Does selective caries removal in combination with antimicrobial photodynamic therapy affect the clinical performance of adhesive restorations of primary or permanent teeth? A systematic review with meta-analysis

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Antimicrobial photodynamic therapy (aPDT) is an adjunct to a selective caries removal (SCR) technique for deep caries lesion treatment. The knowledge about chemical and structural changes affecting the remaining dentin surface after the use of this therapy is still unknown. ***Objective:*** *to answer the following question: Does the SCR technique in combination with aPDT affect the clinical performance of adhesive restorations in deep carious lesions of primary or permanent teeth?* ***Study design:*** *a systematic review was conducted. Five databases, supplemented by trial registers, google scholar, manual search, personal communications, and grey literature were investigated. Randomized clinical trials were included. Two independent reviewers selected the studies, extracted qualitatively the data, and evaluated the risk of bias (using Cochrane Collaboration's tooland Robot Reviewer program). The certainty of the evidence was accessed based on The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. A meta-analysis of comparable data was performed with RevMan software 5.3.* ***Results:*** *A total of 39 articles and 3 studies were found. The final selection included 3 articles with a total of 82 participants. No studies were found on permanent teeth. The studies presented low risk of bias. Considering the treatment in the experimental (SCR + aPDT) or control groups (SCR), no difference on clinical performance of adhesive restorations in deep caries of primary teeth was observed after 6 months (p = 0.78; CI −0.01 (−0.09, 0.07)) or 12 months (p =0.75; CI −0.02 (−0.12, 0.08)). All outcomes presented moderate certainty of evidence mainly due to the small sample size that downgrade the GRADE scores.* ***Conclusions:*** *based on moderate certainty of the evidence, the clinical use of aPDT as an adjuvant of SCR has potential indication for treatment in deep caries of primary teeth. However, studies with more follow up and on permanent teeth are missing with the necessity for further research.*

Keywords: *Dental caries, Dental cavity preparation, Photochemoterapy, Adhesive restoration*

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INTRODUCTION

Minimally invasive dentistry includes early diagnosis, preventive care, and conservative treatment of carious lesions, even when an invasive approach is required, to reduce tooth loss[1]. Previous decade, the caries process was better understood and added to it the improvements in dental materials, have facilitated the provision of more conservative and less invasive treatments[1–3].

Deep carious lesions are characterized by a penetration depth of three-quarters or more of the internal dentinal thickness[4].Conservative techniques of caries removal, such as selective caries removal (SCR)[5], and SCR combined with antimicrobial photodynamic therapy (aPDT)[6,7], have been investigated for the treatment of deep carious lesions. Considerable evidence has proven the efficacy of aPDT. This technique reduces the number of microorganisms[6,8–10] preserves pulp vitality and prevents caries progression[11]. In the literature, the success rates of minimally invasive techniques have been reported[3,12–14]. The systematics reviews respond to the challenge of an unmanageable amount of information by synthesizing research-based evidence and it is presented as a method to transform the information into an accessible format[15].

Although the effect of aPDT on carious dentin in human models has already been evaluated in vitro studies, there is no knowledge about any chemical and structural changes affecting the remaining dentin surface[16,17]. Therefore, using a systematic review method this study aimed to evaluate the scientific evidence of the treatment on deep carious lesions using SCR or SCR in combination with aPDT on the clinical performance of adhesive restorations of primary or permanent teeth.

METHOD

Outline of the question and project registration in a systematic review database

The protocol of the current systematic review was established before the initiation and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020151806) following prisma protocol[18].This systematic review was developed, conducted, following Cochrane methodological guidelines[19], and was described following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[20].

The clinical question, structured using the population, intervention, comparison, and outcome (PICO) framework, was framed as follows: Does the SCR technique associated with aPDT affect the clinical performance of adhesive restorations in deep carious lesions of primary or permanent teeth?

Studies identification and studies selection

An extensive search of articles published until 02 February 2022 was performed to identify the studies that could potentially answer the question asked. The databases consulted were Medline via PubMed, Web of Science, Scopus, Latin American and Caribbean Health Sciences Literature (LILACS), and the Cochrane Library. Medical subject heading (MeSH) terms and free terms were obtained on www.ncbi.nlm.nih.gov/mesh/. Keywords were selected from the DeCS—Health Sciences Descriptors on https://decs.bvsalud.org/. Full search strategies, including used index and free keywords and boolean operators (AND, OR), are presented according to the searched database in Table 1. Furthermore, to detect relevant unpublished manuscripts, conference papers, doctoral dissertations, and other grey literature, OpenGrey (http://www.opengrey.eu), Google Scholar (first 100 returns), and other available digital repositories (https://clinicaltrials.gov/). Finally, to ensure the inclusion of significant studies that may not have been identified through database and grey literature searches, a manual search on the reference list of included studies and personal communications were done.

All obtained articles were saved in a reference management software to remove duplicate articles. Two researchers (TOF and LAA) independently evaluated all titles and abstracts, considering the eligibility criteria. The agreement between the authors was assessed (Kappa statistical index 0.90) was determined. When the title and abstract were inconclusive, the entire paper was read. In this selection, if there was a disagreement of opinions, a third reviewer (LSA) was consulted for consensus.

Randomized clinical trials with no restrictions on language and data were included according to the PICO framework:

Population (P): Dentin carious lesions in primary or permanent teeth

Intervention (I): SCR associated with aPDT

Comparison (C): SCR + aPDT *vs.* SCR

Outcomes (O): Effect on the clinical performance of adhesive restorations

Articles reporting pain, case reports, results in extracted teeth, outside theme, *in-vitro* studies, microscopic analysis, perception, clinical trial protocols, and methods for diagnosis were excluded.

Data Extraction

Two reviewers extracted the data. The agreement between the reviewers (LVF and LAA) was assessed at this stage (Kappa = 0.90), and any doubt was solved by consensus with a third reviewer (MRRC), a specialist in the theme. The extracted data included author/year of publication/country; type of study; evaluated teeth; the age of the participants; sample size; evaluated groups; materials used for the restorations; methods used to assess treatment success; follow-up duration; outcome; and success rate. We also collected data on aPDT parameter: photosensitizer (concentration)/pre-irradiation time, wavelength (nm), irradiation time, energy (J), light source, fluence (J/cm^2), power (W), irradiance (W/cm^2), and area (cm^2).

Risk of bias in individual studies

For the evaluation of the risk of bias, two authors (LVF and LAA) performed the evaluations independently (Kappa = 0.90) using the Cochrane Collaboration's tool[19] and Robot Reviewer program (https://www.robotreviewer.net/). Any divergence was resolved by a third reviewer (LSA). The Cochrane Collaboration's tool[19] presents five domains classified as low (+), high (−), or uncertain (?) risk of bias.

Table 1: Electronic search.

	Database
Pubmed	#1 (((((((((dental caries (MeSH Terms)) OR (Dental caries ((Title/Abstract))) OR (Dental decay (Title/Abstract))) OR (Carious dentin (Title/Abstract))) OR (Decayed (Title/Abstract))) OR (Tooth decay (Title/Abstract))) OR (Carious tissue (Title/Abstract))) OR (Deep caries (Title/Abstract))) OR (Dentinal caries (Title/Abstract))) OR (Caries affected dentin (Title/Abstract)) #2 ((((((((((((((((((((Dental cavity preparation (MeSH Terms)) OR (dental pulp capping (MeSH Terms))) OR (Dental cavity preparation (Title/Abstract))) OR (Dental pulp capping (Title/Abstract))) OR (Partial removal (Title/Abstract))) OR (Incomplete excavation (Title/Abstract))) OR (Stepwise excavation (Title/Abstract))) OR (Incomplete caries remove (Title/Abstract))) OR (Incomplete caries removal (Title/Abstract))) OR (Partial caries removel (Title/Abstract))) OR (Partial caries removal (Title/Abstract))) OR (Partial caries excavation (Title/Abstract))) OR (Minimal intervention technique (Title/Abstract))) OR (Minimally invasive treatment (Title/Abstract))) OR (Minimally invasive dentistry (Title/Abstract))) OR (Conservative dentistry (Title/Abstract))) OR (Indirect pulp treatment (Title/Abstract))) OR (One- step incomplete excavation (Title/Abstract))) OR (Dental pulp capping (Title/Abstract))) OR (One- step partial caries removal (Title/Abstract)) #3 (((((((((tooth, deciduous (MeSH Terms)) OR (Tooth, Deciduous (Title/Abstract))) OR (Deciduous tooth (Title/Abstract))) OR (Deciduous teeth (Title/Abstract))) OR (Deciduous dentition (Title/Abstract))) OR (Primary dentition (Title/Abstract))) OR (Primary teeth (Title/Abstract))) OR (Primary tooth (Title/Abstract))) OR (Permanent teeth (Title/Abstract))) OR (Permanent tooth (Title/Abstract)) #4 (((((((Photochemotherapy (MeSH Terms)) OR (Lasers (MeSH Terms))) OR (Photodynamic therapy (Title/Abstract))) OR (Photochemotherapy (Title/Abstract))) OR (Photochemotherapies (Title/Abstract))) OR (Photodynamic Therapies (Title/Abstract))) OR (aPDT (Title/Abstract))) OR (Antimicrobial photodynamic therapy (Title/Abstract)) #1 AND #2 AND #3 AND #4
Cochrane Library	(Dental decay OR Carious dentin OR Carious lesion OR Decayed OR Tooth decay OR Carious tissue OR Deep caries OR Dentinal caries OR Caries affected dentin):ti,ab,kw AND (Dental cavity preparation OR Dental pulp capping OR Partial removal OR Incomplete excavation OR Stepwise excavation OR Incomplete caries remove OR Incomplete caries removal OR Partial caries remove OR Partial caries removal OR Partial caries excavation OR Minimal intervention technique OR Minimally invasive treatment OR Minimally invasive dentistry OR Conservative dentistry OR Indirect pulp treatment OR One step incomplete excavation OR Dental pulp capping OR One step partial caries removal):ti,ab,kw AND (Deciduous teeth OR Deciduous dentition OR Primary dentition OR Primary teeth OR Primary tooth OR Permanent teeth OR Permanent tooth):ti,ab,kw AND (Photodynamic therapy OR Photochemotherapy OR Photochemotherapies OR Photodynamic Therapies OR aPDT OR Antimicrobial photodynamic therapy):ti,ab,kw
Scopus	#1 (TITLE-ABS-KEY (dental AND caries) OR TITLE-ABS-KEY (dental AND decay) OR TITLE-ABS-KEY (carious AND dentin) OR TITLE-ABS-KEY (carious AND lesion) OR TITLE-ABS-KEY (decayed) OR TITLE-ABS-KEY (tooth AND decay) OR TITLE-ABS-KEY (carious AND tissue) OR TITLE-ABS-KEY (deep AND caries) OR TITLE-ABS-KEY (dentinal AND caries) OR TITLE-ABS-KEY (caries AND affected AND dentin)) #2(TITLE-ABS-KEY (dental AND cavity AND preparation) OR TITLE-ABS KEY (dental AND pulp AND capping) OR TITLE-ABS-KEY (partial AND removal) OR TITLE-ABS-KEY (incomplete AND excavation) OR TITLE-ABS KEY (stepwise AND excavation) OR TITLE-ABS-KEY (incomplete AND caries AND remove) OR TITLE-ABS-KEY (incomplete AND caries AND removal) OR TITLE-ABS-KEY (partial AND caries AND remove) OR TITLE-ABS-KEY (partial AND caries AND removal) OR TITLE-ABS-KEY (partial AND caries AND excavation) OR TITLE-ABS-KEY (minimal AND intervention AND technique) OR TITLE-ABS-KEY (minimally AND invasive AND treatment) OR TITLE-ABS-KEY (minimally AND invasive AND dentistry) OR TITLE-ABS-KEY (conservative AND dentistry) OR TITLE-ABS-KEY (indirect AND pulp AND treatment) OR TITLE-ABS-KEY (one-step AND incomplete AND excavation) OR TITLE-ABS-KEY (dental AND pulp AND capping) OR TITLE-ABS-KEY (one- AND step AND partial AND caries AND removal)) #3 (TITLE-ABS-KEY (deciduous AND tooth) OR TITLE-ABS-KEY (deciduous AND teeth) OR TITLE-ABS-KEY (deciduous AND dentition) OR TITLE-ABS-KEY (primary AND dentition) OR TITLE-ABS-KEY (primary AND teeth) OR TITLE-ABS-KEY (primary AND tooth) OR TITLE-ABS-KEY (permanent AND teeth) OR TITLE-ABS-KEY (permanent AND tooth)) #4 (TITLE-ABS-KEY (photodynamic AND therapy) OR TITLE-ABS-KEY (photochemotherapy) OR TITLE-ABS-KEY (photochemotherapies) OR TITLE-ABS-KEY (photodynamic AND therapies) OR TITLE-ABS-KEY (apdt) OR TITLE-ABS-KEY (antimicrobial AND photodynamic AND therapy)) #1 AND #2 AND #3 AND #4

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Table 1: Continued.

Database	
Web of Science	#1 Dental caries (Topic) or Dental decay (Topic) or Carious dentin (Topic) or Carious lesion (Topic) or Decayed (Topic) or Tooth decay (Topic) or Carious tissue (Topic) or Deep caries (Topic) or Dentinal caries (Topic) or Caries affected dentin (Topic) #2 Dental cavity preparation (Topic) or Dental pulp capping (Topic) or Partial removal (Topic) or Incomplete excavation (Topic) or Stepwise excavation (Topic) or Incomplete caries remove (Topic) or Incomplete caries removal (Topic) or Partial caries remove (Topic) or Partial caries removal (Topic) or Partial caries excavation (Topic) or Minimal intervention technique (Topic) or Minimally invasive treatment (Topic) or Minimally invasive dentistry (Topic) or Conservative dentistry (Topic) or Indirect pulp treatment (Topic) or One- step incomplete excavation (Topic) or Dental pulp capping (Topic) or One- step partial caries removal (Topic) #3 Deciduous tooth (Topic) or Deciduous teeth (Topic) or Deciduous dentition (Topic) or Primary dentition (Topic) or Primary teeth (Topic) or Primary tooth (Topic) or Permanent teeth (Topic) or Permanent tooth (Topic) #4 Photodynamic therapy (Topic) or Photochemotherapy (Topic) or Photochemotherapies (Topic) or Photodynamic Therapies (Topic) or aPDT (Topic) or Antimicrobial photodynamic therapy (Topic) #1 AND #2 AND #3 AND #4
LILACS	(Dental caries OR Dental decay) AND (Dental cavity preparation OR One step partial caries removal OR selective caries removal) AND (Deciduous tooth OR Dentition Permanent) AND (Photodynamic therapy OR Photochemotherapy OR Lasers)
Google Scholar	(Dental caries OR Dental decay) AND (Dental cavity preparation OR One step partial caries removal OR selective caries removal) AND (Deciduous tooth OR Dentition Permanent) AND (Photodynamic therapy OR Photochemotherapy OR Lasers)
OpenSIGLE http://www.opengrey.eu	(Dental caries OR Dental decay) AND (Dental cavity preparation OR One step partial caries removal OR selective caries removal) AND (Deciduous tooth OR Dentition Permanent) AND (Photodynamic therapy OR Photochemotherapy OR Lasers)
https://clinicaltrials.gov/	(Dental caries OR Dental decay) AND (Dental cavity preparation OR One step partial caries removal OR selective caries removal) AND (Deciduous tooth OR Dentition Permanent) AND (Photodynamic therapy OR Photochemotherapy OR Lasers)

Abbreviations: MeSH, Medical subject heading; aPDT, Antimicrobial photodynamic therapy; TITLE-ABS-KEY, TITLE-ABSTRACT-KEYWORD.

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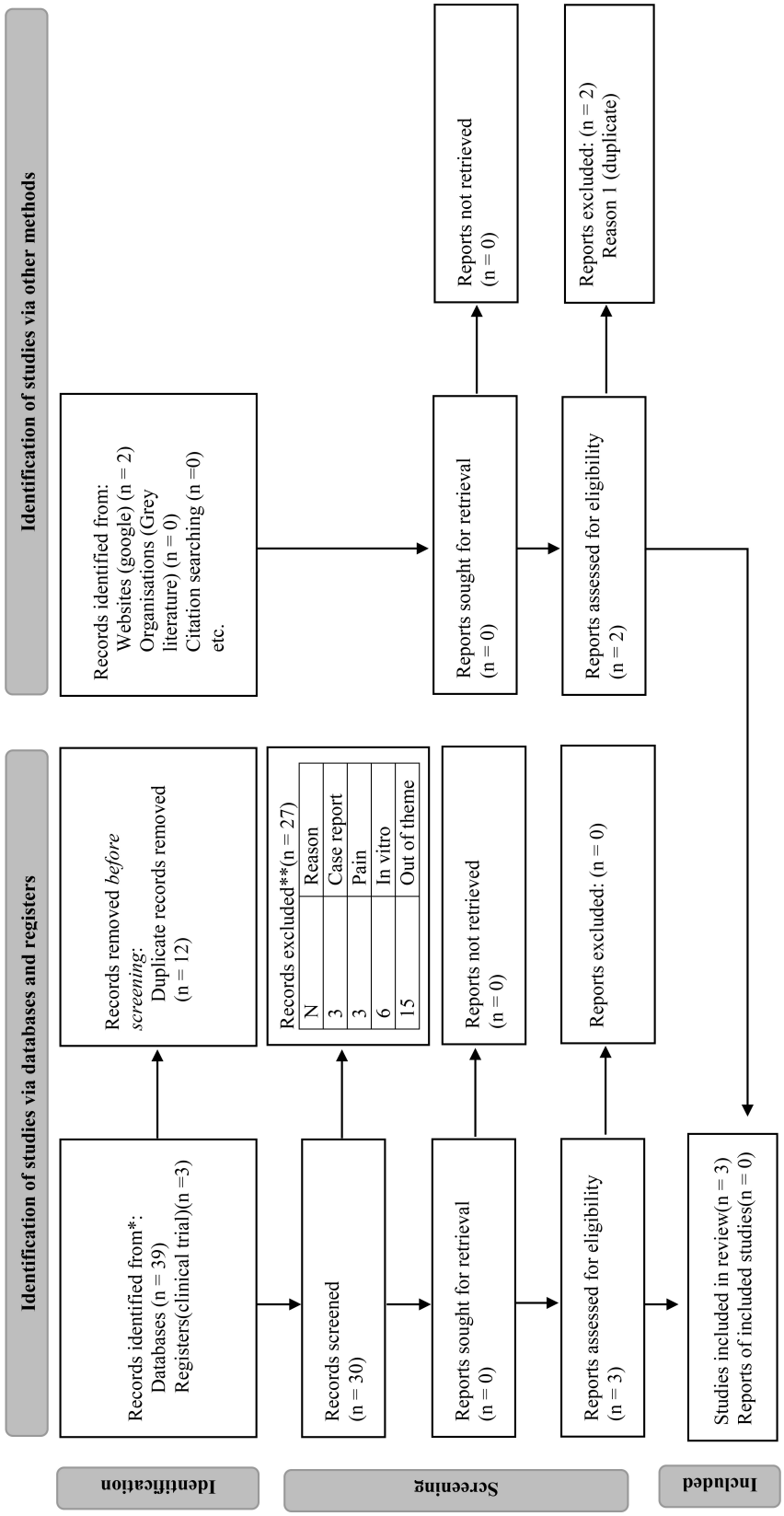

Figure 1: Prisma 2020 flow diagram describing the reports, records and studies identification/selection.

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Effect measures, synthesis methods and reporting bias assessment

The random-effects model was adopted[21]. The calculations and Forest plots were performed with RevMan 5.3 (Review Manager (RevMan), V.5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). obtaining Confidence interval (CI) and considering $p < 0.05$. Dichotomous data were obtained from all studies. The experimental group (SCR + aPDT) versus the control group (SCR) was analyzed. The subgroup analysis included the photosensitizer used (methylene blue) and follow-up duration (6 and 12 months).

In cases of covariables influencing in the stability of the main outcomes, sensibility analysis or meta-regression was planned. The publication bias was planned to be assessed by analyzing funnel plot outcome.

Certainty of the evidence

Two reviewers (LSG and LAA) independently evaluated (Kappa = 0.80) the certainty in the estimates of effects. According to GRADE (Grading of Recommendations Assessment, Development and Evaluation), each domain is classified as not serious, serious, or very serious. Clinical studies domains evaluated were: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Finally, the certainty of the evidence is classified as low, moderate, or high[22].

RESULTS

Studies identification and studies selection

A flowchart of the studies selection of this systematic review is presented in Fig. 1. Initially, 42 studies were found: 24 on PubMed, 05 in Web of Science, 07 in Scopus, 03 in Cochrane Library, none in LILACS and 03 registered trials were found. No article was included from the manual search, google scholar, grey literature, or personal communication. After exclusion of duplicate studies, 30 studies prevailed. After analyzing the titles and abstracts, 27 studies were excluded, resulting 03 studies eligible.

Data Extraction

The three included studies were performed in Brazil and they were randomized controlled trials. Alves *et al*[10] conducted a split-mouth study. Steiner-Oliveira *et al*[8] analyzed the effect of the treatments and clinical and radiographic signs of failure in the restoration; however, they did not explain the method used for this analysis. Alves *et al*[10] evaluated the failure in the restoration using the United States Public Health Service (USPHS) method that analyzes marginal discoloration, retention, color and secondary caries. Faria *et al*[23] used the Fédération Dentaire Internationale (FDI) criterion. Considering the time of follow-up, Steiner-Oliveira *et al*[8] followed the patients for 6 and 12 months after treatment, Alves *et al*[10] for 6 months, and Faria *et al*[23] for 7 days, 6 months, and 12 months (Table 2).

Table 2 illustrates the clinical patterns of the three studies[8,10,23]. It was observed that the age groups were similar, varying between 4 and 10 years; the number of participants ranged from 20 to 32, and the same teeth (primary molars) were analyzed. The material used after SCR with or without aPDT was resin-modified glass ionomer cement[8] and calcium hydroxide cement + glass ionomer + composite resin and glass ionomer cement + composite resin cavities[10] and only composite resin[23]. In the results of individual studies, all of them did not present difference between the experimental (SCR + aPDT) and control (SCR) groups. The success rate was 100%, according to Alves *et al*[10] and Steiner-Oliveira *et al*[8] and 81.2%, according to Faria *et al*[23] (Table 2).

According to the used protocol for aPDT, as shown in Table 3, the wavelength was similar in the three articles (660 nm). All three studies[8,10,23] used the methylene blue photosensitizer (MB); however, Steiner-Oliveira *et al*[8] also used toluidine blue (TB) in Group 2. MB was applied for the same duration (5 minutes) in the three studies[8,10,23].However, the MB concentration was different in the studies: 0.01%[8,23] and 0.005%[10]. The irradiation times were also different: 90 seconds[8,23] and 180 seconds[10]. The energy was reported only in two articles[8,23]. The fluence for the aPDT + MB protocol were different: 320 J/cm^2 [8],640 J/cm^2, [10] and 300 J/cm^2 [23]. All studies used the same power (100 mW)[8,10,23].

Risk of Bias in individual studies

The studies[8,10,23] showed no risk of bias. In all three studies, blinding of the involved patients and professionals could not be performed due to the type of intervention (Item 3). Hence, it was considered not applicable (NA). In cases of doubt, the authors of the studies were contacted (Table 4).

Meta-analysis and the certainty of evidence

In terms of treatment, in the experimental (SCR + aPDT) and control groups (SCR), no difference was observed between the groups after 6 months of follow-up ($p = 0.78$; CI [confidence interval] -0.01-0.09, 0.07)) (Fig. 2). Additionally, no difference was observed after 12 months ($p = 0.75$; CI −0.02 (−0.12, 0.08)) (Fig. 3).

In terms of the used photosensitizer (MB), no difference was observed after 6 months ($p = 0.76$; CI −0.01 (−0.10, 0.07)) (Fig. 4) and 12 months ($p = 0.71$; CI −0.02 (−0.14, 0.09)) (Fig. 5).

This study did not have as many covariables to perform the meta-regression or sensitivity analysis[24]. Publication bias cannot be assessed once there were no subgroup analyses with at least 10 studies included in the meta-analysis[25].

The certainty of the evidence was moderate, since in two studies, the sample sizes were small and could not be considered representative because of the method of sample size calculation used in both articles[8,10]. In these articles, the assessments were divided in microbiological and clinical stages, and sample calculation was based on microbiological reduction and not on the restorations success rate (Table 5).

Table 2: Characteristics of the included studies.

Author, (year)/Country	Type of study	Dentition	Age (years)	Sample (partici-pants)	Groups evaluated	Restorative Materials	Methods to evaluate the treatment success	Time of Follow up	Outcome	Success Rate
Steiner-Oliveira *et al.*, (2015)/Brazil	Randomized clinical trial	Primary Molars	5 to 7	Thirty-two	G1: (Control) Partial caries removal + chlorhexidine G2: Partial caries removal + Photodynamic antimicrobial chemotherapy with light-emitting diode associated with TBO G3: Partial caries removal + Photodynamic antimicrobial chemotherapy with laser associated with MB	resin-modified glass ionomer cement	Clinical signs Radiographic signs Restoration failure	6 and 12 months	After the follow-up periods of both 6 and 12 months, no signs of pain or restoration failure were observed. The radiographs also showed no abnormal images. No differences were found between treatments. No strong correlations were found among any of the clinical variables tested.	100% for all groups analyzed
Alves *et al.*, (2019)/Brazil	Randomized split-mouth clinical trial	Primary Molars	6 to 8	Twenty	G1: (Control) Selective removal of carious tissue G2: selective removal of carious tissue + Photodynamic antimicrobial chemotherapy (low intensity laser-InGaAlP) with 0.005% MB	Deep cavities: calcium hydroxide cement + glass ionomer + composite resin Medium cavities: glass ionomer cement + composite resin	Modified USPHS-(United States Public Health Service): analysis of retention, marginal discoloration, secondary caries, marginal adaptation, and color	7 days and 6 months	No difference was found between the teeth that received the aPDT and those that did not receive it for all the evaluated criteria: retention, marginal adaptation, marginal discoloration, secondary caries, and color. In the 6 months analysis, an inadequate marginal adaptation was observed in 2 restorations, one in each treatment group.	100% for all groups analyzed

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Table 2: Continued.

Author, (year)/Country	Type of study	Dentition	Age (years)	Sample (partici-pants)	Groups evaluated	Restorative Materials	Methods to evaluate the treatment success	Time of Follow up	Outcome	Success Rate
Faria *et al.*, (2022)/Brazil	Randomized clinical trial	Primary Molars	4 to 10	Thirty	G1: (Control) Selective removal of carious tissue G2: selective removal of carious tissue + Photodynamic antimicrobial chemotherapy (low intensity laser-InGaAlP) with 0.01% MB	Composite Resin	FDI Criteria	1 week, 6 and 12 months	No difference was found between the teeth that received the aPDT and those that did not receive.	81.2 % for experimen-tal group and 86.7% for control group

Abbreviations: TBO, toluidine blue; MB, Methylene Blue; aPDT, Antimicrobial photodynamic therapy; FDI, International Dental Federation.

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Table 3: aPDT parameters in the selected studies.

Author/year	Wavelength (nm)	Photosensitizer (concentration)/pre-irradiation time	Removal of Photosensitizer before irradiation	Irradiation time	Irradiation location	Light source	Energy (J)	Fluence (J/cm²)	Power (mW)	Irradiance (mW/cm^2)	Spot (mm^2)
Steiner-Oliveira *et al.*, (2015)	LEDTB-630	LEDTB-TBO 200 μL (0.1 mg/mL)/1 min	The photosensitizer was removed after irradiation (washed out with water and dried with a sterile cotton pellet)	LEDTBO-1 min	WD	LEDTB-Red LED light source	9	LEDTB-30	100	WD	WD
	LMB-660	LMB-MB 200 μL (0.01%) (Chimiolux® Hyrofarma, Belo Horizonte, Minas Gerais, Brazil)/5 min		LMB-90 sec		LMB-Red low power LASER light source		LMB-320			
Alves *et al.*, (2019)	660	0.005% MB photosensitizer/pre-irradiation time was 5 min	The teeth were washed abundantly with water for 1 min.	180 sec	WD	InGaAlP laser	WD	640	100	WD	WD
Faria *et al.*, (2022)	660	0.01% MB photosensitizer/pre-irradiation time was 5 min	The photosensitizer was removed before irradiation (excess removed with sterile cotton)	90 sec	Cavity center at a distance of 3mm	Red low power LASER InGaAlP	9	300	100	WD	3

Abbreviations: aPDT, Antimicrobial photodynamic therapy; MB, Methylene Blue; TBO, toluidine blue; LEDTB, aPDT with LED mediated TBO; LMB, aPDT with laser mediated by MB; WD, Without data; InGaAlP, Indium gallium aluminum phosphorus.

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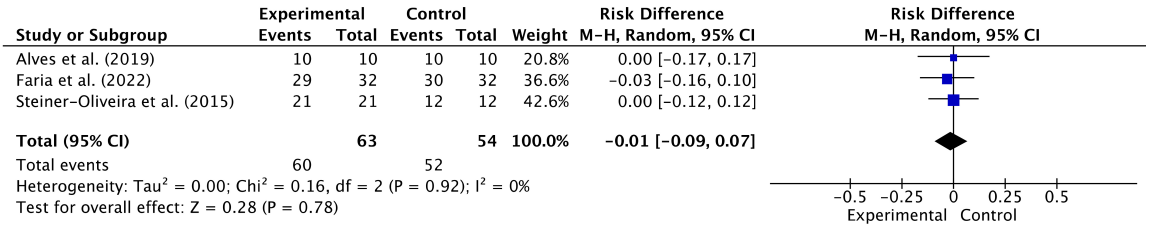

Figure 2: Evaluation of the groups according to the number of successful treatments after the 6-month period. CI: confidence interval.

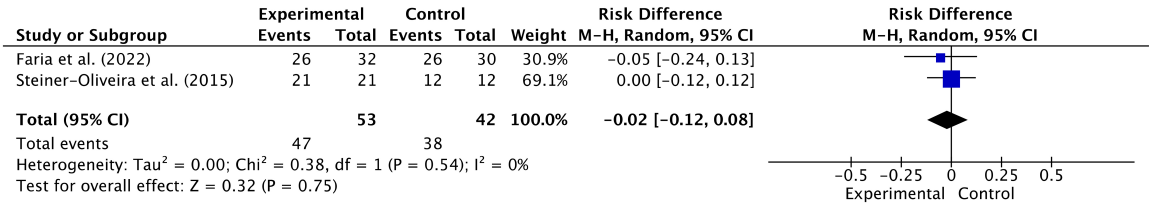

Figure 3: Evaluation of the groups according to the number of successful treatments after the 12-month period. CI: confidence interval.

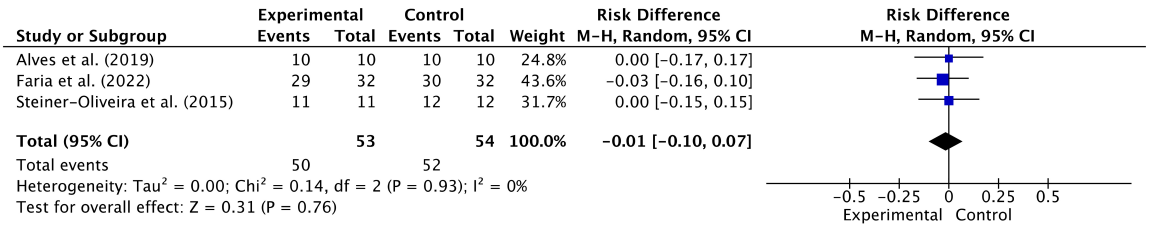

Figure 4: Evaluation of treatment success taking into account the photosensitizer (methylene blue) after 6-months period. CI: confidence interval.

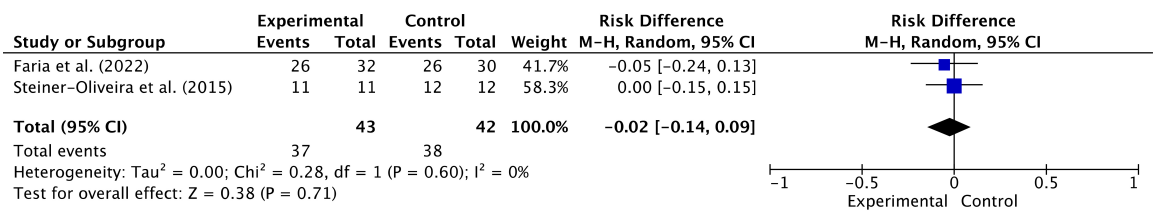

Figure 5: Evaluation of treatment success taking into account the photosensitizer (methylene blue) after 12-months period. CI: confidence interval.

Table 4: Risk of Bias in the selected studies.

	1. Random sequence generation	2. Allocation concealment	3. Blinding of participants and personnel	4. Blinding of outcome assessment	5. Incomplete outcome data	6. Selective reporting
Steiner-Oliveira *et al.*, (2015)	+	+	NA	+	+	+
Alves *et al.*, (2019)	+	+	NA	+	+	+
Faria *et al.*, (2022)	+	+	NA	+	+	+

Note: Yes (+)—low risk of bias; No (−)—high risk of bias: (?) Unclear; NA: not applicable.

Table 5: The certainty of the evidence of studies the treated SCR + aPDT compared to Control (SCR) for deciduous considering the outcomes time of follow-up and photosensitizer.

Certainty assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	aPDT + SCR	SCR	Relative (95% CI)	Absolute (95% CI)	
Evaluation of the groups according to the number of successful treatments after the 6-month period.											
3	randomized trials	not serious	not serious	not serious	serious[a]	none	60/63 (95.2%)	52/54 (96.3%)	RR −0.02 (−0.11 to 0.07)	982 fewer per 1.000 (from 1.000 fewer to 896 fewer)	⨁⨁⨁◯ MODERATE
Evaluation of the groups according to the number of successful treatments after the 12-month period.											
2	randomized trials	not serious	not serious	not serious	serious[b]	none	47/53 (88.7%)	38/42 (90.5%)	RR −0.04 (−0.17 to 0.09)	941 fewer per 1.000 (from 1.000 fewer to 823 fewer)	⨁⨁⨁◯ MODERATE
Evaluation of treatment success taking into account the photosensitizer (methylene blue) after 6-months period											
3	randomized trials	not serious	not serious	not serious	serious[b]	none	50/53 (94.3%)	52/54 (96.3%)	RR −0.02 (−0.11 to 0.07)	982 fewer per 1.000 (from 1.000 fewer to 896 fewer)	⨁⨁⨁◯ MODERATE
Evaluation of treatment success taking into account the photosensitizer (methylene blue) after 12-months period											
2	randomized trials	not serious	not serious	not serious	serious[b]	none	37/43 (86.0%)	38/42 (90.5%)	RR −0.04 (−0.18 to 0.10)	941 fewer per 1.000 (from 1.000 fewer to 814 fewer)	⨁⨁⨁◯ MODERATE

CI: Confidence interval; RR: Risk ratio; aPDT: Antimicrobial photodynamic therapy; SCR: selective caries removal.
Explanations: [a]: Small sample size. The sample size of 2 papers were calculated based on the microbiological analysis; [b]: Small sample size.

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DISCUSSION

This systematic review detected three randomized clinical studies that investigated the failure of restorations after SCR with aPDT. Of them, two studies performed the clinical observation of a reduction in the number of microorganisms and longitudinal follow-up of restorations [8,10]. The other randomized clinical trial performed only the follow-up of restorations [23]. Steiner-Oliveira *et al* [8] and Faria *et al* [23] evaluated SCR in combination with aPDT in longitudinal follow-up (6 and 12 months), but Alves *et al* [10] evaluated a period of 6 months only. The 03 studies used primary teeth and no study was found in permanent teeth.

Various in-vitro studies have simulated the use of composite resin bonded to carious dentin using aPDT. One study [16] analyzed the shear bond strength (adhesive bond integrity) of composite resin bonded to carious dentin using aPDT in combination with MB. The lowest bond strength was observed in Group of aPDT on infected dentin. Another *in vitro* study [17] evaluated the effect of different photosensitizers activated by aPDT on the shear bond strength of composite resin to caries-affected dentin compared to conventional disinfectants such as chlorhexidine. All the tested photosensitizers (MB, curcumin, and indocyanine green) activated by aPDT demonstrated acceptable shear bond strength. Curcumin demonstrated the highest shear bond strength. Therefore, *in vivo* studies are required to detect changes in dentinal surfaces after aPDT. Hence, it is important to evaluate the longevity of these restorations, as long-term effects of aPDT on the tooth substrate submitted to the procedure in clinical studies have not been analyzed, as proposed in this study. Based on the results of these *in vitro* studies, we suggest that clinical experiments should be performed to assess the influence of other photosensitizers on restoration longevity.

From the included articles, Steiner-Oliveira *et al* [8] followed the restorations to determine the level of clinical and radiographic success as well as the presence of failure in the retention of restorations (the author did not use any specific criteria described in the literature). Alves *et al* [10] used the modified USPHS criterion to assess retention, presence of secondary caries, marginal discoloration/adaptation, and color. Faria *et al* [23] used the FDI criteria to evaluate the biological, esthetic, and functional properties of the restorations. Therefore, this meta-analysis was performed by comparing the treated groups (with and without aPDT) for restorative failure. Regardless of the method used to detect the restoration failure, all studies evaluated the use of SCR in combination with aPDT.

Although the follow-up period did not influence the treatment groups in the meta-analysis, this duration of clinical follow-up (6 and 12 months) can be considered a limitation in these studies. For deciduous teeth, the follow-up duration was adequate due to its short period on the oral cavity, but long-term follow-up studies are required for permanent teeth. Another point important to highlight is about the diversity of laser or LED light and photosensitizer protocols. In the included studies, the time of irradiation and dose varied. Despite using different parameters in all studies [8,10,23], the use of aPDT presented satisfactory restoration retention. However, further studies evaluating the influence of these parameters can be done to evaluate this influence.

Considering the photosensitizer, only one study [8] included two groups with different photosensitizers (MB and TB). Therefore, this meta-analysis basically assessed the use of MB as a photosensitizer. The MB concentration was different in the studies: 0.01% [8,23] and 0.005% [10]. However, in both studies, the incidence of failure was low. Other photosensitizers, which also lead to a reduction in the microorganisms, are also used with aPDT, as presented in a systematic review [6]. However, more studies are necessary to detect the influence of other photosensitizers on restoration retention.

The certainty of evidence (GRADE) was influenced by the limited sample size of the studies. This was primarily a concern of the two published studies [8,10]. As highlighted previously, both studies [8,10] were structured into two stages: microbiological and clinical analyses. Thus, the sample size calculation shown in the articles was based only on microbiological analysis, which may have led to a sample bias. Ideally, the calculation should have been based on studies that detected the clinical efficacy, as performed in other studies [3,5,23]. In this way, the sample size would have been more reliable and representative of the expected outcome (clinical efficacy).

This systematic review controlled the risk of bias since it followed on the PRISMA guidelines [18]. The degree of confidence in the results of the review was high. The search was done in several databases. The eligibility criteria, data extraction, risk of bias and GRADE were performed by two researchers. In addition, evaluation instruments established in the literature (risk of bias using the Cochrane Collaboration's tool and RobotReviewer) assessed the risk of bias in the studies. The limitation of this study would be articles related, because none of them showed negative results; thus, emphasizing that the clinical protocol could have been biased. Considering the number of studies included in the meta-analysis not have any restriction for number. In the literature we found some meta-analysis with just two studies however, more studies mean that the meta-analysis have more power and is more exact and reliable. Despite of it, this review is extremely important, because the results enable future authors to delineate their studies aggregating adequate results and revealing the best possible scientific evidence.

Another limitation that we can point relates to the few studies. The risk of publication bias across studies was also not assessed, as it can be assessed only when at least 10 studies are included in the meta-analysis [24].

Minimal invasive treatment in cavitated or non-cavitated teeth can be considered a rational method for the treatment of caries and should be advocated at public, private, and educational levels. The patient should also be informed of the advantages of these techniques compared to traditional restorative procedures. Currently, the techniques for SCR include the use of Carisolv and atraumatic restorative treatment, and various systematic reviews have proven their effectiveness [12,14]. SCR is particularly advantageous in deep carious lesions, since it significantly reduces the risk of pulp exposure compared to total caries removal [2,5]. The use of aPDT as an adjuvant technique can provide a conservative treatment for caries. This is due to its antibacterial property, which provides a virtually total reduction of microorganisms in decayed

dentin, where it can be preserved and consequently prevent pulp exposures. Therefore, the association of aPDT with SCR, which completely removes caries from the dentin walls in order to adhere to the restorative material, is suggested as an association that preserves the tooth structure during caries treatment, according to the current principles of minimal intervention dentistry.

The success of the adhesive restoration presented in this review is additional information that indicates that the association of SCR + aPDT techniques can be used successfully in clinical practice, but these results should be interpreted with caution due to the small number of published studies and the moderate certainty of the evidence. To date, several studies have been conducted on primary teeth, but research on permanent teeth must be carried out to delineate the quality and safety of aPDT.

CONCLUSIONS

The meta-analysis observed that the use of aPDT as an adjuvant has a strong potential for clinical use. However, a database of clinical studies is limited presenting moderate certainty of the evidence. Therefore, the resulting conclusions are limited confirmatory and only available for primary teeth at all what leads to limited significance of the information provided by the investigation.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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