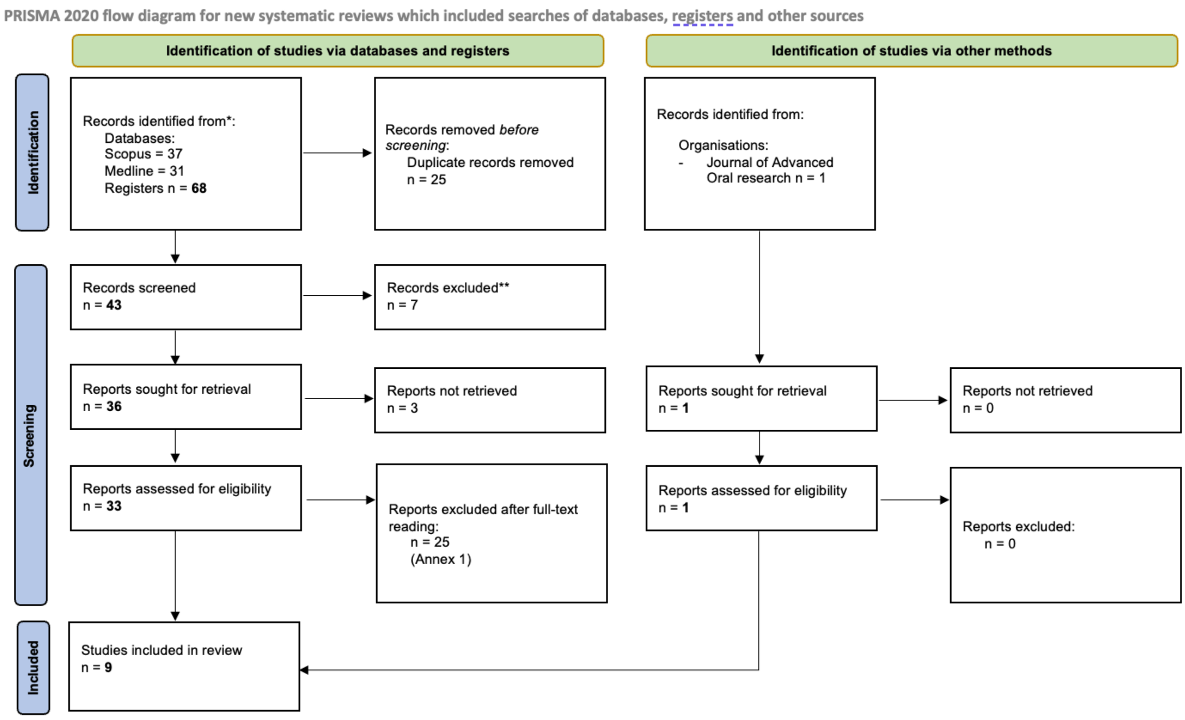
4.1 Study selection and characteristics:

After an electronic search was conducted on Scopus and Medline, 68 articles were obtained. Of these, 37 were from Scopus and 31 from Medline. 25 duplicates were removed and 43 articles were left for screening. These articles were assessed for eligibility based on the exclusion criterions established previously. 7 articles were removed and 36 articles were left for retrieval in which 3 full articles were not found. The 33 articles left were assessed for eligibility based on the inclusion criterions established previously and 25 articles were then excluded. The reason for exclusion was described in Annex 1.

11 articles were retrieved from the electronic database search and one additional article was retrieved from a website. A total of 9 articles were included in the systematic review.

In diagram 2 the process of the study selection is described through the PRISMA flow diagram.

Diagram 2. *Prisma flow chart* *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC,



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 2. The OHAT risk of bias rating tool for in-vitro studies

Risk-of-Bias Questions	Nepal et al. (2020) (33)	Benz et al. (2016) (34)	Radeva et al. (2016) (35)	Winik et al. (2006) (36)	Davis et al. (2003) (37)	Martell et al. (2002) (38)	Aqrabawi (2000) (39)	Post et al. (2010) (40)	Saraswathi et al. (2015) (41)
1. Was administered dose or exposure level adequately randomized?	NR	+	+	+	NR	+	+	+	+
2. Was allocation to study groups adequately concealed?	–	NR	NR	NR	–	NR	NR	NR	NR
3. Did selection of study participants result in the appropriate comparison groups?	X	X	X	X	X	X	X	X	X
4. Did study design or analysis account for important confounding and modifying variables?	X	X	X	X	X	X	X	X	X
5. Were experimental conditions identical across study groups?	++	++	+	+	+	+	+	+	++
6. Were research personnel blinded to the study group during the study?	NR	++	NR	NR	NR	NR	NR	NR	NR
7. Were outcome data complete without attrition or exclusion from analysis?	++	+	–	NR	+	+	++	NR	+
8. Can we be confident in the exposure characterization?	+	++	+	+	+	+	+	+	+

9. Can we be confident in the outcome assessment (including blinding of assessors)?	+	+	NR	+	+	+	+	+	+
10. Were all measured outcomes reported?	++	+	++	+	+	+	++	+	+
11. Were there no other potential threats to internal validity	+	+	+	+	++	++	+	+	+

4.2 Risk of bias assessment

The evaluation of the risk of bias was performed using the OHAT tool. Of the 9 included studies, the study conducted by Radeva et al.(35) was considered to be high risk of bias as it did not demonstrate sufficient information to be able to response to three of the risk of bias questions, signifying incomplete data. Additionally, the reason for exclusion of some of the teeth used in the study was not indicated.

Four studies were considered to be of moderate quality (33,36,37,40) and the remaining four (34,38,39,41) were of high quality showing a low risk of bias. In table 2 the risk of bias tool is described.

4.3 Data extraction: Qualitative synthesis

In table 3. the primary characteristics of the included studies were described. This systematic review included 9 in-vitro studies which fulfilled the inclusion and exclusion criteria, with a total sample of 497 teeth subjected to an apicoectomy. In all the studies, the sealing ability of different root-end filling materials were evaluated. Furthermore, Benz et al. (34), evaluated if the instrument chosen for the root-end resection had an impact on the sealing quality.

The results would show that the instrument for root-resection had no influence on the apical seal. In regard to the sealing ability, they reported a statistically significant difference between MTA and Super EBA ($p<0.0001$). Not one of the

teeth obturated with MTA showed leakage whereas all the teeth in the Super-

EBA group showed leakage .

In the study conducted by Post et al. (40), in addition to a comparison between MTA and amalgam and their sealing ability, the apicoectomy angle and root-resection instrument was also evaluated and its possible effect on the apical seal. They reported that neither cutting angle or instrument had a significant impact on the microleakage. Regarding the materials compared, MTA showed a lower leakage in comparison to Amalgam ($p<0.05$).

Nepal et al. (33) evaluated the apical sealing between GIC, MTA and Biodentine with retrograde cavity preparation using two different burs: a round carbide bur and a round diamond bur. They reported that the use of bur had no impact on the sealing. Moreover, the leakage measurement in the Biodentine group showed the best results. However, no statistical difference was seen between Biodentine and MTA ($p=0.127$ carbide bur and $p=0.496$ diamond bur).

A statistically significant difference was reported between the GIC in comparison to MTA and Biodentine ($p=0.0001$).

Davis et al. (37) stated that the amalgam group had the highest leakage when compared to Super-EBA and MTA. No statistically significant difference was seen between MTA and Super-EBA.

Martell et al. (38) evaluated the sealing ability between Super-EBA, IRM and MTA and they reported that MTA showed the highest sealing capacity with a statistical difference compared to IRM and Super-EBA. No statistical difference was seen between IRM and Super-EBA.

Aqrabawi (39) compared the sealing ability between three root-end filling materials: Amalgam, Super-EBA and MTA. A statistically significant difference was seen between amalgam and Super-EBA ($p<0.01$) and between amalgam and MTA ($p<0.009$). A significant difference was also reported between Super-EBA and MTA ($p<0.05$).

In the study conducted by Saraswathi et al. (41) a significantly less leakage was observed in MTA plus compared to MTA and Biodentine.

Table 3. *Characteristics of the included studies:*

Author (year)	**Root-end filling material N= sample of teeth**	**Apical resection technique**	**Periapical preparation technique**	**Leakage analyzing method**	**Results**
Nepal *et al.* (2020)	Glass ionomer cement = 20 MTA = 20 Biodentine = 20	Diamond disk on straight handpiece	Round carbide or diamond bur	UV spectrophotometer	The MTA and Biodentine group both showed the highest results compared to GIC. No difference was seen between MTA and Biodentine.
Benz *et al.* (2016)	Super-EBA cement = 36 MTA = 36	Lindemann bone cutter or diamond-coated bur	Ultrasonic device	Stereomicroscope at x 10 magnification	MTA presented the best results compared to Super-EBA.
Radeva *et al.* (2016)	MTA = 10 Biodentine = 8	-	Ultrasonic device	Microtome Leica SP1600	No statistical difference was seen between Biodentine and MTA.
Winik *et al.* (2006)	MTA = 10 Cyanoacrylate = 10	Fissure bur	Carbide bur	JEOL JSM-6100 scanning electron microscope	The cyanoacrylate group showed less leakage compared to the MTA group.
Davis *et al.* (2003)	Amalgam = 20 Super EBA = 20 MTA = 20	557 bur	Ultrasonic device	Stereoscopic microscope	MTA and Super-EBA showed higher sealing in comparison to Amalgam.
Martell *et al.* (2002)	Super EBA = 10 IRM = 10 MTA = 10	Low-speed diamond saw	Ultrasonic device	X 2.5 magnification loupes	MTA had the highest sealing. IRM and Super EBA showed similar results.
Aqrabawi (2000)	Amalgam = 25 Super EBA = 25 MTA = 23	Fissure bur	Ultrasonic device	Stereomicroscope x 10 magnification	MTA showed the best results followed by Super-EBA. Amalgam had the worst sealing ability.
Post *et al.* (2010)	Amalgam = 40 MTA = 40	Diamond coated bur	Round carbide bur or Ultrasonic device	Stereoscopic microscope x 25 magnification	MTA showed lower leakage compared to Amalgam.
Saraswathi *et al.* (2015)	Biodentine = 28 MTA plus = 28 MTA = 28	Fissure bur	Diamond bur	Calibrated stereomicroscope x 50 magnification	MTA plus showed least leakage followed by MTA and lastly Biodentine.

5. Discussion

For a successful outcome and correct healing of the apical region after periapical surgery, it is fundamental that an optimal apical sealing is achieved (42).

MTA has long been considered the gold standard material for root-end fillings thanks to its superior properties compared to other materials on the market (43).

On the other hand, it should be mentioned that MTA presents some drawbacks in terms of difficult handling and long setting time. To overcome these drawbacks new materials have been created. One example is Biodentine which is a calcium silicate-based material presenting a faster setting time and substantial physical and biological properties (44).

Three of the included studies evaluated the sealing capacity of Biodentine. Nepal et al. (33) reported there to be no statistical difference between MTA and Biodentine and their sealing ability. Nevertheless, the measurements would show Biodentine to present less leakage measured in mm. Similar results were obtained by Radeva et al. (35) in which the MTA group showed 0.68 mm leakage and the Biodentine group 0.51 mm, however no statistical difference was seen between the two materials.

The similar results between MTA and Biodentine can be explained to the similarities in their composition both being a calcium silicate-based material. While MTA is composed of dicalcium silicate, the main component in Biodentine is tricalcium silicate (45). As mentioned previously, one of the principal setbacks with MTA is the long setting time. By overcoming this, when developing Biodentine a setting accelerator was incorporate resulting in a faster setting time and improved handling properties (46). Torabinejad et al. conducted a study in which the physical and chemical properties of root-end filling materials were compared. They concluded that a retarded setting time leads to higher risk of potential materials loss and modifications of the interface throughout the finishing phase, which is a disadvantage (47).

Three of the included studies compared the leakage quality of Super-EBA. Benz et al. (34) reported in their study that MTA had a much higher sealing capacity compared to Super-EBA with a statistical difference between the two materials. Martell et al. (38) reported similar results between MTA and Super-EBA and additionally, they compared Super-EBA to IRM in which no statistically difference was seen. Moreover, the study conducted by Aqrabawi (39) would also report a statistically significant difference between MTA and Super-EBA.

Contrary to this, Davis et al. (37) concluded that no significant difference was seen in leakage between MTA and Super-EBA. In addition to this, the study also observed a different leakage pattern between the materials. The amalgam showed a leakage in an apical to coronal pattern generally covering the entire root length of where the filling material was placed. The leakage in the MTA and Super-EBA groups followed a circumferential pattern in which an initial washing out of the materials occurred.

Both Super-EBA and IRM are reinforced zinc oxide-eugenol based cements with comparable compositions. Super-EBA holds a much lower quantity eugenol than IRM does. As eugenol is a component that carries several harmful qualities, the lower concentration of this component in Super-EBA could be seen as an advantage in terms of biocompatibility (48). The adverse effect of eugenol is generally linked to local reactions such as hypersensitivity and in some instances cytotoxic effects (49).

Davis et al. (37), Aqrabawi (39) and Post et al. (40), included Amalgam in their study. The result of all of these studies would show amalgam to be the worst material in terms of sealing. In the past, amalgam has been considered to be the conventional root-end filling material. Nonetheless, its use in periapical surgery and dentistry in general has progressively decreased over the last few years and is prohibited in many countries. The reason for this is due to the harmful biological effects produced by the mercury it contains. It is believed that the metallic particles could migrated into the tissue producing inflammation and other toxic effects (50).

Saraswathi et al. was the only study to, in addition to conventional MTA, also include MTA plus. They reported that MTA plus showed superior results in terms of sealing ability compared to conventional MTA. The principal difference between MTA plus and MTA is that it contains much smaller particle size, up to 50% less than the conventional one. This is thought to be an advantage as the small particle size is believed to increase the surface that is accessible for hydration and lead to greater early strength in conjunction with an easier handling (41,51).

Winik et al. (36) was the only study to include cyanoacrylate. They reported that

MTA had a much higher permeability compared to cyanoacrylate, in particular when the retro-preparation was done with laser. Cyanoacrylate showed lowest levels of leakage regardless of the preparation method used.

Cyanoacrylate is a material that mainly has been used in dentistry as an adhesive following extractions and pulp capping. Due to its bonding properties, it can be assessed as a root-end filling material.

In 1984, Torabinejad et al. conducted an in-vitro study evaluating the use of Isopropyl Cyanoacrylate as a potential root canal sealer. They concluded that the material has characteristics that could be considered beneficial when used in the root canal such as bacteriostatic, biocompatible, adhesive to the root canal walls and most importantly it offered a good sealing of the root (52).

Some years later in 1988, Barkhordar et al. conducted an in-vitro study where they evaluated cyanoacrylate as a root-end filling material. Similar results were found and they concluded that it is a material that could potentially be used as a retro-filling material due to the low amount of leakage it had presented (53).

Nepal et al. (33) evaluated glass ionomer as a root-end filling material. They concluded that, of the three materials evaluated ; MTA, Biodentine and Glass ionomer cement, in which the latter had the worst sealing capacity.

In an in-vitro study by Chohan et al. in 2015, four different root-end filling materials were compared: conventional glass ionomer cement, resin-modified glass ionomer cement, polyacid-modified composite and composite resin. Although glass ionomer cements is believed to reduce leakage thanks to their capability of forming chemical bons with tooth structure, they came to the conclusion that the conventional glass ionomer cement was the material to offer least sealing (54).

Of all the materials compared to MTA, Biodentine is the only one that could be comparable in terms of sealing ability. Although MTA is considered the gold standard material, it has some disadvantages and the introduction of newer materials has made it possible to overcome these impediments. The most important material in this sense would be Biodentine as it shows similar results in terms of sealing but it also offers some advantages over MTA in terms of handling. It should also be mentioned that MTA plus, which is a modification of the conventional MTA, also showed great results.

Shah et al. conducted a systematic review in 2018 in which they compared the sealing ability between MTA and Biodentine in extracted human teeth. They reported that Biodentine had a superior marginal adaptation in comparison to MTA and this was thought to be mainly thanks to its small particle size which makes it easier for the material to adapt to the root cavity surface (55). This can also be comparable to the study by Saraswathi et al. where MTA plus was compared to conventional MTA and they concluded that the better results seen by the MTA plus can be explained by its smaller particle size compared to conventional MTA.

In-vitro studies are an important tool when studying how different materials behaves. This can however be seen as a great limitation as the in-vitro conditions are significantly different from in-vivo, and in this case the oral cavity. Although some studies have tried to create some similarities in the conditions when storing the teeth, a complete replica of the oral environment cannot be done. When the material is in contact with saliva, blood and other human liquids or tissues it might behave differently or cause some adverse reactions to its surrounding. While a high sealing is crucial for a superior success rate and clinical outcome, if the material presents other important setbacks in the oral cavity that could present itself in the long-term, its measuring will be difficult due to the restrictions in long-term exposition when conducting in-vitro studies.

Although most of the results from the studies in the present systematic review came to the same or similar conclusion, some showed disparity in the results. This could be explained by the incongruencies in the experimental procedures between each study. The periapical preparation technique was generally performed with either ultrasonic devices or a bur. Some of the studies evaluated if the preparation technique influenced the sealing quality and they all reported that it did not have an impact on the final outcome. Each study followed their own handling protocol and storage condition such as the irrigation solutions, temperature, humidity and material handling. All the nine studies used four different dye solutions for measuring the leakage. Four studies used methylene blue in different concentrations, one studies used toluidine blue, three studies used Rhodamine B in different concentrations and finally one studies used India ink. Blue methylene solution has an advantage of containing molecules with a small weight in its composition which is believed to easier penetrate deeper into the material, hence presenting a higher sensitivity compared to other dye solutions (54). The range of study conduction is a possible factor for inconsistent results and for future studies a more standardized protocol should be made to maintain conformity between the results.

All the nine studies used different instruments for evaluating the leakage depth. Although the use of a stereomicroscope dominated, the differences in magnification could led to a possible multiplicity between the leakage interpretation affecting the final measurement depth result.

6. Conclusion

The selection of root-end filling material is crucial for a high success of an apicoectomy. A wide variety of root-end filling materials are available on the market today with MTA dominating. Many different materials used in dentistry have been suggested and tested as a retro-filling material. Super-EBA and IRM are two examples of dental materials that have been evaluated as a potential root-filling material. Although it has a broad application in dentistry, the results would show inferior sealing ability in comparison to MTA.

Similar to Super-EBA and IRM, glass ionomer cements are frequently used in dentistry. One of the studies included compared GIC to MTA and they reported that it did not offer a greater sealing than MTA.

One of the studies compared MTA to cyanoacrylate and it is the only study in which MTA showed the highest leakage. Despite the promising results, not many studies have been made with this material. More in-vitro studies, and then in vivo-studies, should be made with cyanoacrylate.

Biodentine is a newer dental material and it is the only material studied, apart from one study evaluating cyanoacrylate, that showed results comparable to MTA. It has been made to overcome some of the inconveniences with MTA.

The following root end-filling materials were evaluated in terms of their sealing ability and then compared to the gold-standard material MTA: Glass-ionomer cement, Super-EBA, IRM, Cyanoacrylate, Amalgam and Biodentine. Based on the results obtained, MTA maintains as the material consistently offering the highest sealing and Biodentine is the one material with closest results to MTA

It would be interesting if more clinical studies were made on this material, especially in long-term, both in-vitro and in-vivo to see its potential use as a root-end filling material.

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8.Annex

Annex 1.

Author (Year)	Reason for exclusion
Sumaya et al. (2018)	Excluded as it did not meet the inclusion criteria: literature review
Santi et al. (2018)	Excluded: not relevant to the pico-question
Del Fabbro et al. (2016)	Excluded as it did not meet the inclusion criteria: literature review
Hemasathya et al. (2015)	Excluded as it did not meet the inclusion criteria; a review
Von Arx et al. (2014)	Excluded as it did not meet the inclusion criteria; prospective study
Moradi et al. (2013)	Exclude as it did not meet inclusion criteria: bacterial leakage method for assessing sealing
Bernabé et al. (2013)	Excluded: not relevant to the pico-question
Nair et al. (2011)	Exclude as it did not meet inclusion criteria: used Enterococcus faecalis for assessing sealing
Rosales-Leal et al. (2011)	Excluded: not relevant to the pico-question
Von Arx et al. (2010)	Excluded as it did not meet the inclusion criteria; prospective clinical study
Asgary et al. (2008)	Excluded: not relevant to the pico-question
Perinpanayagam (2009)	Excluded as it did not meet the inclusion criteria; a review
Saghiri et al. (2008)	Excluded: not relevant to the pico-question
Luketic et al. (2008)	Excluded as it did not meet the inclusion criteria: used polymicrobial marker for assessing sealing
Braz et al. (2006)	Excluded: not relevant to the pico-question

Andeling et al. (2002)	Excluded: not relevant to the pico-question (Sealing related to orthograde obturation and not retrograde).
Scheerer *et al.* (2001)	Excluded: the study used Prevotella nigrescens to evaluate the sealing ability
Roy *et al.* (2001)	Excluded: not relevant to the pico-question
Pozza *et al.* (2009)	Excluded: not relevant to the pico-question
Karlovic *et al.* (2005)	Excluded: not relevant to the pico-question
Valois et al. (2004)	Excluded: not relevant to the pico-question
Schultz *et al.* (2005)	Excluded: used molars in their study
Shahi *et al.* (2007)	Excluded: had no comparison group
Kubo *et al.* (2005)	Excluded: had no comparison groups
Pichardo *et al.* (2006)	Excluded: high risk bias/not relevant to the pico-question

Annex 2.
Prisma check list

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	11
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	12
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	13-14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	14
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	14-15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	16-17
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	18
Study characteristics	17	Cite each included study and present its characteristics.	22
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	19-20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	20-21
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-27
	23b	Discuss any limitations of the evidence included in the review.	26-27
	23c	Discuss any limitations of the review processes used.	26-27
	23d	Discuss implications of the results for practice, policy, and future research.	26-27
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Annex 3.
Article

TITLE: "A comparison between the sealing ability of mineral trioxide aggregate and different root-end filling materials used in endodontic microsurgery" – A systematic review"

RUNNING TITLE: Endodontic surgery and sealing ability of root-end filling materials

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ABSTRACT

- *Objectives:* For a successful clinical outcome, a correct apical seal needs to be achieved and this is highly influenced by the material chosen. MTA has long been considered the gold-standard material but as it faces some disadvantages, newer materials have been introduced to overcomes these obstacles. The main objective of the present study was to evaluate the sealing capacity of root-end filling materials used in periapical surgery.
- *Materials and Methods*: Following the guidelines for systematic review (PRISMA), an electronic search was conducted by one independent examiner in Medline and Scopus. The search was made in accordance with the PICO-question "In extracted human teeth treated with apicoectomy, what root-end filling material offers the higher sealing quality measured with a dye solution, in comparison to MTA?".
- *Results:* Following an analysis of 69 studies, 9 articles were included in the study. The studies comparing Biodentine to MTA showed that Biodentine had similar sealing quality to MTA, however no statistical difference could be found between the two materials
- *Conclusions:* MTA maintains as the material offering the highest sealing, although Biodentine shows very promising results that could be superior to MTA. No other material included in the studies demonstrated sealing quality comparable to MTA.

***Keywords**:* "Apicoectomy", "Endodontic microsurgery", "MTA", "Sealing", "Retrograde obturation"

1. INTRODUCTION

In the event of a persistent periapical lesion without signs of healing after an initial root-canal treatment, the clinician can proceed with the following treatment options; nonsurgical retreatment, surgical retreatment or extraction with the possibility of placing an implant (1). If a non-surgical retreatment has been performed and unsuccessful or after a failed primary endodontic treatment, a surgical approach may be indicated. With this procedure, both the intracanal and extra-canal infection can be managed through the resection of the apical portion of the root (2).

Root-end surgery can be divided into traditional endodontic surgery and modern endodontic surgery, also called endodontic microsurgery. When performing a modern endodontic microsurgery an operating microscope is used permitting the surgeon to precisely visualize the surgical area at a high magnification (3).

The principal objective with root-end surgery is to obtain an adequate sealing of the root-apex to prevent recontamination inside the canal system and the choice of root-end filling material highly impacts the outcome. An ideal root-end filling material should hold certain characteristics such as being biocompatible, radiopaque, prevent microleakage and offer high marginal seal, adhere to the root surface and exert antimicrobial action (4).

The conventional filling material has been amalgam, but it has been completely substituted due to several drawbacks and today the gold-standard material is considered to be MTA (5, 6).

Apart from amalgam and MTA, a great variety of restorative and endodontic materials are available to be used for root-end fillings in endodontic microsurgery. These include ethoxy benzoic acid (EBA9, Super-EBA, Glass ionomer cement (GIC), intermediate restorative material (IRM), composite resin, zinc oxide eugenol (ZOE) and most recently biodentine (7).

The objective of the present systematic review is to compare how well different root-end filling materials can create an apical sealing compared to the gold standard material MTA by measuring the leakage using a dye solution.

2. MATERIALS AND METHODS

Protocol and focused question: The present systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (8). The following focus question was employed according to the PICO question: In extracted human anterior teeth treated with apicoectomy (P), what root-end filling material (I) offers the higher sealing quality measured with a dye solution (O), in comparison to MTA (C)?

Selection criteria: The studies were individually screened by one reviewer in accordance with the inclusion and exclusion criteria. Each study was assessed by their title and abstract and any irrelevant study and duplications were removed. For studies in which the title or the abstract did not provide sufficient information full articles were acquired in order to take a final decision.

In-vitro studies performing apicoectomy in extracted human single rooted teeth comparing MTA to different root-end filling materials were included. Furthermore, their sealing ability was evaluated using dye solution measurement.

Studies conducted on animals have been excluded as it may not offer valid results in humans. In addition, clinical cases and case reports were excluded due to potential risk of bias. If the study had a sample size of less than 10 teeth it was considered low and therefore not of interest. studies in which the type of tooth, sample size and filling material were not indicated was not included.

Search strategy: An electronic literature search was conducted on the databases Scopus and Medline. The search was based on in vitro studies evaluating the sealing quality in extracted human teeth using dye solution measurement published between January 2000 and March 2022. Ultimately, the search strategy was organized accordingly:

((MH "Apicoectomy") OR ("periapical surgery") OR ("root-end surgery") OR ("Endodontic microsurgery")) AND (("root-end filling material")) OR (MH "Retrograde Obturation")) AND (("MTA") OR ("mineral trioxide aggregate")) AND (("sealing") OR (“micro-leakage") OR ("sealing ability") OR ("apical seal") OR ("dye") OR ("dye penetration") OR ("dye measurement") OR ("dye solution")).

Risk of bias: A standard tool to assess the risk of bias in in-vitro studies does not exists. The OHAT (National Toxicology Program Office of Health Assessment and Translation) risk of bias rating tool developed a tool used for human and animal studies in which the same questions used for experimental animal studies can be implemented in in-vitro studies (9).

Data extraction: After a comprehensive reading of the included studies, factors present in all the articles providing adequate information regarding the objectives of the study were obtained. These variables were then summarized in a table.

RESULTS: After an electronic search was conducted on Scopus and Medline, 68 articles were obtained. These articles were assessed for eligibility based on the exclusion criterions established previously. 11 articles were retrieved from the electronic database search and one additional article was retrieved from a website. A total of 9 articles were included in the systematic review. In diagram 1. the process of the study selection is described through the PRISMA flow diagram.

Risk of bias assessment: Of the 9 included studies, the study conducted by Radeva et al. (10) was considered to be high risk of bias as it did not demonstrate sufficient information to be able to response to three of the risk of bias questions, signifying incomplete data. Four studies were considered to be of moderate quality (11, 12, 13, 14) and the remaining four (15, 16, 17, 18) were of high quality showing a low risk of bias. In table 1. the process of assessing the risk of bias is described.

Characteristics of included studies: In table 2. the primary characteristics of the included studies were described. This systematic review included 9 in-vitro studies which fulfilled the inclusion and exclusion criteria, with a total sample of 497 teeth subjected to an apicoectomy. In all the studies, the sealing ability of different root-end filling materials were evaluated. Furthermore, Benz et al. (15) evaluated if the instrument chosen for the root-end resection had an impact on the sealing quality and they reported that it did not influence the sealing. Regarding the leakage of the materials studies, they reported a statistically significant difference between MTA and Super EBA ($p<0.0001$).

In the study conducted by Post et al. (14) in addition to a comparison between MTA and amalgam and their sealing ability. They reported that neither cutting angle or instrument had a significant impact on the microleakage and that MTA showed a lower leakage in comparison to Amalgam ($p<0.05$).

Nepal et al. (11) evaluated the sealing of glass ionomer cement, MTA and Biodentine using two different burs. They reported that the bur had no impact on the sealing. Moreover, Biodentine showed least leakage although no statistical difference was seen between Biodentine and MTA. A statistical difference was reported between GIC in comparison to MTA and Biodentine.

Davis et al. (13) reported that amalgam had the highest leakage compared to Super-EBA and MTA. No statistical difference was seen between MTA and Super-EBA.

Martell et al. (16) reported that MTA had the highest sealing with a statistical difference in comparison to IRM and Super-EBA. No statistical difference between IRM and Super-EBA.

Aqrabawi (17) reported a statistical difference between Super-EBA and MTA, Amalgam and Super-EBA and amalgam and MTA.

In the study conducted by Saraswathi et al. (18) a significantly less leakage was observed in MTA plus compared to MTA and Biodentine.

4. DISCUSSION:

Three of the studies included in the review evaluated the sealing of Biodentine. Both Nepal et al. (11) and Radeva et al. (15) reported that Biodentine showed less leakage measured in mm but no statistical difference was seen between MTA and Biodentine.

As MTA and Biodentine carry similarities in their composition, both being a calcium silicate-based material, this could explain the similar results between the two materials. Although MTA has great advantages, its principal setback is the long setting time. By overcoming this, when developing Biodentine a setting accelerator was incorporated. (19).

Torabinejad et al. conducted a study where the physical and chemical properties of different root-end filling materials were compared and they concluded that a delayed setting time leads to potential material loss and changes in the interface of the finishing phase, seen as a disadvantage. (20)

Three studies compared the sealing of Super-EBA. Benz et al. (15) reported that MTA had a higher sealing capacity in comparison to Super-EBA with a statistical difference. Similar results were reported by Martell et al. (16) and Aqrabawi (17).

Contrary to this, Davis et al. (13) reported no significant difference of the leakage between MTA and Super-EBA. Additionally, they observed a different leakage pattern between the materials were MTA and Super-EBA had a circumferential pattern with an initial washing out whereas Amalgam had a leakage in an apical to coronal pattern covering the entire root length.

Davis et al. (13) Aqrabawi (17) and Post et al. (14) all included Amalgam in their study. The result of all of these studies would show amalgam to be the worst material in terms of sealing. Amalgam has been considered to be the conventional root-end filling material. Nonetheless, its use in periapical surgery and dentistry in general has progressively decreased (21).

Saraswathi et al. was the only study to, in addition to conventional MTA, also include MTA plus. They reported that MTA plus showed superior results in terms of sealing ability compared to conventional MTA.

Winik et al. (12) was the only study to include cyanoacrylate. They reported that MTA had a much higher permeability compared to cyanoacrylate.

Nepal et al. (11) evaluated glass ionomer, MTA and Biodentine in which they came to the conclusion that glass ionomer cement offered the worst sealing.

In an in-vitro study by Chohan et al. in 2015, four different root-end filling materials were compared: conventional glass ionomer cement, resin-modified glass ionomer cement, polyacid-modified composite and composite resin. Although glass ionomer cements is believed to reduce leakage thanks to their capability of forming chemical bonds with tooth structure, they came to the conclusion that the conventional glass ionomer cement was the material to offer least sealing (22).

Of all the materials compared to MTA, Biodentine is the only one that could be comparable in terms of sealing ability. Although MTA is considered the gold standard material, it has some disadvantages and the introduction of newer materials has made it possible to overcome these impediments.

In-vitro studies are an important tool when studying how different materials behaves. This can however be seen as a great limitation as the in-vitro conditions are significantly different from in-vivo, and in this case the oral cavity. Although some studies have tried to create some similarities in the conditions when storing the teeth, a complete replica of the oral environment cannot be done. When the material is in contact with saliva, blood and other human liquids or tissues it might behave differently or cause some adverse reactions to its surrounding.

Although most of the results from the studies in the present systematic review came to the same or similar conclusion, some showed disparity in the results. This could be explained by the incongruencies in the experimental procedures between each study. The periapical preparation technique was generally performed by either ultrasonic devices or a bur. Some of the studies evaluated if the preparation technique influenced the sealing quality and they all reported that it did not have an impact on the final outcome. Each study followed their own handling protocol and storage condition such as the irrigation solutions, temperature, humidity and material handling. These factors could have an impact on the final results of the studies.

5. CONCLUSIONS

The following root end-filling materials were evaluated in terms of their sealing ability and then compared to the gold-standard material MTA: Glass-ionomer cement, Super-EBA, IRM, Cyanoacrylate, Amalgam and Biodentine. Based on the results obtained, MTA maintains as the material consistently offering the highest sealing and Biodentine is the one material with closest results to MTA

It would be interesting if more clinical studies were made on this material, especially in long-term, both in-vitro and in-vivo to see its potential use as a root-end filling material.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in this study.

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Diagram 1. *Prisma flow Chart From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC,*

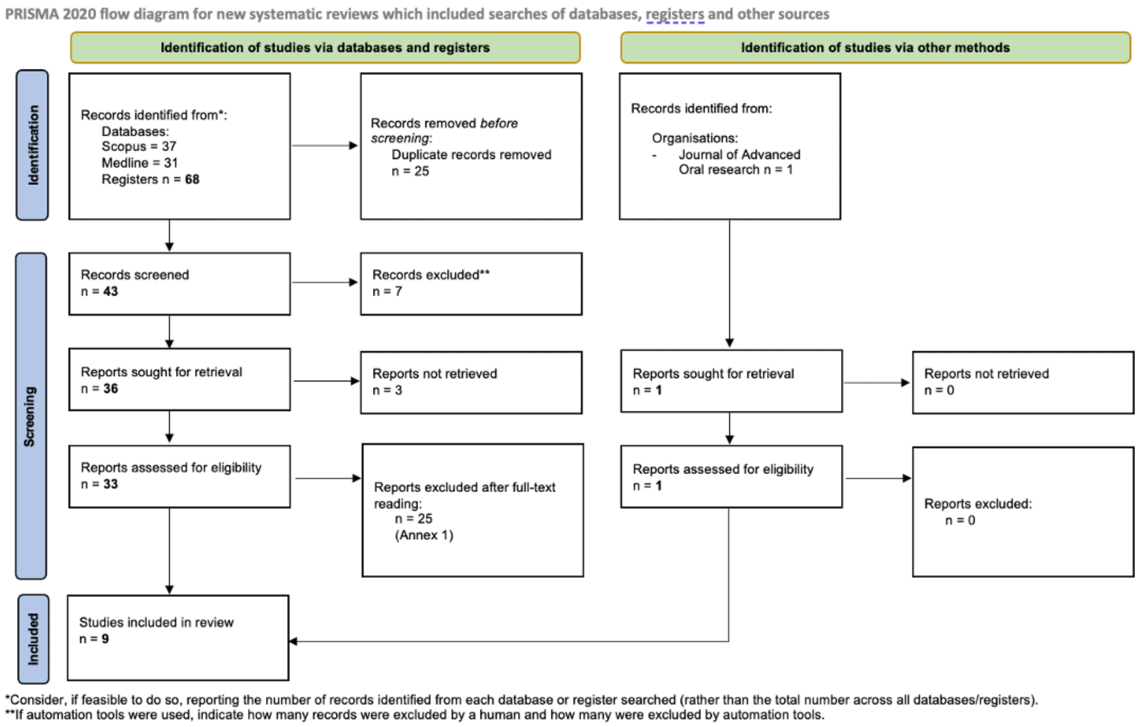

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Table 1. The OHAT risk of bias rating tool for in-vitro studies

Risk-of-Bias Questions	Nepal et al. (2020) (11)	Benz et al. (2016) (15)	Radeva et al. (2016) (10)	Winik et al. (2006) (12)	Davis et al. (2003) (13)	Martell et al. (2002) (16)	Aqrabawi (2000) (17)	Post et al. (2010) (14)	Saraswathi et al. (2015) (18)
1. Was administered dose or exposure level adequately randomized?	NR	+	+	+	NR	+	+	+	+
2. Was allocation to study groups adequately concealed?	–	NR	NR	NR	–	NR	NR	NR	NR
3. Did selection of study participants result in the appropriate comparison groups?	X	X	X	X	X	X	X	X	X
4. Did study design or analysis account for important confounding and modifying variables?	X	X	X	X	X	X	X	X	X
5. Were experimental conditions identical across study groups?	++	++	+	+	+	+	+	+	++
6. Were research personnel blinded to the study group during the study?	NR	++	NR	NR	NR	NR	NR	NR	NR
7. Were outcome data complete without attrition or exclusion from analysis?	++	+	–	NR	+	+	++	NR	+
8. Can we be confident in the exposure characterization?	+	++	+	+	+	+	+	+	+

9. Can we be confident in the outcome assessment (including blinding of assessors)?	+	+	NR	+	+	+	+	+	+
10. Were all measured outcomes reported?	++	+	++	+	+	+	++	+	+
11. Were there no other potential threats to internal validity	+	+	+	+	++	++	+	+	+

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Table 2. *Characteristics of the included studies:*

Author (year)	**Root-end filling material N= sample of teeth**	**Apical resection technique**	**Periapical preparation technique**	**Leakage analyzing method**	**Results**
Nepal *et al.* (2020)	Glass ionomer cement = 20 MTA = 20 Biodentine = 20	Diamond disk on straight handpiece	Round carbide or diamond bur	UV spectrophotometer	The MTA and Biodentine group both showed the highest results compared to GIC. No difference was seen between MTA and Biodentine.
Benz *et al.* (2016)	Super-EBA cement = 36 MTA = 36	Lindemann bone cutter or diamond-coated bur	Ultrasonic device	Stereomicroscope at x 10 magnification	MTA presented the best results compared to Super-EBA.
Radeva *et al.* (2016)	MTA = 10 Biodentine = 8	-	Ultrasonic device	Microtome Leica SP1600	No statistical difference was seen between Biodentine and MTA.
Winik *et al.* (2006)	MTA = 10 Cyanoacrylate = 10	Fissure bur	Carbide bur	JEOL JSM-6100 scanning electron microscope	The cyanoacrylate group showed less leakage compared to the MTA group.
Davis *et al.* (2003)	Amalgam = 20 Super EBA = 20 MTA = 20	557 bur	Ultrasonic device	Stereoscopic microscope	MTA and Super-EBA showed higher sealing in comparison to Amalgam.
Martell *et al.* (2002)	Super EBA = 10 IRM = 10 MTA = 10	Low-speed diamond saw	Ultrasonic device	X 2.5 magnification loupes	MTA had the highest sealing. IRM and Super EBA showed similar results.
Aqrabawi (2000)	Amalgam = 25 Super EBA = 25 MTA = 23	Fissure bur	Ultrasonic device	Stereomicroscope x 10 magnification	MTA showed the best results followed by Super-EBA. Amalgam had the worst sealing ability.
Post *et al.* (2010)	Amalgam = 40 MTA = 40	Diamond coated bur	Round carbide bur or Ultrasonic device	Stereoscopic microscope x 25 magnification	MTA showed lower leakage compared to Amalgam.
Saraswathi *et al.* (2015)	Biodentine = 28 MTA plus = 28 MTA = 28	Fissure bur	Diamond bur	Calibrated stereomicroscope x 50 magnification	MTA plus showed least leakage followed by MTA and lastly Biodentine.