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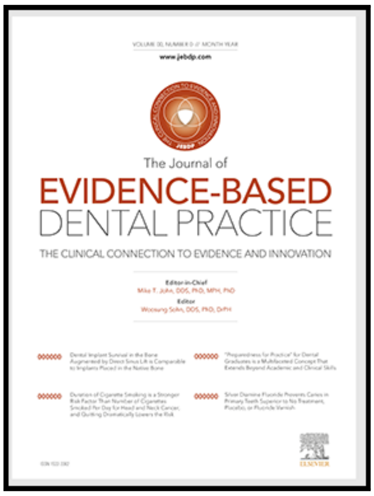

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Efficacy of hemostatic agents in endodontic surgery: A systematic review and network meta-analysis

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Abstract

Objective: Adequate hemostasis is a critical step in endodontic surgery. It facilitates the procedure and affects the success and prognosis of the operation. This systematic review and network meta-analysis (NMA) aimed to systematically assess the efficacy of hemostatic agents in endodontic surgery and to identify the most effective.

Methods: PubMed, Scopus, Embase, Cochrane Library, Web of Science, ProQuest, and EBSCO*host* databases were searched up to December 2020. We included randomized controlled trials (RCTs) evaluating the efficacy of different hemostatic measures in endodontic surgery, and their risk of bias was assessed using Cochrane's randomized trial tool (RoB 2.0). Frequentist network meta-analysis was conducted, with Odds Ratios and 95% confidence intervals (OR, 95% CI) as effect estimates using the "netmeta" package in R. The quality of evidence was assessed using the CINeMA approach.

Results: Six RCTs involving 353 patients (mean age 48.12 years) were included. NMA revealed that aluminum chloride achieved higher hemostatic efficacy than epinephrine (OR= 2.55, 95% CI [1.41, 4.64]), while there was non-significant difference when compared with PTFE strips+ epinephrine (OR= 1.00, 95% CI [0.35, 2.90]), electrocauterization (OR= 2.67, 95% CI [0.84, 8.46]), or ferric sulfate (OR= 8.65, 95% CI [0.31, 240.92]). Of all hemostatic agents, aluminum chloride ranked first in control bleeding during endodontic surgery (P-score= 0.84), followed by PTFE strips+ epinephrine (P-score= 0.80), electrocauterization (P-score= 0.344), epinephrine (P-score= 0.34), ferric sulfate (P-score= 0.18). The quality of evidence was very low.

Conclusions: Based on the limited data, aluminum chloride provides better hemostasis than epinephrine, while there was no significant difference between the remaining hemostatic agents used in endodontic surgery, which could help clinicians achieve adequate hemostasis and give insight to future RCTs. Given insufficient evidence, future RCTs addressing this evidence gap are required.

Keywords: *Bleeding, Endodontic surgery, Evidence-based dentistry, Hemostasis, Hemostatic agent, Network meta-analysis.*

Introduction

Endodontic surgery is an alternative surgical procedure aimed to preserve the necrotic tooth when conventional root canal treatment is failed or cannot be performed [1, 2]. It provides surgical access to the contaminated apical part of the root, followed by removing the associated extra-radicular infection and placing a retrograde filling to adequately seals the root canal system and prevent the leakage between the root canal system and the extra-radicular tissues [3].

According to the European Society of Endodontology, endodontic surgery is indicated for the following conditions: 1) radiographic symptoms of periapical lesions associated with obstructed canals, 2) clinical or radiographic signs associated with extruded material, 3) persistent pathology that cannot be treated with conventional root canal therapy, and 4) root perforation that is not accessible through the coronal root opening [4]. Endodontic surgery's success is based on many factors, including proper diagnosis, appropriate case selection, operator skills, accurate management of the soft and hard tissues, and apical seal [3, 5, 6].

Adequate hemostasis is a critical step during endodontic surgery. It facilitates the procedure and improves the success and prognosis of the surgery [7, 8]. In the absence of adequate hemostasis, bleeding will obscure the anatomical landmarks and reduce vision [9, 10]. Also, adequate hemostasis provides a dry field at the surgical site, improving the surgery's quality by facilitating the surgical procedure, reducing time, and decreasing post-surgical complications such as hemorrhage, swelling, and reducing patient pain during surgery [11-13]. Also, it provides a suitable environment to place the moisture-sensitive retrograde filling materials [14].

The ideal hemostatic agent should be biocompatible, easy to apply, has an immediate effect, does not adversely affect the healing process, and relatively inexpensive [9]. Several agents have been used to control bleeding, including cotton and gauze, bone wax [11], collagen-based products [3, 12], a mixture of surgical wax and fibers of calcium alginate [15], vasoconstrictors (e.g., epinephrine) [16, 17], calcium sulfate [14], ferric sulfate [16, 18], aluminum chloride [8, 19-22], and electrocauterization [20]. However, many hemostatic agents have been used to control bleeding during endodontic surgeries, there is no universal consensus regarding selecting the best hemostatic agent, and the choice is usually based on the operator's preference. In order to address this knowledge gap, we performed a systematic review with network meta-analysis (NMA) summarizing the efficacy of the available bleeding control measures used in endodontic surgery.

The role of NMA in informing clinicians and decision-makers is becoming more prominent, as many health conditions have many competing treatments, and the meta-analysis (pairwise) is limited to provide a direct comparison of only two interventions by using a statistical combination of the results. The NMA provides comparisons between multiple treatments by integrating direct and indirect estimates to determine the best based on ranking their probability of having significant effects [23-25]. Therefore, NMA seemed to be the highest level of evidence in treatment recommendations and decision-making [26, 27]. Many NMA has been performed in endodontics to overcome the knowledge gap in specific topics, such as local anesthesia [28-30] and the safety and efficacy of drugs used in non-surgical endodontics procedures [31, 32]. To our knowledge, this is the first meta-analysis investigating the effectiveness of hemostatic agents in endodontic surgery and aimed to answer the following question: what is the most effective hemostatic agent used in endodontic surgery?

Methods

Protocol and registration

This study follows the PRISMA guidelines for reporting systematic reviews incorporating network meta-analyses of health care interventions [33], and protocol has been registered in the INPLASY database (No. INPLASY202120038) [34].

Eligibility criteria

We constructed the inclusion criteria based on the PICO process as the following: P: Patients requiring endodontic surgery, I: Aluminum chloride, C: Other types of hemostatic measures (PTFE strips + epinephrine, electrocauterization, epinephrine, and ferric sulfate), O: Bleeding control. Since transitivity (validity of indirect comparisons) is highly influenced by randomization, we included only randomized controlled trials that assessed the efficacy of hemostatic agents in endodontic surgery without time or language restrictions [24, 25]. Exclusion criteria were non-randomized clinical trials, observational studies, animal studies, in-vitro studies, case reports and series, reviews, book chapters, and personal opinions.

Information sources and search

A comprehensive electronic search was conducted using the following databases: PubMed, Scopus, Embase, Cochrane Library, Web of Science, as well as ProQuest and EBSCO*host* for grey literature. The final search was updated on December 20, 2020. Besides, the Journal of Endodontics, International Endodontic Journal, and Australian Endodontic Journal were searched. The reference lists of pertinent reviews on the subject were checked for possible additional studies. Appendix Table S1 illustrates the detailed search strategy that has been implemented.

Study selection

Two independent evaluators (AK, MH) conducted the literature search and screened the articles. If the agreement was not achieved, a third researcher should resolve the disagreement (AS).

Data collection

Two independent evaluators (AK, ES) collected the following data for each study: authors, year of publication, country, study design, study setting (location and operator), sex (male: female), mean age, medical condition, number of patients in each group, results relevant to hemostatic efficacy, and funding source. Any disagreement was resolved by the third author (AS).

Quality assessment

Quality assessment of the included studies was performed by two independent authors (AK, FA) following the Cochrane risk of bias tool for randomized trials (RoB 2.0) [35]. Any disagreement was resolved by discussion. This tool has five domains: risk of bias due to the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.

Quality of studies was classified as a low risk of bias if all five domains have no risk of bias, some concerns risk of bias if there is one or more of the domains have an unclear risk of bias, or high risk of bias if one of the domains has a high risk of bias. We used the "robvis" package to display the risk of bias assessment [36].

Data synthesis

Pairwise meta-analysis was performed to assess all direct comparisons between different hemostatic agents using the random effect model (RevMan version 5.3- Cochrane collaboration). Frequentist network meta-analysis (NMA) was implanted using the statistical package "netmeta" [37, 38] in the R program (version 4.0.2) [39]. Dichotomous data were pooled as the odds ratio (OR) with a 95% confidence interval (CI). Significant differences were considered when the 95% CI did not include 1 for OR. Heterogeneity was defined as the variability of results across studies, in which $I^2<50\%$ indicates low heterogeneity, and $I^2\geq50\%$ indicates significant heterogeneity. Studies were compared using a random effect model. Inconsistency between direct and indirect estimates was assessed by net-split function in the "netmeta" package and measured by generalized Cochran's Q statistics for multivariate meta-analysis as described by Krahn and his colleagues [40]. Depending on the point estimates and standard errors of the estimated frequentist network meta-analysis, P-score was used to rank the treatments, in which a higher value indicates better performance. P-scores calculate the degree of confidence, indicating that one treatment is better than the other, which is an average for all comparable treatments [41].

Confidence of evidence

The certainty of cumulative evidence was evaluated using the Confidence in Network Meta-Analysis (CINeMA) approach [42-44]. The confidence was graded as "high," "moderate," "low," or "very low" based on the following domains: study limitations, publication bias, indirectness, imprecision, heterogeneity, and incoherence.

Results

Study selection

The electronic and manual searches identified (n=1,938) articles, of which (n=57) were excluded because of duplication. The remaining (n=1,863) articles were screened by titles and abstracts, of which (n=1,833) articles were excluded as irrelevant. The full-texts of 30 studies were reviewed; six studies met the inclusion criteria [8, 16, 19-22], while the other 24 articles were excluded because they did not meet the inclusion criteria [7, 9, 11-15, 17, 45-58]. (Figure 1 and Appendix Table S2)

Study characteristics

Six RCTs were included in this systematic review [8, 16, 19-22]. The total number of participants included was 353 patients (mean age 48.12 years), including both genders. Surgeries were performed in the esthetic maxillary zone [20], the maxillary or mandibular areas (anterior to the 2nd premolars) [21], and the posterior maxillary zone (first and second molars) [22]. Peñarrocha-Oltra et al. [20] included a single tooth in the esthetic zone (upper incisors, canines, and premolars), while Peñarrocha-Oltra et al. [21] included one or two contiguous teeth, either maxillary or mandibular between the right to left second premolars, whereas excluded multi-rooted posterior teeth. The remaining studies included both maxillary and mandibular teeth. Table 1 presents a summary of the main characteristics of the included studies.

Risk of bias within studies

Overall, five studies [8, 19-22] were considered to have some concerns risk of bias, and one study [16] was considered to have a high risk of bias.

The study by Vickers et al. was assessed as a high risk of bias because it has some concerns in multiple domains. It has some concerns in the first domain (*Bias arising from the randomization process*) due to no details about the allocation concealment, in the second domain (*Bias due to deviations from the intended interventions*), fourth domain (*Bias in the measurement of the outcome*) due to no information about the blinding process, and in the fifth domain (*Bias in the selection of the reported result*) because no protocol found [16].

Five studies [8, 19-22] were identified as some concerns risk of bias as all of them had a low risk of bias in all domains except in the fifth domain (*Bias in the selection of the reported result*) because we did not find protocols in all of them to compare them with the reported results. Figure 2 summarizes the quality assessment of the included studies.

Hemostatic efficacy

In all studies, the surgical operator determined the efficacy of hemostatic agents. All included studies identified adequate hemostasis as complete control of bleeding that provides a dry surgical area during the root-end filling process. However, there was a variation in the definition of inadequate hemostasis, described by three studies as no hemorrhage control (i.e., persistent bleeding that impaired vision in the surgical field) [8, 16, 20]. The other studies defined it as minor intermittent bleeding that continues after using the hemostatic material (i.e., that permitted the root-end filling procedure) [19, 21, 22]. (Table 1)

Presentation of network geometry

The comparisons between different hemostatic agents included five interventions (20% ferric sulfate, epinephrine, aluminum chloride, electrocauterization, PTFE strips+ epinephrine. Since aluminum chloride is the most common agent used in RCTs, it was contrasted with all available therapies, resulting in five comparisons, as shown in the network graph. (Figure 3)

Pairwise meta-analysis

The pooled estimate of direct comparisons showed that aluminum chloride had higher hemostatic efficacy compared to epinephrine (OR= 2.55, 95% CI [1.41, 4.64], P=0.002) with no heterogeneity (I^2=0%, P=0.87), and electrocauterization (OR= 2.67, 95% CI [0.84, 8.46], P=0.10). Whereas there is no significant difference in control bleeding between aluminum chloride and PTFE strips + epinephrine (OR= 1.00, 95% CI [0.35, 2.90], P=1.00) with no heterogeneity (I^2=0%, P=0.59), as well, between epinephrine and ferric sulfate (OR= 3.39, 95% CI [0.13, 89.37], P=0.14). (Figure 4)

Network meta-analysis

The network estimate revealed that aluminum chloride achieved higher hemostatic efficacy than epinephrine (OR= 2.55, 95% CI [1.41, 4.64]). However, there is no substantial change in control bleeding when compared aluminum chloride with PTFE strips+ epinephrine (OR= 1.00, 95% CI [0.35, 2.90]), electrocauterization (OR= 2.67, 95% CI [0.84, 8.46]), and ferric sulfate (OR= 8.65, 95% CI [0.31, 240.92]). The heterogeneity of the network meta-analysis was not significant (Cochran's Q=0.32, p=0·85, τ^2=0, tau=0, I^2=0% [0.0%; 35.2%]). (Table 3 and Appendix Figure S1)

Treatments' ranking

The ranking P-score showed that aluminum chloride was the best hemostatic agent (P-score= 0.84), followed by PTFE strips+ epinephrine (P-score= 0.80), electrocauterization (P-score= 0.344), epinephrine (P-score= 0.34), ferric sulfate (P-score= 0.18). (Appendix Table S3)

Publication bias

Given the limited number of included studies (less than ten studies), the publication bias assessment by comparison-adjusted funnel plot was not applicable [59]. (Appendix Figure S2)

Quality of evidence

Due to the limited number of studies included and the small sample, the evidence's certainty was mainly decreased due to incoherence and imprecision. The quality of cumulative evidence was very low for all comparisons. Details of rating the quality of evidence were summarized in Table 4. (Appendix Figure S3)

Discussion

In this study, we systematically assessed the available evidence regarding the efficacy of various hemostatic measures to control bleeding in endodontic surgery. We found that aluminum chloride was more effective than epinephrine in control bleeding, while there was no significant difference between the remaining hemostatic agents used in endodontic surgery. Overall, there is very little evidence about bleeding control during endodontic surgery, as we identified only six RCTs, mainly from Spain. Most of the included studies were of high quality; however, all RCTs (except for one study [8]) and even non-randomized trials assessed the efficacy of hemostatic agents during surgery without evaluating their adverse effects, postoperative complications, or healing potential; that may affect the body of evidence on the choice of hemostatic interventions. Therefore, we cannot recommend using a specific hemostatic agent during endodontic surgery.

Aluminum chloride ($AlCl_3$) is widely used as a hemostatic agent because it is clinically effective, easy to apply, cheap, and commercially available. The effectiveness of aluminum chloride to control bleeding during endodontic surgery is well-documented in the literature [8, 19-22, 50, 57]. It reacts chemically with blood proteins and is distinguished by its acidic properties. These characteristics make it a suitable hemostatic agent due to the blood's high protein content [60]. Aluminum chloride acts by creating a barrier formed by the coagulated blood proteins that prevent blood flow from the arteries, thus preventing its possible systemic side effects. This mechanism may provide sufficient hemostasis, even in patients with bleeding disorders [60, 61].

On the other hand, aluminum chloride is a paste-based agent that causes the substance to adhere to bony crypt walls, making it difficult to remove its remnants [53]. Animal studies have shown a marked inflammatory response associated with the residuals particles that cause localized foreign body reactions and may delay healing [50, 53, 57]. Although it is easy to wash with saline since it is hydrophilic, it is still not recommended due to the possibility of leaving traces in the cancellous bone [57]. Such complications can be wholly eliminated by cleaning the surgical site with a bone curette and freshening the bone defect is using a small round bur, and filling the root end with a filling material such as mineral trioxide aggregate (MTA) to avoid direct contamination by water spray [8, 50, 57]. Besides, studies found that patients treated with aluminum chloride had better healing after one year compared to epinephrine, but the difference was not significant [7, 8].

To overcome this limitation, there is a strong need for materials that achieve adequate hemostasis during endodontic surgery and can also be removed easily or resorbed physiologically without complications, particularly in the posterior areas where the complete removal of remnants is more difficult. Peñarrocha-Oltra et al. first proposed the use of PTFE strips as an addition to epinephrine-impregnated gauze in endodontic surgery [21, 22]. PTFE is characterized by many features that make it a good option to use in endodontic surgery [62, 63]. PTFE is relatively inert, making it biocompatible without allergic reactions, and has low surface energy, which leads to a very low coefficient of friction that means that it can be removed without any residuals [64, 65]. Also, it has high thermal stability, rendering it autoclavable without impacting its physical characteristics [63]. Consequently, the application of PTFE as an adjunct to epinephrine acts as a mechanical barrier to control bleeding in the surgical site, as well as provides good handling efficiency in treating areas around bleeding anatomical structures (e.g., maxillary sinus) and complicated anatomical features (e.g., multi-rooted teeth) [21, 22]. Based on this NMA, PTFE strips + epinephrine is the second-ranked in control bleeding during endodontic surgery, but this ranking should be viewed cautiously.

On the other side, calcium sulfate (CaS), also known as "Plaster of Paris," acts mechanically by serving as a physical barrier to achieving hemostasis [46, 66]. It is a distinctive agent that is inexpensive, fast set, and easy to remove and apply [67]. CaS is characterized by excellent biocompatibility with no adverse effects on outcomes, lack of inflammatory reactions [45, 53], and some debates about whether it may improve healing [45, 53, 67, 68]. Also, it is completely resorbable and does not impair the MTA's function, which ensures that it can be removed or left in-situ without any concerns and no risk of use near bleeding anatomical structures (e.g., maxillary sinus) [45, 53, 67-69]. The hemostatic efficacy of CaS was clinically assessed and was about 100% effective in controlling bleeding during endodontic surgery [14]. The CaS was used as a hemostatic agent after dental extraction in patients undergoing anticoagulant therapy [70] and for control of bleeding during surgical-exposure of impacted teeth prior to orthodontic treatment [71]. Although CaS was not included in this study since the only clinical trial evaluated was a non-randomized trial [14], we recommend considering it for potential RCTs due to its distinctive characteristics in different clinical situations.

Epinephrine is one of the most common hemostatic agents used in endodontic surgery. It stimulates the alpha-adrenergic receptors that cause vasoconstriction, and it has the least cytotoxic effect [13, 56]. Consequently, applying a cotton pellet or gauze impregnated with epinephrine will act by the chemical action of epinephrine and the mechanical action of a cotton pellet or gauze [10]. As a result, there is a risk of traces of fibers at the surgical site that may delay healing through inflammation and foreign body reactions [72]. Therefore, it is recommended to remove it carefully followed by rigorous irrigation [10]. Also, there have been some questions about the use of vasoconstrictors (e.g., epinephrine) as a local hemostatic agent that can exert systemic cardiovascular effects in addition to its use in local anesthesia [13, 73, 74]. Clinical studies have denied these concerns in healthy patients and have shown that epinephrine has reasonable hemostatic efficacy without changes in pulse rate or blood pressure [16, 17].

Electrocauterization is a useful tool for achieving hemostasis by exerting an electrical heat, which causes blood and tissue proteins to coagulate and prevents blood flow, leaving an eschar that the body is trying to slough [50, 75]. As such, no foreign substance is inserted into the bony crypt with this method [50]. However, there was a concern about the effect on healing due to the thermal damage to the bone tissue [76]. Jensen et al. showed delayed healing, signs of superficial necrosis with minimal bone formation, and an adverse tissue reaction related to necrotic zones were observed in the initial healing process [50]. To avoid the potential complications, coagulum tissues should be removed with a bone curette and freshened the superficial bone layer with a rotary instrument to minimize the adverse tissue reactions [50].

Ferric sulfate (FS) is a necrotizing agent with very low pH (0.8-1.6) [77], as it acts chemically by interacting with blood proteins leading to coagulation [18, 75]. It is easy to use, inexpensive, has been reported to achieve hemostasis in less than 1 min, and sustained for up to 5 min [18, 78]. However, it is cytotoxic [53, 56], and when used in maximum concentrations and left in situ, results in bone damage, extreme foreign body reactions, and abscess formation [18, 78]. Also, it could induce mild foreign body reactions but did not hinder bone healing [57, 78]. Accordingly, complete removal must be due to potential inflammatory reactions associated with its remains [53, 57, 78]. Ferric sulfate coagulum can be easily removed using a curettage and saline irrigation [78].

This study has some limitations; the first is the small sample size and the restricted number of included studies. Second, the included studies did not assess the influence of hemostatic agents on healing, long-term success rates, and patient-reported outcomes.

Conclusion

Based on our findings, aluminum chloride provides better hemostasis than epinephrine but was non-significant compared to other hemostatic agents, and there was no significant difference between the other hemostatic measures in endodontic surgery. Therefore, high-quality RCTs with a large sample size and long follow-ups are required to compare the efficacy of hemostatic agents and to assess their effect on healing. Based on the limited body of evidence, we cannot recommend using a specific hemostatic agent during endodontic surgery at present.

Author Contributions:
Conceptualization: A.G.A.K.; Methodology: A.G.A.K., F.S.A., and A.S; Data collection: A.G.A.K., E.M.S., M.M.A.H.; Data analysis: A.G.A.K., M.S.A.S.; Writing original draft preparation: A.G.A.K., F.S.A., M.S.A.S.; Writing—review and editing: F.S.A., A.S., and A.G.A.K.; Supervision: A.S., F.S.A. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest Statement

The authors deny any conflicts of interest related to this study

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Appendix Table S1: Search strategies

PubMed	((("Hemostatics"[Mesh] OR "Hemostatics" [Pharmacological Action]) AND ("Periapical Diseases/drug effects"[Mesh] OR "Periapical Diseases/drug therapy"[Mesh] OR "Periapical Diseases/surgery"[Mesh] OR "Periapical Diseases/therapy"[Mesh])) OR ("Periapical Tissue/drug effects"[Mesh] OR "Periapical Tissue/surgery"[Mesh])) OR ("Dental Pulp Diseases/drug effects"[Mesh] OR "Dental Pulp Diseases/drug therapy"[Mesh] OR "Dental Pulp Diseases/surgery"[Mesh])
Cochrane Library	**#5 (#1 OR #2) AND (#3 OR #4)** : #1 MeSH descriptor: [Hemostatics] explode all trees #2 MeSH descriptor: [Hemostasis] explode all trees #3 MeSH descriptor: [Endodontics] explode all trees #4 MeSH descriptor: [Periapical Diseases] explode all trees
Scopus	(("hemostasis") OR ("hemostatic agents") OR ("Surgical Hemostasis") OR ("Hemostatic Techniques") OR ("Hemostases")) AND (("endodontic surgery") OR ("apical surgery") OR ("periapical surgery") OR ("periradicular surgery") OR ("apicoectomy"))
Embase	**#3 #2 AND #1** #2: 'hemostasis'/de OR 'hemostasis'/exp OR 'hemostatic agents' OR 'surgical hemostasis' OR 'hemostatic techniques'/de OR 'hemostatic techniques'/exp OR 'hemostases' #1: 'endodontic surgery'/de OR 'endodontic surgery'/exp OR 'apical surgery' OR 'periapical surgery' OR 'periradicular surgery' OR 'apicoectomy'/de OR 'apicoectomy'/exp

Web of Science	**#3 #2 AND #1** #2: TS=("endodontic surgery") OR TS=("apical surgery") OR TS=("periapical surgery") OR TS=("periradicular surgery") OR TS=("apicoectomy") *Databases= WOS, BCI, KJD, MEDLINE, RSCI, SCIELO, ZOOREC* *Timespan=All years, Search language=Auto.* #1: TS=("hemostasis") OR TS=("hemostatic agents") OR TS=("Surgical Hemostasis") OR TS=("Hemostatic Techniques") OR TS=("Hemostases") *Databases= WOS, BCI, KJD, MEDLINE, RSCI, SCIELO, ZOOREC* *Timespan=All years, Search language=Auto*
ProQuest	AB("endodontic surgery") OR AB("apical surgery") OR AB("periapical surgery") OR AB("periradicular surgery") OR AB("apicoectomy") **AND** AB("hemostasis") OR AB("hemostatic agents") OR AB("Surgical Hemostasis") OR AB("Hemostatic Techniques") OR AB("Hemostases")
EBSCO*host*	AB("endodontic surgery") OR AB("apical surgery") OR AB("periapical surgery") OR AB("periradicular surgery") OR AB("apicoectomy") **AND** AB("hemostasis") OR AB("hemostatic agents") OR AB("Surgical Hemostasis") OR AB("Hemostatic Techniques") OR AB("Hemostases")

Appendix Table S2: Excluded studies after the full-text screening

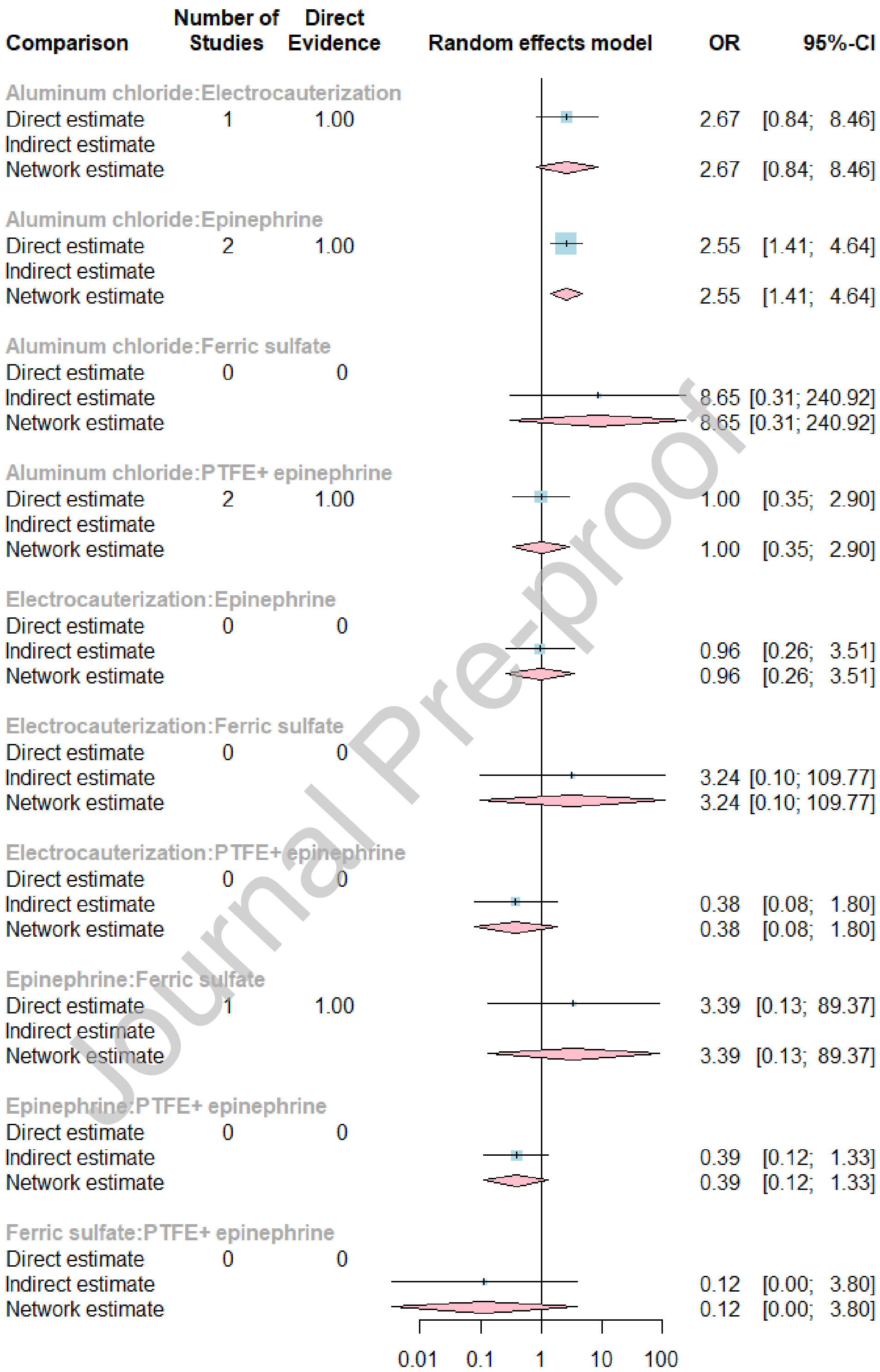
Author (Year)	Title	DOI	Reason for exclusion
Selden (1970)	Bone wax as an effective hemostat in periapical surgery	10.1016/0030-4220(70)90095-2	Case series
Gutmann (1993)	Parameters of achieving quality anesthesia and hemostasis in surgical endodontics	-	Literature review
Lemon et al. (1993)	Ferric Sulfate Hemostasis: Effect on Osseous Wound Healing. I. Left In Situ for Maximum Exposure	10.1016/S0099-2399(06)80681-3	Animal study
Jeansonne et al. (1993)	Ferric Sulfate Hemostasis: Effect on Osseous Wound Healing, II, With Curettage and Irrigation	10.1016/S0099-2399(06)80682-5	Animal study
Witherspoon and Gutmann (1996)	Haemostasis in periradicular surgery	10.1111/j.1365-2591.1996.tb01360.x	Literature review
Kim and Rethnam (1997)	Hemostasis in endodontic microsurgery	-	Literature review
Sauveur et al. (1999)	The control of haemorrhage at the operative site during periradicular surgery	10.1046/j.1365-2591.1999.00191.x	Case report
Apaydin and Torabinejad (2004)	The effect of calcium sulfate on hard-tissue healing after periradicular surgery	10.1097/00004770-200401000-00003	Animal study

Vy et al. (2004)	Cardiovascular Effects and Efficacy of a Hemostatic Agent in Periradicular Surgery	10.1097/00004770-200406000-00001	Non-randomized trial
Von Arx et al. (2006)	Haemostatic agents used in periradicular surgery: an experimental study of their efficacy and tissue reactions	10.1111/j.1365-2591.2006.01152.x	Animal study
Jensen et al. (2010)	Haemostatic effect and tissue reactions of methods and agents used for haemorrhage control in apical surgery	10.1111/j.1365-2591.2009.01637.x	Animal study
Azargoon et al. (2011)	Assessment of hemostatic efficacy and osseous wound healing using HemCon dental dressing	10.1016/j.joen.2011.02.023	Animal study
Maestre-Ferrín et al. (2011)	Hemostatic agents used in apical surgery: a review.	10.4317/jced.3.e310	Literature review
Scarano et al. (2012)	Hemostasis Control in Endodontic Surgery: A Comparative Study of Calcium Sulfate versus Gauzes and versus Ferric Sulfate	10.1016/j.joen.2011.09.019	Non-randomized trial
Peñarrocha-Diago et al. (2012)	Pain and swelling after periapical surgery related to the hemostatic agent used: Anesthetic solution with vasoconstrictor or aluminum chloride	10.4317/medoral.17782	Observational study
Peñarrocha-Diago et al. (2013)	Influence of hemostatic agents upon the outcome of periapical surgery: dressings with anesthetic and vasoconstrictor or aluminum chloride	10.4317/medoral.18002	Retrospective study
Coaguila Llerena et al. (2015)	Agentes hemostáticos en cirugía periapical. Revisión de literatura Hemostatic agents in apical surgery. A review	-	Literature review & Non-English Study
Clé-Ovejero et al. (2016)	Haemostatic agents in apical surgery. A systematic review	10.4317/medoral.21109	Systematic review
Nabavizadeh et al. (2016)	Comparison of the Hemostatic Activity of Quercus persica Jaub. & Spach. (Oak) With Ferric Sulfate in Bony Crypts	10.1177/2156587215593378	Animal study
Mc Goldrick et al. (2017)	Trial finds better haemostasis with aluminium chloride during periapical surgery	10.1038/sj.ebd.6401240	Editorial
Menéndez Nieto et al. (2018)	New perspectives in periapical surgery: Hemostasis	-	Literature review
Brignardello-Petersen (2019)	There may be no differences in the success of periapical surgery when using aluminum chloride or epinephrine as hemostatic agent during surgery	10.1016/j.adaj.2018.09.013	Editorial
Mena-Álvarez et al. (2019)	Histological analysis of different local haemostatic agents used for periapical surgery: An experimental study with Sprague-Dawley rats	10.1111/aej.12332	Animal study
Phumpatrakom et al. (2020)	In vitro cytotoxicity of some hemostatic agents used in apicoectomy to human periodontal ligament and bone cells	10.4103/sej.sej_8_19	In-vitro study

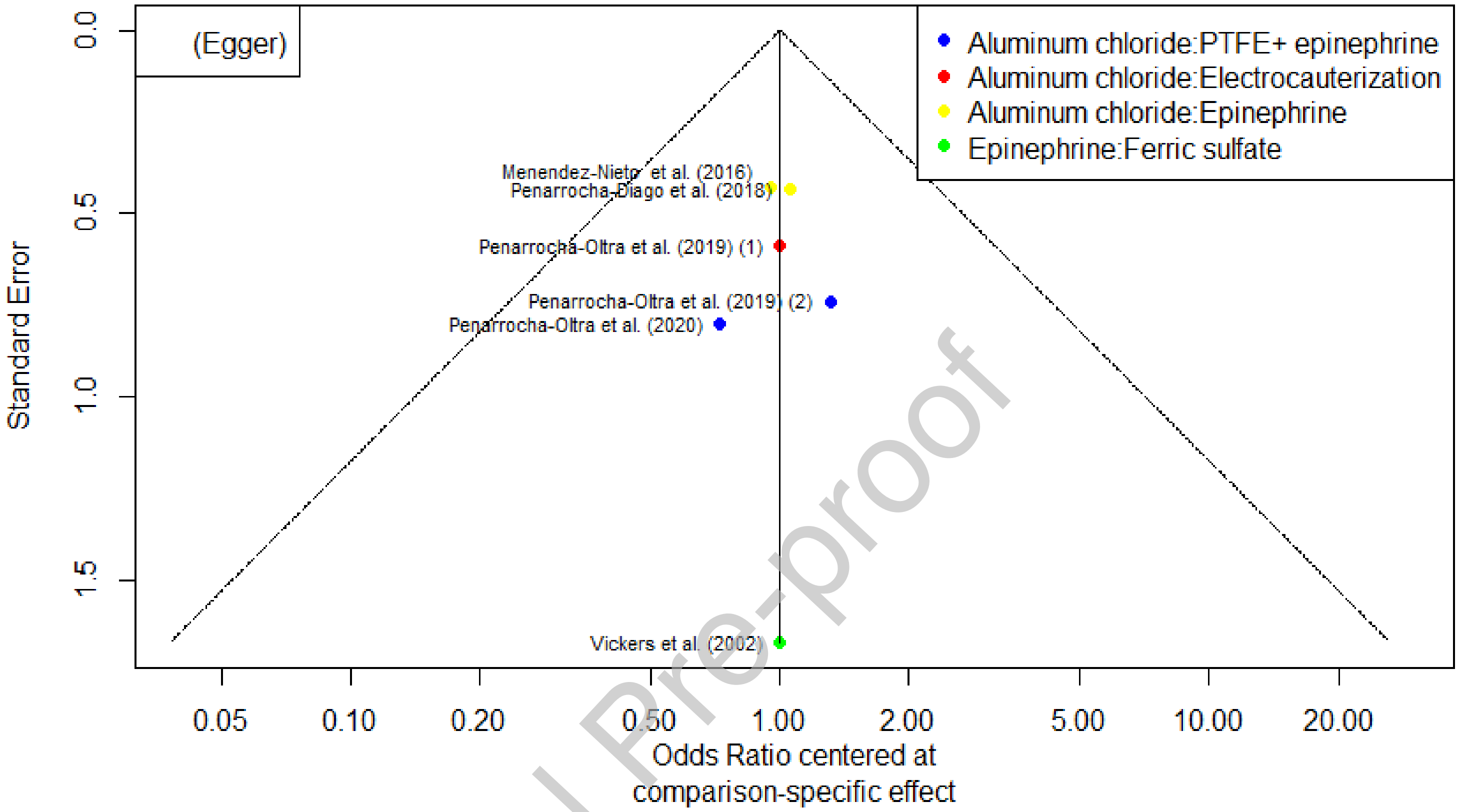
Appendix Table S3: Results of network meta-analysis

Intervention	OR [95% CI]	Q statistics**		Rank	P-scores*
		Q	*p-value*		
Aluminum chloride	Reference			1st	0.84
PTFE+ epinephrine	1.00 (0.34, 2.90)	0.29	0.59	2nd	0.80
Electrocauterization	0.37 (0.12, 1.19)	---	---	3th	0.344
Epinephrine	0.39 (0.22, 0.71)	0.03	0.87	4th	0.34
Ferric sulfate	0.12 (0.00, 3.22)	---	---	5th	0.18
Heterogeneity/ Inconsistency	τ^2= 0; tau = 0; I^2 = 0% [0.0%; 35.2%]				
P-value heterogeneity (within design)	0.85				
P-value inconsistency (between design)	---				
Number of studies	**6**				

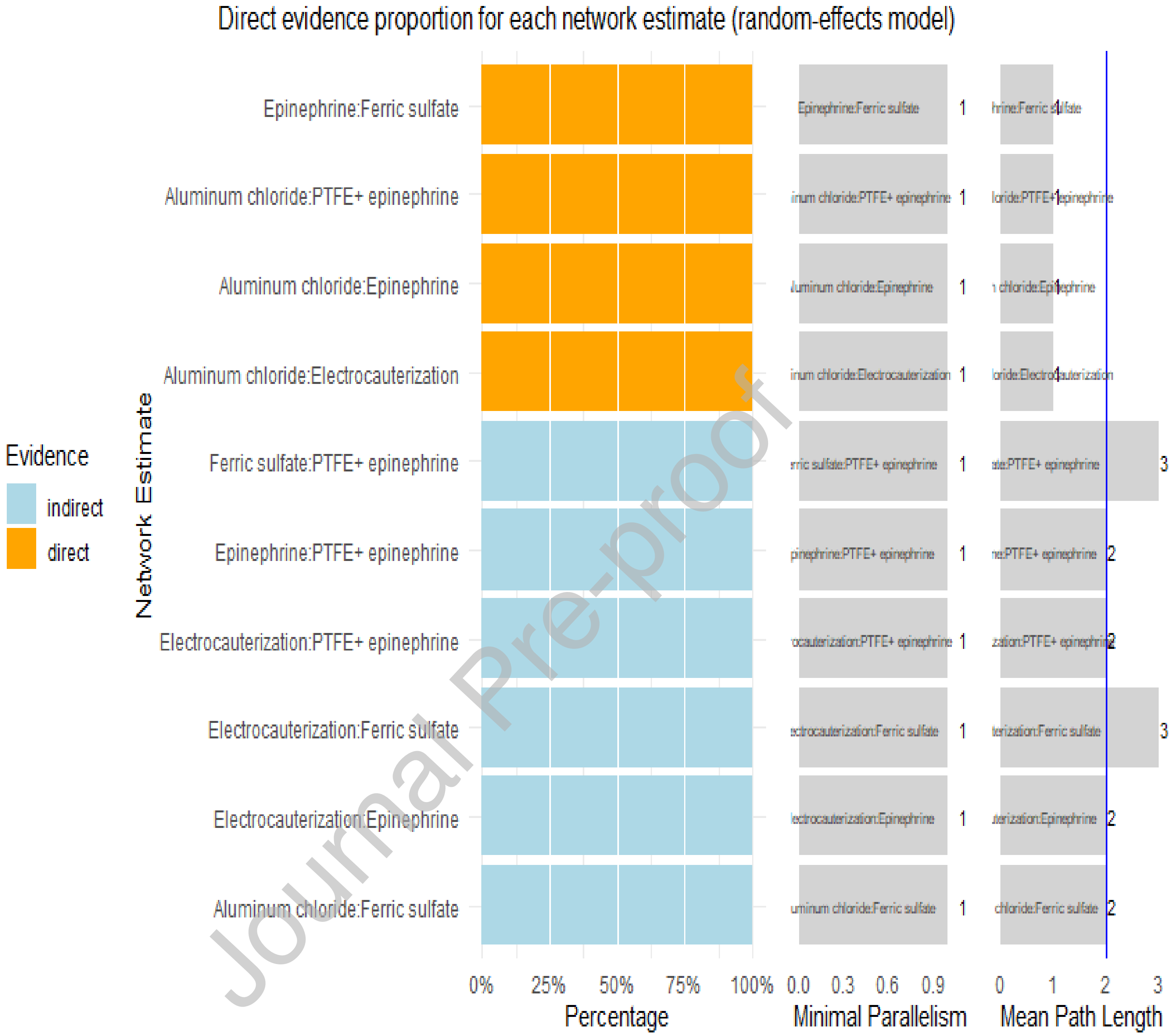
**Higher value of P-scores indicates better hemostatic efficacy*
*** Q statistics to assess homogeneity / consistency*



Appendix Figure S1: Forest plot visualizes the net-split results by summarizing the direct and indirect effect estimates in all comparisons



Appendix Figure S2: Comparison-adjusted Funnel Plot assesses the publication bias in the network meta-analysis and reveals the symmetry distribution between studies around the zero line.
Due to the limited number of comparisons, the p-value of Egger's Test is not available.



Appendix Figure S3: Direct-evidence plot shows the proportion of direct and indirect contributions in each comparison. Comparison with lower minimal parallelism values and more than two in Mean Path Length means that the results should be viewed with caution.

In NMA, Cautions should be taken when considering the results of these comparisons: Ferric sulfate vs. PTFE + epinephrine, and Ferric sulfate vs. Electrocauterization.

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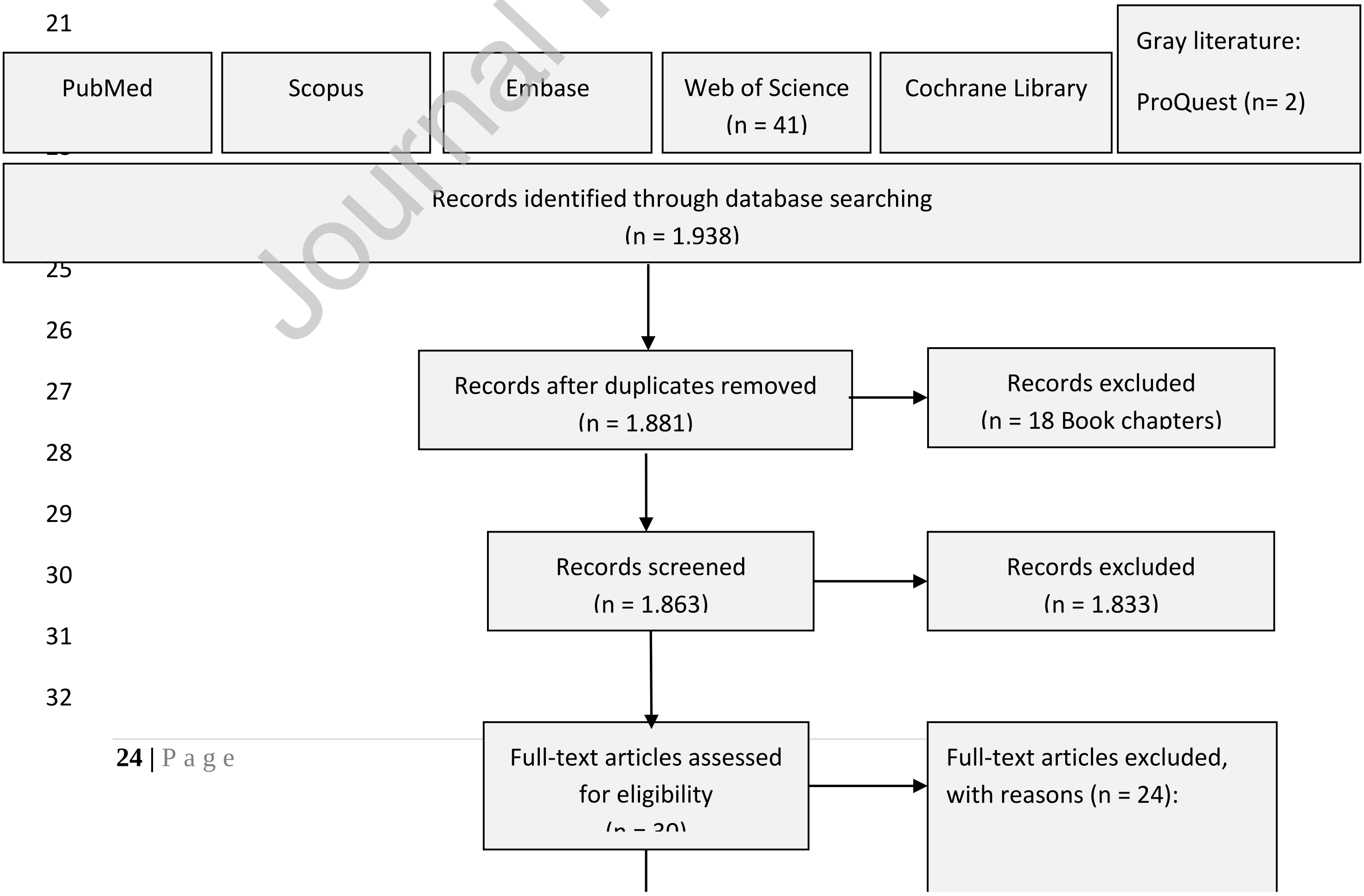


Figure 1: PRISMA flow diagram illustrates the process of literature search and study selection.

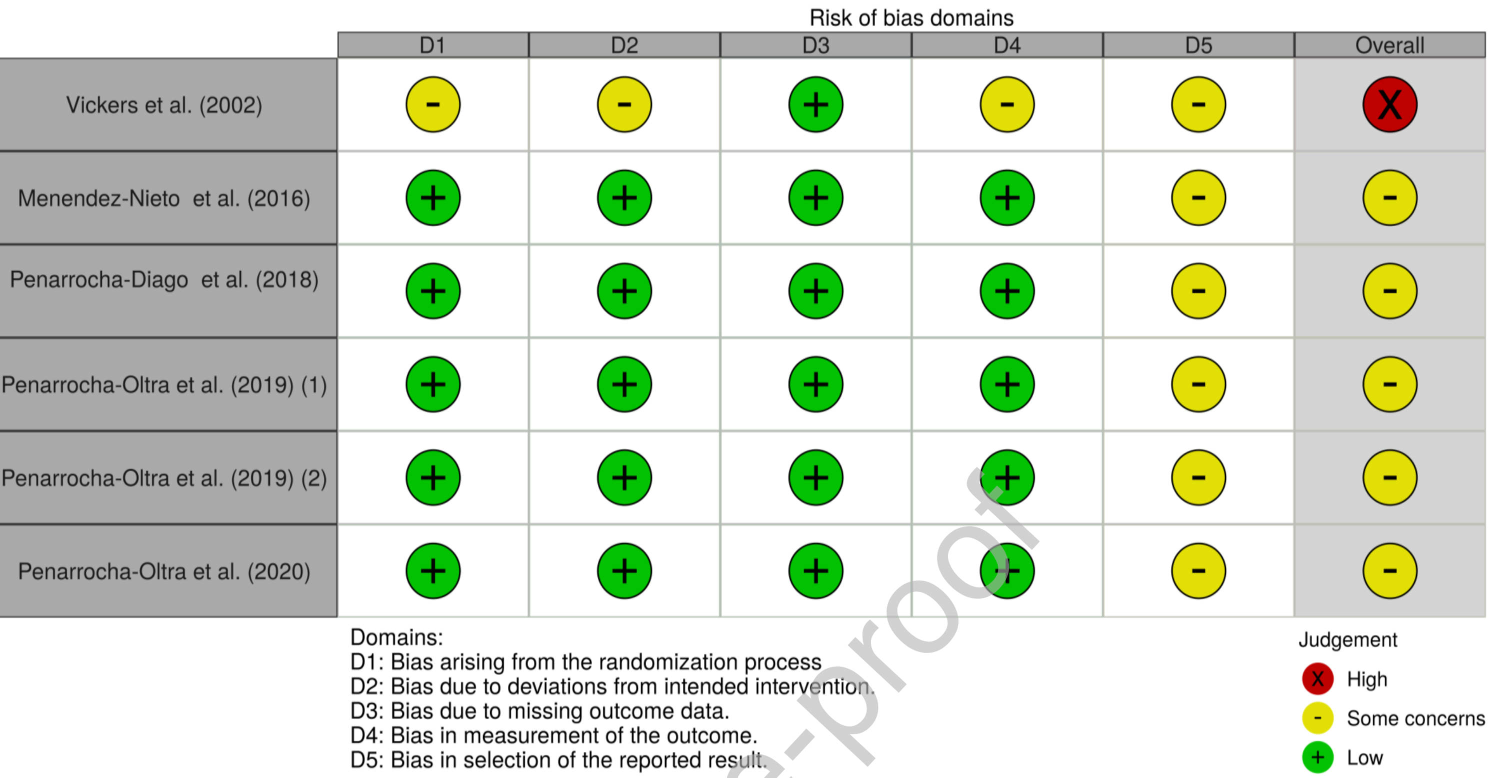
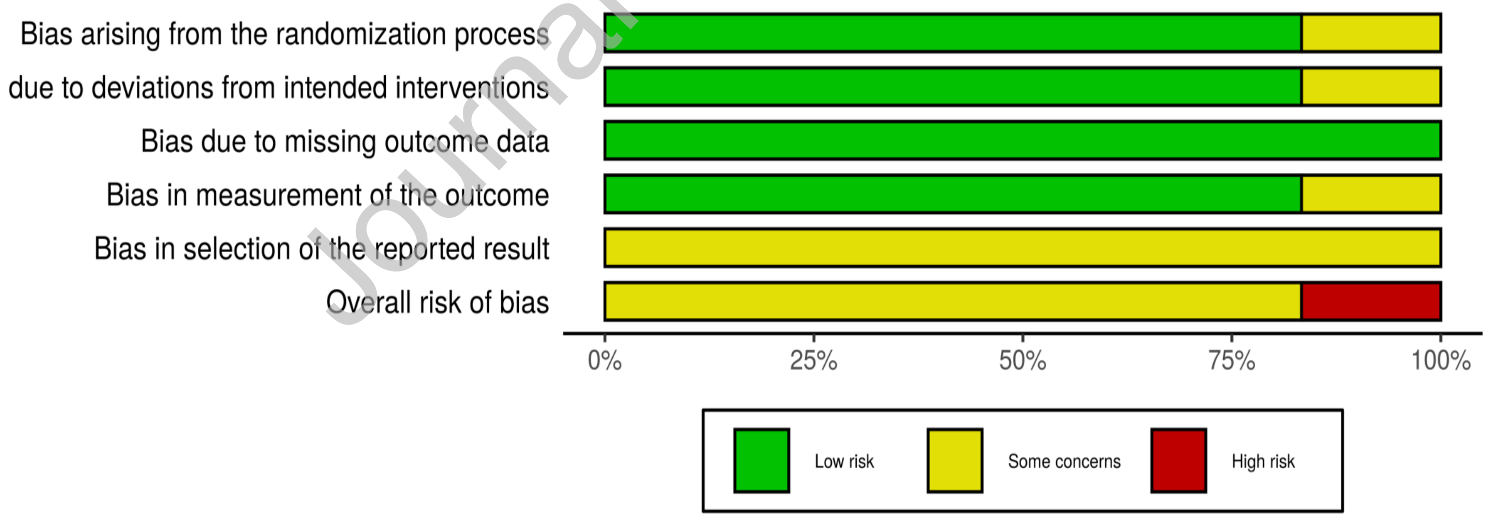


Figure 2: A) Risk of bias summary indicates each risk of bias for each included study.



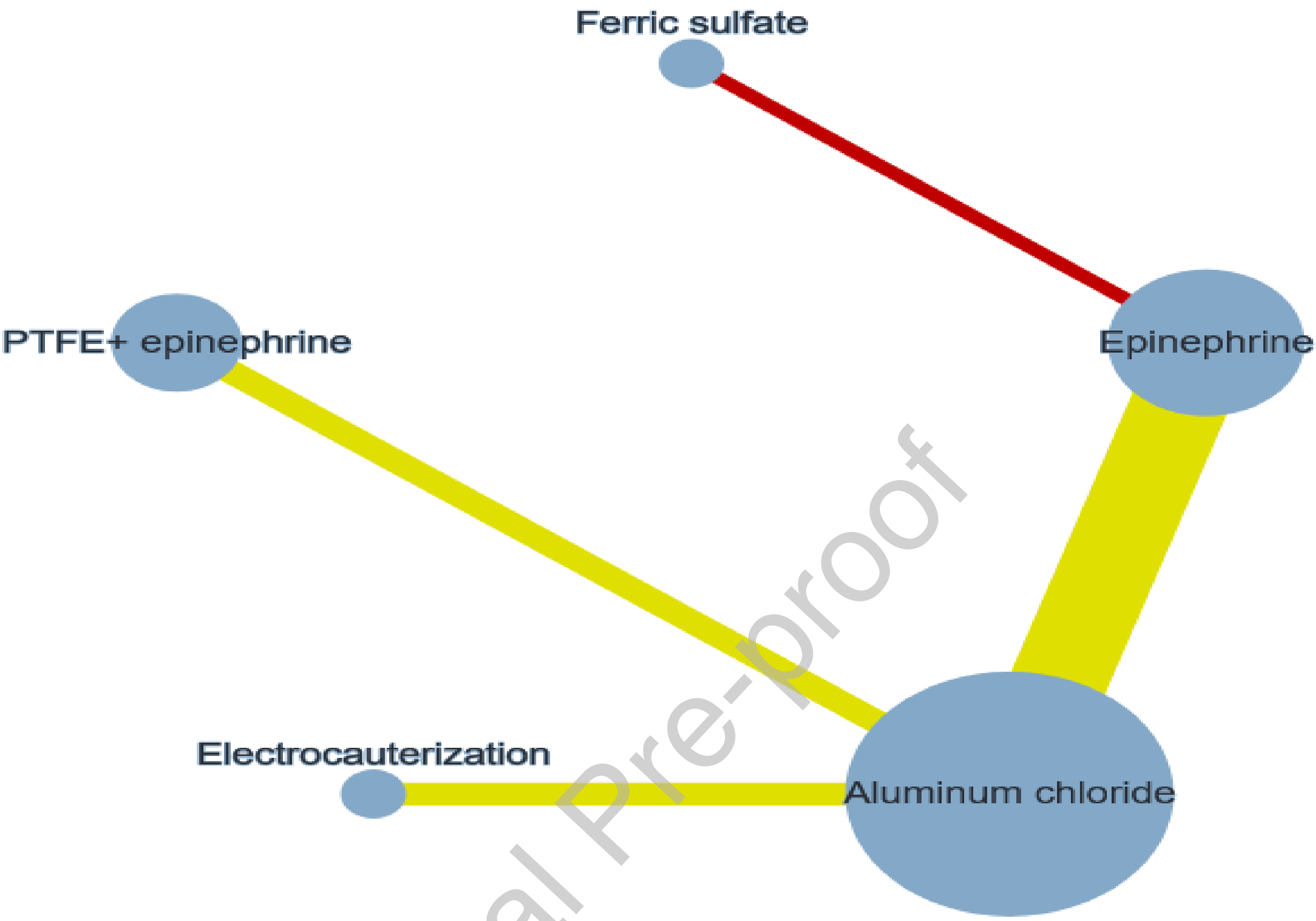


Figure 2: B) Risk of bias graph summarized each risk of bias item presented as percentages across all included studies.

Figure 3: Network plot of hemostatic agents used in endodontic surgery. The node's size represents the number of studies, while the width of the edges represents the sample size, and its color represents the risk of bias.

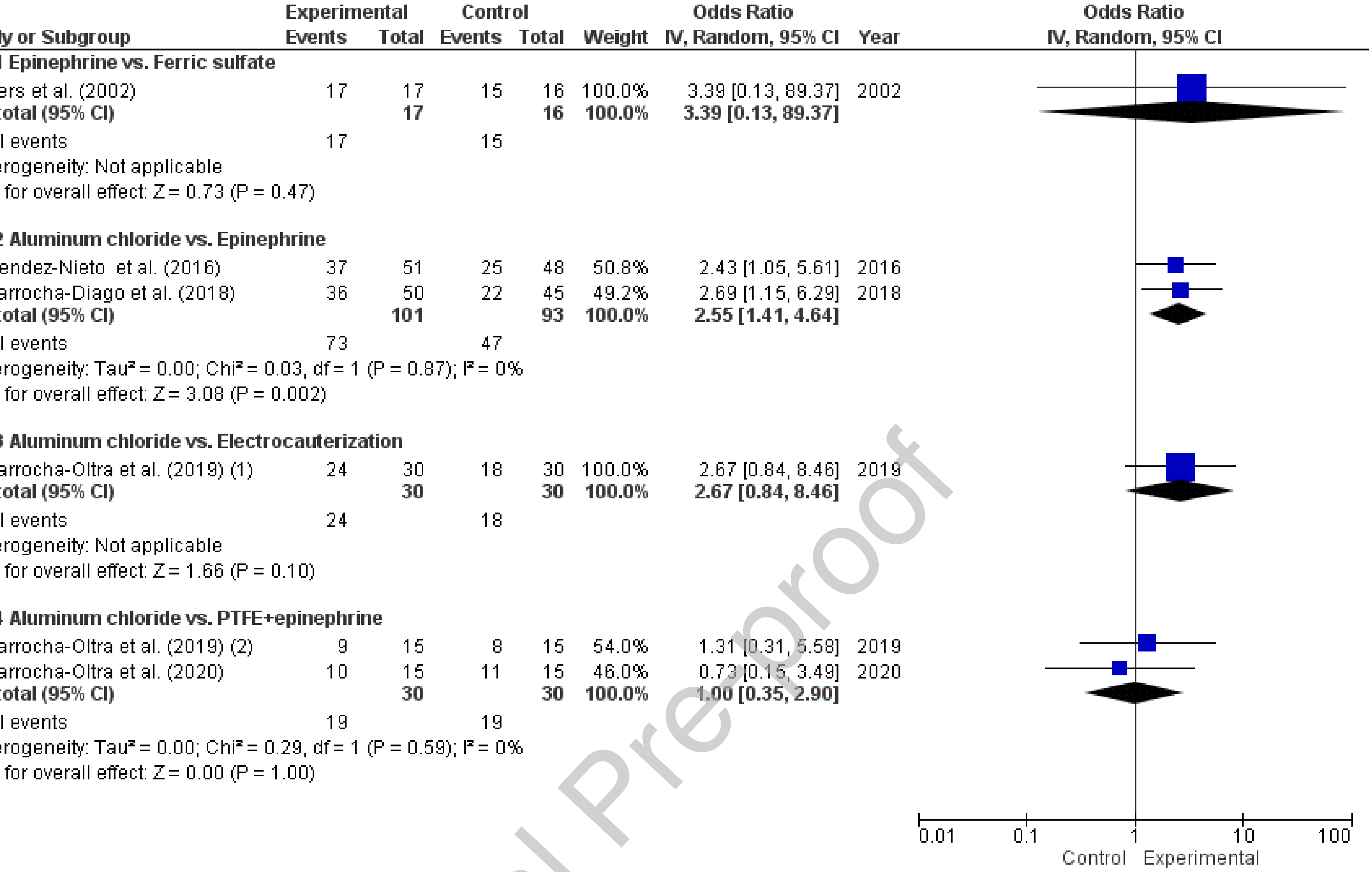


Figure 4: Forest plot showed direct comparisons (pairwise meta-analysis) of different treatments in terms of hemostatic efficacy.

Table 1: Main characteristics of the included studies

Authors (Years) Country	Study design Location Operator	Hemostatic agent	Participants	Hemostatic efficacy	Funding

		Experimental	*Comparator*	**Age** *Mean ±SD* **(Medical status)**	**Sample size** *(M/F ratio)*	**N.** ***Exp.***	**N.** ***Com.***	***Exp.***	***Com.***	
Vickers et al. (2002)[16] USA	RCT University Endodontic resident	Racemic-epinephrine cotton pellets (Racellet #3, Pascal Company, Inc., Bellvue, WA)	20% Ferric sulfate (Viscostat, Ultradent, South Jordan, UT)	NR (ASA I or II)	39 (NR)	17	16	100%	93.75%	NR
enendez-Nieto et al. (2016)[19] Spain	RCT University Oral surgeon	Aluminum chloride (Expasyl™; Produits Dentaires Pierre Rolland, Merignac, France)	Gauzes with epinephrine (B-Braun, 1 mg/mL; Rubı, Barcelona, Spain)	47.5 ±15 (NR)	99 (36:63)	51	48	72.5%	52.1%	None
enarrocha-Diago et al. (2018)[8] Spain	RCT University Oral surgeon	Aluminum chloride (Expasyl™; Produits Dentaires Pierre Rolland, Merignac, France)	Gauzes with epinephrine (B-Braun, 1 mg/mL; Rubı, Barcelona, Spain)	47.5 ±15 (NR)	95 (67:28)	50	45	72%	48.9%	None
enarrocha-Oltra al. (2019) (1)[20] Spain	RCT University Oral surgeon	Aluminum chloride (Expasyl™; Produits Dentaires Pierre Rolland, Merignac, France)	Electrocauterization (Ball electrode; Servotome Classic; Satelec/ Acteon, Norwich, England)	46 ±15.4 (NR)	60 (19:41)	30	30	80%	60%	None
enarrocha-Oltra al. (2019) (2)[21] Spain	RCT University Oral surgeon	Aluminum chloride (Expasyl™; Produits Dentaires Pierre Rolland, Merignac, France)	PTFE strips+ epinephrine	51.6 ±14.8 (ASA I or II)	30 (16:14)	15	15	60%	53.3%	None
enarrocha-Oltra et al. (2020)[22] Spain	RCT University Oral surgeon	Aluminum chloride (Expasyl™; Produits Dentaires Pierre Rolland, Merignac, France)	PTFE strips+ epinephrine	48 ±10.8 (ASA I or II)	30 (8: 22)	15	15	66.7%	73.3%	None

***Abbreviations**: RCT, randomized clinical trial; PTFE, Polytetrafluoroethylene; ASA, American Society of Anesthesiologists; M, male; F, female; NR, not reported.

Table 2: League table of network meta-analysis of hemostatic efficacy

Aluminum chloride	2.67 (0.84, 8.46)	**2.55 (1.41, 4.64)**	8.65 (0.31, 240.92)	1.00 (0.35, 2.90)

0.3750 (0.12, 1.19)	***Electrocauterization***	0.9579 (0.26, 3.51)	3.2446 (0.10, 109.77)	0.3752 (0.08, 1.80)
0.39 (0.22, 1.33)	1.04 (0.28, 89.37)	***Epinephrine***	3.39 (0.13, 3.83)	0.39 (0.12, 0.71)
0.12 (0.00, 3.22)	0.31 (0.01, 10.43)	0.30 (0.01, 7.79)	***Ferric sulfate***	0.12 (0.00, 3.80)
1.00 (0.34, 2.90)	2.67 (0.55, 12.82)	2.55 (0.75, 8.65)	8.65 (0.26, 284.31)	***PTFE+ epinephrine***

The cells contain the odds ratio (OR, 95% confidence interval) of the treatment. Odds ratios <1 favor the intervention specified in the row. The bolded values are statistically significant. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment.

Table 3: Certainty of evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
Aluminum chloride vs. Electrocauterization	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Major concerns	***Very low***
Aluminum chloride vs. Epinephrine	2	Some concerns	Undetected	No concerns	No concerns	Major concerns	Major concerns	***Very low***
Aluminum chloride vs. PTFE+ epinephrine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
Indirect evidence								
Aluminum chloride vs. Ferric sulfate	--	Major concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	***Very low***