Objectives: Resin infiltration is a minimally invasive technique for treating noncavitated proximal caries. It slows/stops the carious lesion progression rate by creating a diffusion barrier inside the porous enamel lesion body. The aim was to evaluate the efficacy of resin infiltration on noncavitated proximal carious lesions in primary and permanent teeth.

Materials and Methods: The records were obtained using electronic and other sources. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to ensure transparent reporting. Eligible studies were randomized controlled trials evaluating the efficacy of resin infiltration for noncavitated proximal carious lesions by comparing it with control/placebo. Each included study was assessed concerning the “risk of bias” using the Cochrane Collaboration’s “risk-of-bias” assessment tool. High risk-of-bias studies were excluded from the meta-analyses due to selective reporting matters. The statistics were performed by RevMan software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) utilizing the random effect model. The GRADE approach was implemented for assessing the quality of evidence.

Results: From 106 studies identified, 17 were assessed for eligibility. After “risk-of-bias” assessment, two meta-analyses were conducted to eliminate the limitation of the significant heterogeneity between trials inspecting primary teeth (n = 2) and permanent teeth (n = 3). $I^2 = 0\%$ indicates the absence of statistical heterogeneity. The risk of carious lesions’ progression with resin infiltration was significantly lower in primary (risk ratio [RR]; 95% confidence interval [CI]: 0.48; 0.30–0.75, $P = 0.001$) and in permanent teeth (RR; 95% CI: 0.19; 0.11–0.33, $P < 0.00001$) compared to that of control/placebo. The GRADE approach revealed high quality of evidence.

Conclusion: The available evidence conveys high confidence that proximal resin infiltration has superior efficacy in slowing/arresting the carious lesions’ progression rate in comparison to conventional management modalities.

Keywords: Efficacy, permanent teeth, primary teeth, proximal carious lesions, resin infiltration
and cutting instruments in the conventional invasive treatment of proximal lesions sacrifice substantial amounts of sound tooth structure. This violates the concept of minimally invasive dentistry (MID)\(^4\) which involves excavating the least possible amount of dental tissues.\(^5\) Consequently, resin infiltration was invented.\(^6\) This method is considered a micro-invasive treatment, a subcategory of MID.

Micro-invasive treatment entails conditioning noncavitated proximal lesions (NCPLs) by organic acids that result in the loss of few micrometers of the tooth substance.\(^3\) Resin infiltration, in particular, implies etching NCPL/s that has/have a radiographic depth of E2 (caries reaching the inner half of enamel) or D1 (caries ending in the outer third of dentin) by 15% hydrochloric acid gel for 120 s and soaking the lesion with a low-viscosity resin.\(^8\) This technique slows/stops the NCPLs’ progression rate by creating a diffusion barrier inside the porous enamel lesion body rather than on top of it like other sealants, i.e., bonding adhesives.\(^3\)

Furthermore, esthetics can be enhanced by this technique as it is used for masking white-spot lesions (WSLs). The pores of WSLs are usually filled with saliva that has a refractive index (RI) of 1.33. On the other hand, the RI of enamel is 1.62. This difference in light scattering between WSLs and the surrounding enamel is masked when those pores are infiltrated with resin (RI = 1.46), which has similar optical properties to enamel.\(^9\)\(^,\)\(^10\)

In spite of the growing clinical use of resin infiltrates, its efficacy on noncavitated proximal caries in primary and permanent teeth is not fully reported. The present review was undertaken to answer the question – Is resin infiltration of NCPLs an efficacious method for carious lesions’ control in primary and permanent teeth? We assumed that proximal resin infiltration might yield positive outcomes. Hence, the aim of this study was to evaluate the efficacy of resin infiltration on NCPL/s in primary and permanent teeth.

### Materials and Methods

The review proposal was submitted to the research center of Riyadh Elm University, and the Institutional Review Board approval was obtained (RC/IRB/2018/896).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to ensure transparent reporting.\(^11\) Accordingly, the records were collected electronically and manually. Seven electronic sources were searched by the Medical Subject Headings terms and the most reported keywords. The search was conducted following the search syntax of every electronic source. The search strategy is presented in Table 1. No filters were applied during the search except for language; studies were limited to English only. Afterward, the manual search was conducted by examining the reference lists of related studies in an attempt to find relevant data that were not identified by the electronic search. The PRISMA flow diagram enhanced the records handling process. Duplicated records were automatically excluded using EndNote X8 software (Clarivate Analytics, Philadelphia, Pennsylvania, USA).\(^12\) We modified the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) criteria reported by Ammari and others\(^13\) and referred to them in the eligibility assessment of the full-text records.

The PICOS inclusion criteria were as follows:

- **Population (P):** Humans with NCPL/s
- **Intervention (I):** Resin infiltration of proximal carious lesions
- **Comparison (C):** Resin infiltration compared to placebo or different material/technique (control groups)
- **Outcome (O):** NCPLs’ progression rate assessed by bitewing radiographs
- **Study design (S):** Randomized controlled trials (RCTs) with a minimum of a 12-month follow-up.

If one or more of these criteria was missing, the study was excluded.

The risk of bias of the included studies was assessed using the Cochrane Collaboration “risk-of-bias” assessment tool.\(^14\) This tool has seven domains, which are the random sequence generation, where each included study was assessed by evaluating the method of randomization that allocates the groups of intervention and control. The allocation concealment was inspected to assure the random allocation. After

| Table 1: Literature search strategies |
|--------------------------------------|
| **Electronic source** | **Search strategy** |
| EBSCOhost | Most reported terms: |
| PubMed | a. Resin infiltration OR caries infiltration AND proximal lesions OR proximal caries |
| Wiley Library | b. Sealing AND resin infiltration OR caries infiltration AND proximal lesions OR proximal caries |
| Cochrane Library | MeSH terms: (((“Cariostatic agents/therapeutic use” [MAJR] OR “Dental caries/prevention and control” [MAJR]) AND “Disease Progression” [MeSH terms]) AND “Humans” [MeSH terms]) AND “Resins, synthetic/therapeutic use” [MAJR] |
| Google Scholar | |
| OpenGrey | |
| OpenThesis | |
| PubMed | |

MeSH=Medical Subject Headings
that, blinding of operators, participants, and outcome examiner/s to the allocation was assessed. We graded studies as having a low risk in the “incomplete outcome data” domain when they had ≤25% dropout rate, and the reasons for participant dropout were clarified. To evaluate “reporting bias,” the selective reporting domain was examined; in which failure to mention, the prespecified outcomes was considered a high-bias risk. Moreover, each trial was evaluated as a whole to ensure the absence of other sources of bias. Any study with a high risk of bias in one or more domains was excluded from the meta-analysis.

Heterogeneity assessment was performed by analyzing “clinical,” “statistical,” and “methodological” heterogeneity. For clinical heterogeneity, studies were assessed in terms of diversity between them by identifying the following in each study: participants’ age, setting (primary care or secondary care), teeth types (primary or permanent teeth), moisture control (rubber dam isolation or cotton roll isolation), the operative procedure, and the variation of the comparator between studies (fluoridated toothpaste, dental floss, fluoride varnish, and no treatment). Furthermore, F and Chi-square tests were used to measure the statistical heterogeneity. Methodological heterogeneity was examined by assessing the difference in bias risk between the included studies in each meta-analysis.

The statistics were performed by RevMan software (Review Manager, version 5.3; the Cochrane Collaboration, Copenhagen, Denmark). Subsequently, the attained evidence was appraised by implementing the GRADE approach.

RESULTS

SEARCH RESULTS

The flow diagram of the study selection is shown in Figure 1. At first, 106 records were identified. After removing duplicates automatically by Endnote X8 software (Clarivate Analytics, Philadelphia, Pennsylvania, USA), forty-six records remained for screening. This phase comprised inspecting the titles and abstracts for relevance to our PICOS inclusion criteria. Accordingly, 29 records were excluded; 28 of them were not RCTs, and one record was excluded because it was not written in English. Afterward, the full texts of the 17 remaining records were also assessed for eligibility in reference to our PICOS criteria. Seven trials met the criteria and were included in the qualitative synthesis (systematic review). The characteristics of the included studies are present in Table 2, and the reasons for exclusion of the other ten papers are justified in Figure 1. Aside from the PICOS criteria, two studies were excluded at this step since they were published as abstracts only; the missing data hindered further appraisal.

RISK-OF-BIAS ASSESSMENT

Following the criteria listed in the Cochrane Collaboration’s risk-of-bias assessment tool, each of the seven included trials was examined for “risk of bias” concerning seven domains [Figure 2].

Random sequence generation

All the trials had a split-mouth design. Consequently, every participant in each study received both intervention (resin infiltration) and control/placebo. The distribution method of intervention and its comparator on NCPLs within each participant ensured randomization. Therefore, we judged all the trials to be at low risk of bias for this domain.

Allocation concealment

Four out of the seven papers were at low risk of bias. They reported adequate concealment measures for random allocation of intervention and control/placebo to NCPLs. Such measures were placing the random sequence inside sealed envelopes and letter coding of each NCPL management strategy whereas the remaining three studies did not report any means of allocation concealment and therefore were judged to have an unclear risk of bias. However, they were not excluded because this was not likely to affect the outcomes.

Blinding of participants and personnel

Considering the significant difference between the procedures of resin infiltration and control/placebo, blinding of operators was not applicable. Moreover, unblinding of participants was not likely to affect the outcome since we depended only on bitewing radiographs for outcome assessment and not on the participants’ subjective statements. As a consequence, and following the Cochrane Collaboration’s criteria, all the included RCTs were appraised as having a low risk of bias.

Blinding of outcome assessment

We judged all the seven trials as having a low risk of bias concerning this domain, as reasonable blinding of outcome investigator/s to intervention and comparator allocation was described. This was implemented either by directly blinding outcome investigator/s to the allocation or by involving an outer radiography specialist to assess the pairwise radiographs. As reported, this specialist was blinded to the study design.

Incomplete outcome data

The dropout rate of participants in the seven studies was ≤25%. The reasons for dropout were sufficiently clarified in all the trials. Besides, the split-mouth design of the seven RCTs reduced the chance of missing a comparator to the intervention or vice versa. As a result,
this domain was judged to be at low risk of bias in all the seven studies.

Selective reporting
Five studies reported all the prespecified outcomes and therefore were judged to have a low risk of bias.\cite{17,19,22,23} In contrast, two trials were at high risk of bias since they failed to mention all their prespecified outcomes. Ekstrand \textit{et al.}\cite{20} did not report the results of their 6-month clinical assessment, and the radiographic evaluation was incomplete. Meanwhile, Martignon \textit{et al.}\cite{21} aimed at assessing the NCPLs’ progression rate annually for 3 years. However, they only reported the results of the 1st-year follow-up. Consequently, those two were excluded from the meta-analysis.

Other bias
There was no indication for other sources of bias in all the included studies, so they were judged to be at low risk for this domain.

HETEROGENEITY ASSESSMENT
Two of the remaining five studies had an unclear risk of bias when the allocation concealment domain was assessed. Therefore, “methodological heterogeneity” with respect to the risk of bias existed between the five studies. In addition, the diversity of teeth types reflected “clinical heterogeneity;” two trials assessed the efficacy of resin infiltration on NCPLs in primary teeth, and the other three evaluated that in permanent teeth. As a matter of fact, primary teeth have lower mineral
Efficacy of resin infiltrate in early carious lesions

Outcome assessment

Comparison

6 months
Population (followed = 3).
Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Scoring caries progression in bitewing radiographs

Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Pairwise radiographic comparison of baseline and follow-up bitewing radiographs

Authors and year of publication | Study design | Population (followed period) | Intervention | Comparison | Outcome assessment method |
--- | --- | --- | --- | --- | --- |
Ammari et al., 2017 | Split-mouth controlled randomized clinical trial | 42 children (42 lesion pairs) | 6 and 12 months | Resin infiltration of NCPLs in primary molars Infiltrant: Icon®, (DMG, Hamburg, Germany) | Test group (fluoridated toothpaste + flossing + infiltration) Control group (fluoridated toothpaste + flossing) | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |
Arthur et al., 2017 | Double-blind split-mouth placebo-controlled randomized clinical trial | 17 participants (27 lesion pairs) | 36 months | Resin infiltration of NCPLs Infiltrant: Icon® (DMG, Hamburg, Germany) | Test lesion: resin infiltration followed by FV Control lesion: Only FV | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |
Ekstrand, Bakhshandeh and Martignon 2010 | Split-mouth controlled randomized clinical trial | 39 children | 6 months and 12 months | Resin infiltration of NCPLs Infiltrant resin: Triethylene glycol dimethacrylate-based resin, camphorquinone, additives; DMG, Hamburg, Germany | Test group (infiltration: DMG Icon preproduct and FV) Control group (FV) | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |
Foster Page et al., 2017 | Split-mouth placebo-controlled randomized controlled trial | 69 children | 6, 12, and 24 months | Resin infiltration of NCPLs Infiltrant: DMG Icon preproduct | Test group (infiltration: DMG Icon preproduct and FV) Control group (FV) | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |
Martignon et al., 2012 | Split-mouth controlled randomized clinical trial | 37 participants (each had at least 3 NCPLs) | 36 months (annual follow-up) | Resin infiltration of NCPLs Infiltrant: ICON® preproduct (DMG, Hamburg, Germany) | Test-A (Infiltration: ICON-preproduct; DMG) Test-B (Sealing: Prime-Bond NT; Dentsply) Control-C (Placebo) | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |
Meyer-Lueckel, Bitter and Paris 2012 | Split-mouth placebo-controlled randomized clinical trial | 19 young adults (25 lesion pairs) | 18 and 36 months | Resin infiltration of NCPLs Infiltrant: Icon, preproduct; DMG, Hamburg | Placebo treatment | Pairwise radiographic comparison and DSR of baseline and follow-up bitewing radiographs |
Meyer-Lueckel et al., 2016 | Split-mouth placebo-controlled randomized clinical trial | 79 participants (218 lesion pairs) | 10 and 18 months | Resin infiltration of NCPLs Infiltrant: Icon; DMG, Hamburg, Germany | Placebo treatment | Pairwise radiographic comparison of baseline and follow-up bitewing radiographs |

NCPLs=Noncavitated proximal lesion/s, FV=Fluoride varnish, DSR=Digital subtraction radiography, DMG=Dental milestones guaranteed company

content[24] relative to permanent teeth.[25] Accordingly, two meta-analyses were conducted separating the included RCTs based on teeth types in order to preserve the coherence of evidence. Another demonstration of clinical heterogeneity is the dissimilarity of comparators among studies. The studies included in the meta-analyses compared the resin infiltration to each of the following:

1. Fluoridated toothpaste and dental floss (n = 1)
2. Fluoride varnish (n = 1)
3. No treatment (n = 3).

### Statistical analysis

We conducted both meta-analyses using the random effect model due to the presence of “methodological heterogeneity” in terms of bias risk. Each meta-analysis had one study with an unclear risk of bias concerning allocation concealment. Meanwhile, the remainder of the
included trials had a low-bias risk. In the meta-analysis of permanent teeth [Figures 3], the follow-up of studies ranged from 18 to 36 months. Similarly, the primary tooth meta-analysis [Figure 4] had a follow-up range of 12–24 months. In both meta-analyses, the included trials measured the carious lesions’ progression by radiographic pairwise comparison. Moreover, one RCT utilized two outcome assessment methods: radiographic pairwise comparison and digital subtraction radiography (DSR).[17] Despite the higher accuracy of DSR over the pairwise comparison, the outcome obtained by the pairwise comparison was the one included in our meta-analysis, to maintain homogeneity between the included trials. Technically, in both forest plots, the effect measure was the risk ratio (RR), and the effect estimate of each NCPL management modality was assessed by inspecting the caries progression rate of each included trial. The weight of each study in each meta-analysis was gauged by the Mantel-Haenszel method because it has better statistical features when the events are few.[14] As a result, the risk of NCPLs’ progression with resin infiltration was significantly lower in primary (RR; 95% confidence interval [CI]: 0.48; 0.30–0.75, P = 0.001) and in permanent teeth (RR; 95% CI: 0.19; 0.11–0.33, P < 0.00001) compared to that of control/placebo. The I² = 0% in both forest plots indicates the absence of statistical heterogeneity.

**QUALITY OF EVIDENCE**

The GRADE approach[16] revealed high quality of evidence [Table 3].[26]

**DISCUSSION**

This evidence confirms the results of former *in vitro*[27] and *in situ* studies[28] which found that resin infiltration is
Summary of findings:

Elrashid, et al.: Efficacy of resin infiltrate in early carious lesions

Efficacious in arresting/slowing the NCPLs’ progression rate. More importantly, our meta-analyses revealed that proximal resin infiltration had superior efficacy over conventional management methods in preventing further NCPLs’ progression. Such methods were fluoridated toothpaste and dental floss, fluoride varnish, and no treatment. This could be attributed to the fact that such methods demand a high level of patient compliance. On the contrary, proximal resin infiltration does not require any effort from the patient. Furthermore, the resin infiltrant will continuously act as a barrier inside the NCPL. Meanwhile, conventional management modalities are intermittent in nature, which might allow more demineralization/remineralization cycles even in highly compliant patients. Based on that, the concept of hygienic measures as an adjunctive treatment for NCPLs seems more rational than the notion behind utilizing them as a particular management strategy. Furthermore, one of the excluded trials\(^\text{[20]}\) found that resin infiltration, in conjunction with fluoride varnish, was efficacious in controlling the proximal caries progression in primary molars. The other excluded study\(^\text{[21]}\) showed that infiltration and sealing were superior over placebo in limiting NCPLs’ progression for permanent teeth. However, there was no significant difference between infiltration and sealing.

Risk-of-bias assessment is crucial in evaluating the quality of evidence. In general, high risk-of-bias studies lower the quality of meta-analyses;\(^\text{[14]}\) thus, they were excluded to protect our quality of evidence. Accordingly, selective reporting of the outcomes increased the bias risk in two of the trials. As a consequence, they were excluded. Furthermore, unclear bias risk regarding allocation concealment was identified in another two RCTs. However, this was not likely to affect the outcomes of both trials; therefore, they were not excluded.

In adherence to the GRADE approach\(^\text{[16]}\) and for complete and consistent evaluation of the quality of evidence, in each study, additional aspects were appraised besides the risk of bias. Those aspects were as follows: (1) study design, (2) consistency, (3)
directness, and (4) precision. The quality of evidence was ranked as high in both meta-analyses, where all the aspects evaluated displayed high quality, since (1) the study design of all the trials included in both meta-analyses was a randomized controlled design. (2) Consistency is defined as the similarity of effect estimates between studies; both meta-analyses were consistent. Technically, (3) the outcome measures, interventions, and participants were similar between studies in each meta-analysis, and by definition, this indicated directness. In addition, precision domain lowers the quality if the number of events was few. Interestingly, (4) despite the few number of studies included in each meta-analysis, the quality of evidence was not affected when the number of events was appraised using the GRADE computer program.[26]

CONCLUSION

The available evidence conveys high confidence that proximal resin infiltration has superior efficacy in slowing/arresting the NCPLs’ progression rate in comparison to conventional management modalities. Further high-quality RCTs with long-term follow-up are recommended to increase this evidence and to allow the estimation of proximal resin infiltration longevity.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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