| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
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| **TITLE** | | |  |
| Title | 1 | Effectiveness of stepwise or selective in comparison to non-selective caries removal in managing deep caries in vital permanent teeth:  A systematic review with trial sequential, pairwise and network meta-analyses |  |
| **ABSTRACT** | | |  |
| Abstract | 2 | Introduction: The aim of this systematic review was to assess the available evidence related to the effectiveness of stepwise (SW) or selective excavation (SE) when compared to non-selective caries excavation (NSE) for the management of permanent teeth with deep carious lesions without signs of irreversible pulpitis.  Methods: This systematic review was conducted according to Cochrane guidelines. Literature search was performed using several databases including English language only. Pairwise and network meta-analysis (NMA) was conducted. 19 out of 819 studies were included. The outcomes assessed were dental pulp exposure and the measure ‘success’ defined as tooth not having complications after a follow-up (i.e., without dental pulp exposure following treatment, no dental pulp complications after treatment, no periapical lesion, no severe/unbearable pain, no restoration failure or tooth extraction).  Findings: The Risk of Bias analysis revealed that more than 50% of the studies had high risk of bias. In addition, the GRADE assessment for the outcomes showed that most of the evidence was low and very low quality. Based on the results of the NMA, SW had the highest success rate (RR: 1.11, 95% CI: 1.00–1.23, with NSE as the reference), followed by SE (RR: 1.06, 95% CI: 0.97–1.16, with NSE as the reference). However, the difference was not statistically significant. In most cases, SE was the treatment of choice in relation to carious lesion depths with the threshold of >2/3 of the dentine thickness and SW was advocated only in cooperative patients due to the two-step procedures.  Interpretation: Within the limitations of this review, the effect of remaining carious dentine could not be assessed with respect to the success rate for each intervention. Therefore, long-term well organized multi-centre randomized controlled trials (RCTs) are still required to provide concrete evidence.  Funding: This study was not supported by any sponsor or funder |  |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Deep lesions are more likely to harbour few viable micro-organisms, whereas extremely deep lesions often involve microbial contact with the dental pulp, inflammation, partial necrosis, and sometimes hyperplastic pulp.  Vital pulp therapy incorporating either SW or SE has become widely suggested procedure performed in permanent teeth with deep carious lesions without any signs or symptoms of irreversible pulpal changes. Both SE and SW were reported to reduce the risk of dental pulp exposure and post-operative complications (i.e., pain and discomfort) significantly in comparison to complete excavation. However, there is lack of clear standard operating procedures and long-term evidence with respect to the concept of leaving carious dentine in well-defined deep stages of carious lesions. |  |
| Objectives | 4 | The aim of this systematic review was to assess the available evidence related to the effectiveness of stepwise (SW) or selective excavation (SE) when compared to non-selective caries excavation (NSE) for the management of permanent teeth with deep carious lesions without signs of irreversible pulpitis. |  |
| **METHODS** | | |  |
| Eligibility criteria | 5 | The inclusion criteria included:  • Clinical studies, including randomised and non-randomised controlled trials (prospective or retrospective), cohort studies, and case-control studies  • Studies involving patients with deep caries without signs of irreversible pulpitis, who were candidates for deep caries excavation (with some flexibility in the definition of 'deep' in the selected studies)  • Treatment interventions included selective caries removal (SE), stepwise caries removal (SW), or non-selective (complete) caries removal (NSE) procedures  • Studies using older terminology for caries removal methods, such as indirect pulp capping, as long as the methods align with SE, SW, or NSE. When the term ‘indirect pulp capping’ term has been used (e.g. as in the study by Orhan et al., according to the classical definition which was invasive in comparison to the SW/SE technique. However, the scrutiny of the methodology revealed that one-step indirect pulp capping can be interpreted as close to SE, whereas the two-step indirect pulp capping could be compared to the SW technique. In contrast, Manhas et al. (20) recently reported that indirect pulp capping was performed according to the original definition as being invasive and close to the NSE.  • In the study by Orhan et al. both permanent and primary teeth were treated, in this analysis only permanent teeth were included.  • Studies where the outcome was assessing any positive effect such as the absence of pulpal complications (+/- dental pulp exposure. +/- dental pulp sensibility, +/- apical pathosis), patient-related outcomes or the arrestment of caries progression.  The exclusion criteria were:  • Laboratory-based/in vitro studies  • Case reports  • Studies that focus on primary teeth  • Studies with a follow-up period shorter than one year for assessing survival or success rates. |  |
| Information sources | 6 | Literature search was performed using Cochrane Review, PubMed (Medline), Ovid, Web of Science, Embase, Scopus, Open Gray in English language up to July 2023. Three reviewers critically assessed the studies for eligibility according to inclusion and exclusion criteria. Any disputes between the reviewers were handled by the fourth independent reviewer. Searches in the ClinicalTrials.gov database and in the references of the included studies (cross-referencing), were also conducted. Search on Gray literature was performed using Google, Greylit, and OpenGrey. Medical Subject Headings (Mesh) terms, keywords, and other free terms related to PICO question were employed with Boolean operators (OR, AND) to combine searches. The same keywords were used for all search platforms followed the syntax rules of each database and the search terms were modified for each database. |  |
| Search strategy | 7 | |  |  | | --- | --- | | Focused Question | *Is there a difference in the efficacy of either SW, SE, and NSE in permanent teeth?*’ | | Population (#1)  General population with evidence of deep caries associated with no or non-spontaneous pain or signs of reversible pulpitis in immature and mature permanent teeth.  Inclusion. Randomised Controlled Trials [RCTs], Comparative Clinical trials [CCTs, non-randomised and longitudinal observational studies.  Exclusion Criteria. Case reports/Case series, Expert opinions, Studies on primary teeth, Laboratory-based studies | (((tooth) OR (teeth)) OR (''human tooth'')) OR (''human teeth'')) OR (permanent tooth) OR (“mature tooth”) OR (‘immature permanent tooth”) OR (''mature teeth”) OR (‘immature permanent teeth”) OR (“deep caries'')) OR (“asymptomatic caries”')) OR (“extensive caries”) OR (''reversible pulpitis'')) OR (''pulpitis'')) OR (caries)) OR (''dentine caries'')) OR (''dentin caries'')) OR (''dentine caries\*'')) OR (''deep dental caries\*'')) OR (''dental caries lesion\*'')) OR (''dental carious lesion\*'')) OR (''carious lesion\*'')) OR (deep decay\*))) | | Intervention (#2)  Patients with deep caries lesions and no or non-spontaneous pain or signs of reversible pulpitis in immature and mature permanent teeth step-wise or selective caries removal. | Intervention ((''step-wise'') OR (selective caries removal)) OR (caries removal”) OR (“selective removal”) OR (“step-wise removal”)) OR (''selective caries treatment'')) OR (''step-wise treatment'')) OR (“selective caries excavation”) OR (“incomplete caries removal”) OR (“minimally invasive caries removal”) OR (“minimally invasive treatment”) OR (“minimally invasive caries treatment”) OR (“caries excavation”) AND ((treatment\*) OR (restorative treatment\*) OR (selective treatment\*) OR (pulp treatment\*) OR (“Atraumatic”) OR (“Atraumatic treatment”) OR (‘Atraumatic Restorative Treatment”)) | | Comparisons (#3)  Patients receiving non-selective caries removal in immature or mature permanent teeth. | ((nonselective caries removal)) OR (nonselective removal) OR ("nonselective caries treatment") OR ("nonselective treatment") OR ('complete caries removal') | | Outcomes (#4)  Risk of Failure: requiring endodontic treatment (direct capping (one + two surfaces), partial or total pulpotomy, pulpectomy) or restorative retreatment (restoration broken or lost) or extraction.  Additional outcome(s):   * Patient reported outcomes: pain, tenderness, swelling, need for medication, OHRQoL * Tooth function (restoration longevity) | (reversal of caries\*) OR (reversal of carious lesion\*)) OR (“reversal of dental caries”)) OR (''caries arrest'')) OR (''mineral uptake'')) OR (''ion uptake'')) OR (''mineral gain'')) OR (''ion release'')) OR (''mineral release'')) OR (arrestment)) OR (“tooth survival”) OR (“loss of vitality”) OR (“restoration failure”) OR (“restorative failure”) OR (pulp exposure) OR (abscess) OR (sinus) | | Search combination | #1 AND #2 AND #3 AND #4 | | Language | English language | | Databases and web search engines | Cochrane Review, PubMed (Medline) and Ovid, Open Gray | |  |
| Selection process | 8 | Three independent reviewers (SR, HC, and AB) conducted an initial screening of titles and abstracts from the search results by assessing them against the inclusion and exclusion criteria to identify potential primary studies. Based on a consensus of the authors, the studies that failed to meet the eligibility criteria were excluded, and the full texts of the selected studies were retrieved for further evaluation. |  |
| Data collection process | 9 | During the data extraction stage, the same reviewers independently assessed the full texts of studies deemed relevant in the initial screening. Duplication of data extraction was carried out using a pre-established and piloted spreadsheet. If any data were incomplete or missing, the study authors were contacted for clarification, allowing a two-week response period. Disagreements among the reviewers were resolved through discussion with a fourth reviewer (LB). For studies with more than two groups or multiple studies reporting the same data, the relevant data were only extracted. The following details were collated in the excel spreadsheet for each included study in the final review. |  |
| Data items | 10a | Success was defined as not having any complications (including dental pulp exposure during treatment, dental pulp complications after treatment, periapical lesion, severe/unbearable pain during follow-up visits, restoration failure and tooth extraction) |  |
| 10b | Name of the first author (if two authors, both were named), publication year, type of study design, total number of participants, gender, trial design, intervention vs. control, depth of dental caries in selected teeth, depth of caries in cases included (definition of deep caries), amount of remaining caries after caries excavation, follow-up length, and outcome measures. |  |
| Study risk of bias assessment | 11 | Cochrane risk of bias tool was used for quality assessment of RCT, whilst ROBINS-I tool was used for non-randomized studies. This tool consists of seven domains to evaluate risk of bias: bias due to confounding, selection bias, classification bias, bias due to deviation from intended intervention, bias due to missing data, bias due to measurement of outcome, and bias in the selection of reported result. Each domain was assessed to have low, moderate, serious, critical risk of bias or no information where a judgement cannot be based on information available i.e., unclear. Each study was assessed and graded for quality of evidence by both reviewers (SR, HC) independently. Critical appraisal of the included studies was performed using the modified version of Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. |  |
| Effect measures | 12 | When the included studies were homogeneous in nature, a quantitative meta-analysis was considered. Random models were reported to calculate the weights, odds ratio (OR) for rare events (events occurring less than 10-20% in dataset) and risk ratio (RR) for common events with 95% confidence interval (CI). The effect measure used was the relative risk (RR). |  |
| Synthesis methods | 13a | Data were analysed quantitatively, and when quantitative assessment was not possible, the results were reported qualitatively. When the included studies were homogeneous in nature, a quantitative meta-analysis was considered. |  |
| 13b | Data were analysed quantitatively, and when quantitative assessment was not possible, the results were reported qualitatively. When the included studies were homogeneous in nature, a quantitative meta-analysis was considered. |  |
| 13c | When the included studies were homogeneous in nature, a quantitative meta-analysis was considered. Random models were reported to calculate the weights, odds ratio (OR) for rare events (events occurring less than 10-20% in dataset) and risk ratio (RR) for common events with 95% confidence interval (CI). |  |
| 13d | In the pairwise meta-analysis, studies were included if there were three or more papers available in the relevant field. For the meta-analysis of subgroups, the Mantel-Haenszel (M-H) method was used. In addition, subgroup analyses were performed based on the length of follow-up, depth of caries in the included teeth, and type of study, whenever possible. The forest plot and funnel plots were calculated based on them. |  |
| 13e | Heterogeneity was assessed quantitatively by I² Statistic, Tau² (τ²) Statistic, and Chi-Squared (Q) test. |  |
| 13f | Trial Sequential Analysis (TSA) was applied to the success outcome and SW pulp exposure to assess the conclusiveness of the meta-analysis. The TSA program (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Denmark) was used to adjust for heterogeneity among the included trials and to calculate the required information size (RIS). The RIS in a meta-analysis is defined as the number of events or patients from the included studies necessary to accept or reject the statistical hypothesis. Relative Risk Reduction (RRR) is a key parameter for TSA analysis as this estimates the intervention effect and calculates the required sample size. The formula for RRR is typically based on observed data from the previous studies, however one can also include clinical expectations and calculate the TSA with different RRR values |  |
| Reporting bias assessment | 14 | Publication bias was assessed using the funnel plots. |  |
| Certainty assessment | 15 | The evidence for each outcome effect estimate was graded according to the GRADE working group criteria. |  |
| **RESULTS** | | |  |
| Study selection | 16a | The initial electronic database search generated 819 results from six sources: Web of Science (n=54), Embase (n=25), Ovid (n=20), PubMed (n=49), Cochrane library (n=35), Scopus (n=636). All studies were then imported into Covidence software for screening (https://www.covidence.org/). After removing 366 duplicates (358 identified by Covidence and eight manually), 453 studies were screened according to the title and abstract. Subsequently, a total of 107 studies were reviewed with full texts. These studies were further assessed for eligibility and 88 studies were excluded due to incorrect study design, wrong intervention, wrong comparator, wrong patient population, non-English language, and ongoing studies with no available results. |  |
| 16b | seven studies detected through previous reviews and five detected through citation search, however these were duplicates and excluded. Subsequently, a total of 19 studies were included in the systematic review for data extraction. The screening process was conducted and recorded in accordance with the PRISMA statement. The flow chart is available in the manuscript. |  |
| Study characteristics | 17 | Seven studies compared the SE to NSE technique. Four studies compared the SW to NSE technique, whilst one compared the SW with NSE (originally addressed as indirect pulp capping). Six studies compared the SW with SE. Only one of these studies assessed three treatments (SE, SW, NSE) together. Two out of 19 were non-randomized studies. The characteristics of included studies are presented in Table 2. |  |
| Risk of bias in studies | 18 | Out of the 17 RCT studies listed, nine studies (52.9%) were categorized as having an overall high risk of bias. Six studies (35.3%) presented with overall moderate risk of bias, indicating some concerns in one or more domains. Two studies (11.8%) were categorized as having an overall low risk of bias. When examining the specific domains, domain 2 (bias due to deviations from intended intervention) showed the highest number of studies with high risk. There were seven studies rated as high risk in this domain. Conversely, domain 4 (bias in measurement of the outcome) had 16 studies rated as low risk. The two non-randomized studies were categorized as having an overall moderate risk of bias (Tables 3 and 4). Details of each domain of Cochrane’s Tool are reported in the supplementary materials (Table S1). |  |
| Results of individual studies | 19 | Success of the treatment  The forest plot of success rate when SE was compared to the SW technique showed that there was non-significant difference in the success rates in both groups (RR = 1.00, 95% CI: 0.92, 1.09, p>0.05 Figure 2a). There was no heterogeneity reported, and all studies included were RCTs. SW treatments were successful in comparison to the NSE (RR: 1.23, 95% CI: 0.99-1.52). However, the heterogeneity was significantly high (p<0.01) (Fig. 4a). The SE compared to NSE technique in seven studies (Figure 5a-c). A non-significant increase in success rates was noted (RR = 1.10 [0.98; 1.23]) indicating variability in the study results as the CI included 1. The moderate level of heterogeneity (I² = 60%) suggested that the results of these studies were inconsistent (Figure 5a).  Exposure of dental pulp  The included studies reported that dental pulp exposure was significantly high in the NSE in comparison to the SW technique (exposures happening in both sessions) (RR:0.52, 95% CI: 0.30-0.91, I² = 0, Figure 6). Similarly, all included studies suggested that pulp exposure is significantly high in NSE in comparison to SE (RR:0.11, 95% CI; 0.05-0.31, I² = 0, Figure 6).  Root canal therapy  The pooled estimates reported low numbers of dental complications after treatment (referred as need for root canal therapy after treatment) in the SE in comparison to the NSE technique, however the difference was insignificant (OR: 0.89, 95% CI: 0.16-4.86, I² = 44%) with moderate heterogeneity (p>0.01, Figure 7). The pooled estimates reported slightly high rate of complications in SW when compared to the NSE technique however the difference was insignificant (OR: 1.18, 95% CI: 0.15-9.50, I² = 54%) with moderate heterogeneity (p>0.01) (Figure 7).  Apical radiolucency and radiographic related complications (Qualitative analysis)  Two studies specifically mentioned clinical and radiographic failure in terms of apical radiolucency when compared to SW to NSE. The cases in the SE group experienced failure in comparison to the NSE technique (OR: 5.48, 95 % CI: 0.62- 48.24, p>0.05). The carious lesion penetration was more than half of the dentine prior to the treatment. This trend was also observed in lesions penetrating 2/3 or more of the dentine in another study. As a separate note, a slightly high failure was observed with the SE when compared to the NSE technique, OR:2.11, 95 % CI:0.17 to 25.55, p>0.05), however none of these findings were statistically significant. Comparing the rate of periapical radiolucency in the SW and NSE groups, Bjørndal et al. showed an insignificant difference in a one-year study (OR: 1.04 95% CI: 0.25; 4.25, p>0.05). At five year follow-up, the apical radiolucency occurred more often in the NSE in comparison to the SW technique, however the two groups were statistically insignificant (OR:1.60, 95% CI: 0.50-5.04, p>0.05). In addition, Maltz et al. reported only one case of apical radiolucency (as confirmed by radiograph) in the SW group (OR:3.35, 95% CI: 0.13-83.37, p>0.05) in comparison to the SE technique.  Postoperative pain (Qualitative analysis)  The amount of unbearable pain was measured in the second year follow-up of study by Duman et al. and the rate was identical for both groups (3/19 cases in SE and NSE groups). In this respect, Rando-Meirelles et al. reported that only one patient felt pain during the pulp sensibility test after a period of one year. However, there was no case of unbearable pain in the SE and NSE groups.  Bjørndal et al. compared the rate of unbearable pain in SW and NSE groups for a period of one and five years. The cases with unbearable pain were slightly more likely in the SW when compared to NSE groups, however this was statistically insignificant (OR:1.20, 95% CI: 0.42- 3.40) and (OR 1.02, 95% CI: 0.34-3.02) respectively.  Restoration failure and tooth extraction (Qualitative analysis)  Restoration failure between SE and NSE groups was explored in the study by Casagrande et al. In the 36 month follow up, 15.4% of cases presented with restorative failures when compared to the NSE (2.0 %), however the difference was statistically insignificant (p>0.05). The authors also reported that teeth restored with resin modified glass ionomer cement restorations had more failure than those restored with the resin composite restorations (p<0.001). In addition, the use of a base/liner material under the restorations lowered the survival rate (p>0.05).  Interestingly, after a mean observation time of 62 months, three cases required extraction in the SW group only when compared to the NSE groups. One case presented with tooth fracture, whilst two presented with unknown reasons. Regarding the restoration material, the success rate of dental amalgam was similar to resin composite restorations (86.6% and 83%, respectively), and these restorations deemed to be successful and comparable (p>0.05).  When SW was compared to the SE technique, Jardim et al. reported that the restoration survival following of the use SW and SE techniques in a five year period. The rate of restoration failure in the SE was slightly high in comparison to the SW, however this was statistically insignificant (OR 1.21, 95% CI: 0.56-2.61, p > 0.05). It should be noted that 96% of the restoration failures were due to the restoration fracture and 4% due to secondary caries.  Labib et al. reported only one case of tooth extraction in the SE group due to unbearable pain. In addition, Maltz et al. reported two cases of tooth fracture and extraction in the SW and none in the SE group after three years.  Remineralisation (Qualitative analysis)  Pratiwi et al. assessed the amount of remineralisation in the SE and NSE groups for a period of four weeks after the MTA application. The authors reported that remineralisation was evident in the affected dentine either by removing only some parts or all the infected dentine in the deep carious lesions. However, there were no differences in both groups with respect to remineralisation by measuring the pixel gray value with the Digora™ Optime system (Soredex Corp., Tuusula, Finland) and calculating using the computer software system (p>0.05). |  |
| Results of syntheses | 20a | Out of the 17 RCT studies listed, nine studies (52.9%) were categorized as having an overall high risk of bias. Six studies (35.3%) presented with overall moderate risk of bias, indicating some concerns in one or more domains. Two studies (11.8%) were categorized as having an overall low risk of bias. When examining the specific domains, domain 2 (bias due to deviations from intended intervention) showed the highest number of studies with high risk. There were seven studies rated as high risk in this domain. Conversely, domain 4 (bias in measurement of the outcome) had 16 studies rated as low risk. The two non-randomized studies were categorized as having an overall moderate risk of bias (Tables 3 and 4). Details of each domain of Cochrane’s Tool are reported in the supplementary materials (Table S1). |  |
| 20b | The forest plot of success rate when SE was compared to the SW technique showed that there was non-significant difference in the success rates in both groups (RR = 1.00, 95% CI: 0.92, 1.09, p>0.05 Figure 2a). SW treatments were successful in comparison to the NSE (RR: 1.23, 95% CI: 0.99-1.52). However, the heterogeneity was significantly high (p<0.01) (Fig. 4a). The SE compared to NSE technique in seven studies (Figure 5a-c). A non-significant increase in success rates was noted (RR = 1.10 [0.98; 1.23]) indicating variability in the study results as the CI included 1. The moderate level of heterogeneity (I² = 60%) suggested that the results of these studies were inconsistent (Figure 5a).  The included studies reported that dental pulp exposure was significantly high in the NSE in comparison to the SW technique (exposures happening in both sessions) (RR:0.52, 95% CI: 0.30-0.91, I² = 0, Figure 6). Similarly, all included studies suggested that pulp exposure is significantly high in NSE in comparison to SE (RR:0.11, 95% CI; 0.05-0.31, I² = 0, Figure 6).  The pooled estimates reported low numbers of dental complications after treatment (referred as need for root canal therapy after treatment) in the SE in comparison to the NSE technique, however the difference was insignificant (OR: 0.89, 95% CI: 0.16-4.86, I² = 44%) with moderate heterogeneity (p>0.01, Figure 7). The pooled estimates reported slightly high rate of complications in SW when compared to the NSE technique however the difference was insignificant (OR: 1.18, 95% CI: 0.15-9.50, I² = 54%) with moderate heterogeneity (p>0.01) (Figure 7). |  |
| 20c | Subgroup analysis by follow-up period suggested that SW has higher success rates in the short term (RR:1.36, 95% CI:1.15-1.60, I² = 0), however long-term evidence was unclear, with significant variability between study results (I² = 84%, Figure 4b). The subgroup analysis based on caries depth was not possible as all studies had similar caries depth for the selected teeth. When sub-grouped by the type of studies, SW was significantly more successful than NSE when the teeth were selected randomly amongst the RCTs (RR:1.34, 95% CI:1.22-1.48, I² = 0) (Figure 4c). When studies sub-grouped by follow-up period, a high success rate for SE in comparison to the NSE technique was observed for one year follow-up with the random effects model being marginally significant (RR:1.15, 95% CI: 1-1.32), without heterogeneity. In the two-year follow-up, no significant difference between success of SE and NSE was observed (RR:1.16, 95% CI:0.57-2.39). There was no heterogeneity, however the wide confidence interval in random model is showing large uncertainty. In this respect, the short-term success rate of SE was high in comparison to the NSE (marginally significant), however with respect to long-term success, there was not enough data to draw a conclusion (Figure 5b). Meta-analysis subgrouped by caries depth showed that there is no significant overall difference in the success rates of SE compared to NSE techniques in treating dental caries, regardless of caries depth with the deepest being > 2/3 of dentine thickness (Figure 5c). When subgrouped by study type (Fig. 5d), it was noted that in RCTs the difference was highly significant (1.16, 95% CI: 1.07-1.25, I² = 0). |  |
| 20d | An NMA of the success rates of the three treatments (SE, NSE, and SW) was conducted to synthesize the available evidence from the entire network of trials by integrating both direct and indirect estimates (Figure 9a). The success rate following the SW technique was high when compared to the NSE (RR: 1.11, 95% CI: 1.00–1.23, p < 0.05), though the confidence interval includes 1, indicating borderline significance (Figure 9b). In addition, the RR indicated that the success rate of the SE technique was high when compared to the NSE (RR: 1.06, 95% CI: 0.97–1.16, p<0.05), however the confidence interval also includes 1, suggesting insignificant difference (Figure 9b). |  |
| Reporting biases | 21 | It should be noted that Maltz et al. (37) reported the combined complications for cases that either completed or failed to complete the SW protocol. Consequently, the success rate was not unable to be calculated precisely for the cases that completed the protocol, as the data for cases that completed and failed to complete the protocol were reported together. Therefore, this was excluded from the NMA. Notably, the number of studies to assess the symmetry of the funnel plot was limited (Figure 3). |  |
| Certainty of evidence | 22 | The GRADE assessment for the outcomes related to dental pulp exposure, root canal therapy, success rate, apical radiolucency, postoperative pain, restorative failure, and tooth extraction showed that most of the evidence is low quality (Table 5). |  |
| **DISCUSSION** | | |  |
| Discussion | 23a | The current meta-analyses separated the treatment groups in order to reduce heterogeneity. In addition, the focus was on permanent teeth not a combined analysis of both dentitions.  The present NMA showed a high success rate for SW versus NSE with borderline significance, and a high success rate for SE versus NSE, although this comparison was statistically insignificant. In addition, the SW technique was only slightly better than SE in terms of success rates.  SE and SW techniques had high success rates in comparison to the NSE in short term follow-up visits and their benefits in long term (when compared to the NSE) was inconclusive. Subsequently, within the NMA, a subgroup analysis was performed based on the depth of dental caries in the selection of teeth for caries removal. Since the focus on well-defined extensive caries penetration depth as a prognostic variable in research is relatively new, there was insufficient data available. However, a trend could be noted within the non-randomised study by Oz et al. In their methodology, cases with less caries depth were allocated to the NSE group and cases with deep lesions reaching the pulp cavity on the radiograph (extremely deep caries) were in the SW group. Their rationale for choosing SW for the deepest lesions might have be flawed, as more recent microbiological evidence related to radiographic penetration depths indicates that the presence of microorganisms in such lesions carries a very high risk of already harboring pulp infection. In summary, extremely deep carious lesions should not be treated to avoid pulp exposure since the pulp is already infected. Similar histological observation was made decades ago however without a radiographical reference, this information is limited to be implemented in clinical practice. |  |
| 23b | The area of clinical practice lacks high-quality evidence. Therefore, the search strategy was extended to include other types of studies such as observational and not only RCTs. For meta-analysis, the advantages of including both observational studies and RCTs could outweigh the disadvantages by enhancing the evidence base, increasing precision, and providing real-world relevance, despite potential biases (confounding bias and placebo effect) and variability in study quality (50). In addition, some of the subgroup analyses included limited studies which may reduce the statistical power to detect differences between subgroups. Therefore, interpretation of the results of subgroup analyses with a small number of studies needs to be reported with caution. The subgroup of long-term follow-up was statistically indifferent between the treatments, however the wide range of 95% CI of pooled ratio suggested insufficient data. It would be of clinical relevance to evaluate long-term survival in future RCTs. |  |
| 23c | We limited publications to English languages. |  |
| 23d | Future studies are required to monitor the carious lesion activity before and after interventions to investigate the effect of residual carious dentine on the success of treatment and restorative materials i.e., bonding abilities of the materials used on residual carious dentine. It could be speculated that lesions having leathery retained carious may not need the second stage approach as the retained carious dentine provides evidence of lesion arrestment. |  |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | The study protocol was registered with the PROSPERO international prospective register of systematic reviews (CRD42023441817). |  |
| 24b | The study protocol was registered with the PROSPERO international prospective register of systematic reviews (CRD42023441817).. |  |
| 24c | We increased the database search from Cochrane Review, PubMed (Medline) and Ovid to Cochrane Review, PubMed (Medline), Ovid, Web of Science, Embase, Scopus, Open Gray. |  |
| Support | 25 | This study was not supported by any sponsor or funder. |  |
| Competing interests | 26 | The authors have no conflicts of interest to declare. |  |
| Availability of data, code and other materials | 27 | All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author. |  |

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