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COMPARISON OF HEALING EFFICACY AND PAIN LEVELS FOLLOWING PERIODONTAL SURGERY USING CYANOACRYLATE TISSUE ADHESIVE AND SUTURING TECHNIQUES: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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INTRODUCTION

Periodontitis, a world's most prevalent infectious dental conditions, can lead to destruction of the supporting and surrounding tooth structure.[1] The term "periodontitis" is buildup of two words, i.e., "periodont-" meaning "structure surrounding the teeth" and "itis" means "inflammation." Periodontal diseases are inflammatory and destructive diseases of the dentogingival complex associated with specific periodontal pathogens that colonize the tooth surface, gingival margin and subgingival environment.[2,3] Periodontal diseases lead to damage of the periodontal tissues supporting the teeth (bone and connective tissue) and affect the quality of life of the affected individuals: poor alimentation, tooth loss, social and financial problems.[4]

Globally as estimated by Who, 11% of the adult population are affected by Periodontitis. [5,6] Nonetheless, in a recent systematic review reported that in the Indian population, the overall prevalence of periodontal disease was 51% and 19% suffered from severe periodontitis.[7]

An array of treatment modalities ranging from simple nonsurgical therapy to periodontal plastic surgery and regenerative procedures have been performed for this highly prevalent disease.[8] The main goal of periodontitis treatment is the elimination of modifiable risk factors.[8] Nonsurgical periodontal therapy (NSPT) i.e. scaling and root planning is the first preferred step in the management of periodontal Diseases. This makes them the "Cornerstone or cause related periodontal therapy".[9]

Despite NSPT being the basic and important step in periodontitis treatment, in moderate to severe periodontitis, and when non-surgical methods have failed, Surgical modalities are preferred. Literature reveals various surgical techniques for root coverage procedures which includes free epithelialized gingival graft, lateral sliding flaps, subepithelial connective tissue graft, semilunar flap, coronally advanced flap, and guided tissue regeneration. These techniques have its own advantages and disadvantages with varied success rates.[10,11] Several factors influence the outcomes of periodontal surgery. Close postoperative adaptation of the flap onto the prepared root surface and the maintenance of this adaptation for a period of time holds the key to the reestablishment of a healthy dentogingival unit.[12-14]

Sutures aid in approximation of the flap in the surgical site and ensures wound and bleeding management.[15] Traditionally, numerous materials such as silk, nylon, steel, catgut, polyglycolic-polylactic acid derivatives have been utilized for suturing.[16]

Braided silk is the most commonly used material for closing oral wounds.[16,17] Though these suture materials allows easy manipulation, good knot security and are economical. They do have some disadvantages like requirement of second appointment to remove the suture, and inconvenience to the patient.[18] It also shows a 'wicking' phenomenon, which makes the suture a site for bacteria to retain and enter the tissue, giving place to secondary infection.[18]

Tissue adhesive materials called cyanoacrylates was discovered and synthetized by a German chemist in 1949, to overcome limitations of sutures'

disadvantages.[18] With tremendous upgradation of the cyanoacrylates, N-butyl cyanoacrylate (NBC), a biocompatible tissue adhesive has been utilized for the purpose of wound closure.

Numerous studies have been conducted by utilizing cyanoacrylate as a tissue adhesive. Sadatmansouri et al that cyanoacrylate tissue adhesive had no significant differences in level of pain, healing rate, plaque index, and probing depth compared to the control group. The authors emphasized that cyanoacrylate adhesive can be a good alternative to sutures due to its additional advantages such as short time of placement, patient comfort, resistance to infection, hemostatic properties, and no need for suture removal.[19]

Despite these evidences, there is no comprehensive data evaluating the effectiveness of cyanoacrylate, exclusively in Periodontal surgery. The present study focuses on this lacunae and aims to evaluate and compare the effectiveness of cyanoacrylates as a tissue adhesive to suturing in terms of healing and post-op pain.

AIM AND OBJECTIVES

Aim

The present study aims to evaluate and compare the effectiveness of cyanoacrylates as a tissue adhesive to conventional suturing in terms of healing and post-operative pain by systematic review and meta-analysis.

Objectives

The objective is to compare the healing effects of cyanoacrylates as a tissue adhesive and conventional suturing in patients undergoing periodontal surgery. It aims to evaluate differences in healing, post-op pain, and parameters assessing plaque accumulation by assessing the gingival index, plaque index. By analyzing clinical outcomes, the study seeks to provide evidence-based recommendations for optimizing the application of the cyanoacrylates with multiple advantages that includes strong bonding in the presence of moisture to the tissues, workable polymerization time, biodegradability, and bacteriostatic ability.

MATERIAL AND METHODS

Protocol

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, ensuring transparent reporting of the review process. Additionally, the systematic review protocol was registered on the PROSPERO platform, enhancing transparency and accountability in the research process (Registration number:).

Focused Question

"Is cyanoacrylate tissue adhesive better than conventional suturing in terms of healing and post-operative pain?"

The question for the current systematic review was formulated based on the PICOS criteria: (Table 1)

Table 1: Pico Criteria.

P	Patient undergoing periodontal surgery
I	Application of cyanoacrylates tissue adhesive
C	Conventional suturing
O	Primary outcome: soft tissue healing and postoperative pain

Information sources and Search strategy

The data search was primarily conducted electronically, adhering to the principles of a systematic review. Several renowned databases were utilized, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Google Scholar, and PubMed, employing MeSH terms, text words, and Boolean operators. The search was restricted to articles published up to December 31, 2024. Only studies published in English or those with a detailed summary in English were included. Additionally, the reference lists of both included and excluded studies were examined to identify any further relevant reports.

A set of keyword combinations were used to search the literature in all the databases to ensure that all relevant articles were screened. (Table 2)+

Table 2: Search Strategy for Systematic Review on tissue adhesives in periodontal surgery.

PICO Element	Key Concepts	Search Terms (Keywords & MeSH)	Boolean Operators
Population	periodontal surgery	"Periodontitis", "periodontal surgery", "periodontal plastic surgery" "surgery", "surgical management", "periodontal regeneration", "Periodontal flap surgery"	Combined with AND
Intervention	Tissue adhesive	"cyanoacrylate", "N-butyl cyanoacrylate" , "Tissue adhesive"	Combined with AND
Comparison	Traditional suturing methods	"conventional suturing", "polylactic acid" "silk", "catgut"	Optional (included in some searches)
Outcomes	Efficacy & clinical outcomes	"Healing index", "pain", "post-op pain", "post-operative pain"	Combined with AND
Study	Relevant study types	"randomized controlled trial", "RCT", "Comparative clinical	Combined with AND

Designs		trial". "Non randomized controlled trial"	

1. For PUBMED and MEDLINE: the following search limits were set. (Table 3)

Filter
- Title/Abstract
- Clinical Trial
- Publication date up to 31/12/2024
- Human study
- English language

Table 3: Search strategy for PubMed and Medline.

S. No	Category	Search terms
1.	Population	("Periodontitis" [Title/Abstract]) OR ("periodontal surgery" [Title/Abstract]) AND ("periodontal plastic surgery" [Title/Abstract]) OR ("surgery" [Title/Abstract]) OR ("surgical management" [Title/Abstract]) OR ("periodontal regeneration" [Title/Abstract]) OR ("Periodontal flap surgery" [Title/Abstract])
2.	Intervention	("cyanoacrylate" [Title/Abstract]) OR ("N-butyl cyanoacrylate" [Title/Abstract]) OR ("Tissue adhesive" [Title/Abstract]) AND ("conventional suturing" [Title/Abstract]) OR ("polylactic acid" [Title/Abstract]) OR ("silk" [Title/Abstract]) OR ("catgut" [Title/Abstract])
3.	Outcome	("Healing index"[Mesh]) AND ("pain]) AND ("post-op pain" [Title/Abstract])) AND ("post-op pain" [Title/Abstract])
4.		1 AND 2 AND 3

2. **For CENTRAL Cochrane:** The search on CENTRAL Cochrane was carried out in a similar way and word variations were applied. (Table 4)

Filter-
- Title/Abstract/Keywords
- Clinical Trial
- Human Trial
- Publication date upto 31/12/2024

Table 4: Search strategy for Cochrane.

S. No	Category	Search terms
1.	Population	#1 MeSH descriptor: [("periodontal surgery"] explode all trees
		#2 (("Periodontitis" [Title/Abstract])) OR ("periodontal surgery" [Title/Abstract])) AND ((("periodontal plastic surgery" [Title/Abstract])) OR ("surgery" [Title/Abstract])) OR ("surgical management" [Title/Abstract]))) OR ("periodontal regeneration" [Title/Abstract]))] OR ("Periodontal flap surgery" [Title/Abstract])) : ti,ab,kw (Word variations have been searched)
2.		#1 or #2
3..	Intervention	#3 MeSH descriptor: ["Cyanoacrylate"] explode all trees
		#4 ("cyanoacrylate" [Title/Abstract])) OR ("N-butyl cyanoacrylate" [Title/Abstract])) OR ((("Tissue adhesive" [Title/Abstract])): ti,ab,kw (Word variations have been searched)
4.		#3 or #4
5	Comparison	#5 MeSH descriptor: ["conventional suturing"] explode all trees
6		#6 ("conventional suturing" [Title/Abstract])) OR ("polylactic acid" [Title/Abstract])) OR ("silk" [Title/Abstract])) OR ("catgut" [Title/Abstract])): ti,ab,kw (Word variations have been searched)
		#2 or #4 or #5 or #6

3. Google scholar: The search on Google Scholar was carried out by using the keywords - "periodontal surgery", "tissue adhesive", "cyanoacrylate", "conventional suturing", "soft tissue healing".
4. Scopus and Embase: The search on Scopus and Embase was done as follows; TITLE-ABS-KEY("periodontal surgery", "tissue adhesive", "cyanoacrylate", "conventional suturing", "soft tissue healing".)

The references of all eligible studies identified by the search were checked to find other relevant studies, while the grey literature search was not made systematically.

Eligibility criteria

Inclusion Criteria

1. Studies published in English with full-text availability.
2. Human studies only.

3. Studies published between January 1, 2000, and December 31, 2024.
4. Study designs: only Randomized Controlled Trials (RCTs),
5. Studies evaluating the effectiveness of cyanoacrylates tissue adhesive placed in patients undergoing periodontal surgery for the purpose of wound closure.

Exclusion Criteria

1. Systematic reviews with or without meta-analysis, Non - randomized controlled trials, cohort, and comparative studies case reports, case series, and expert opinions were excluded.
2. Articles are available in languages other than English
3. Animal research or in vitro studies.
4. Only abstracts or articles where full-text versions were not available
5. Studies not evaluating the effectiveness of cyanoacrylates tissue adhesive placed in patients undergoing periodontal surgery for the purpose of wound closure.

Study Selection

The study selection process consisted of two stages. Initially, two reviewers independently evaluated the chosen articles based on their titles and abstracts. Using predefined selection criteria, the studies were categorized as either relevant or irrelevant. Subsequently, the full texts of the relevant studies underwent a second and final analysis, again applying the same criteria. Irrelevant articles were excluded. If needed, a third author was consulted.

Data Collection Process

From the finalized papers, the following information was retrieved.

Study Characteristics

- First author and publication year
- Country of origin
- Study design (RCT)
- Study period and duration of follow-up
- Sample size (total and per group)
- Funding sources and conflicts of interest

2. Participant Characteristics

- Demographic data (age, gender)
- Periodontal surgery (type, location)
- Inclusion/exclusion criteria
- Baseline comparability between groups

3. Intervention Details

- Tissue adhesive used (type)
- Intervention group methodology
- Comparator group methodology

4. Outcome Data

- Primary outcomes:
  - o Healing index
  - o Pain scores

5. RESULTS

- Key findings with measures of effect
- Statistical significance
- Adjustments for confounding

Risk of Bias and Quality Assessment

To determine the validity of the included RCTs, a tool developed by the Cochrane Collaboration was used to assess the risk of bias in clinical trials. Using this tool, the reviewer evaluated the risk of bias of the selected studies using the following parameters: random sequence generation, allocation concealment, blinding of participants and personnel, analysis intention (blinding of outcome assessment), incomplete outcome data, selective reporting (selection of the reported results), and other types of bias not considered previously (e.g., design bias, contamination bias). The methodological quality of each study was classified as low, high, or unclear risk.

Data Synthesis

A narrative synthesis of the findings will be provided based on the included studies, structured around the type of intervention, target population characteristics, type of outcome, and intervention content. Summaries of intervention effects for each study were calculated by risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). Meta-analysis was performed due to the adequate availability of data and the homogeneity of the indices.

Statistical Analysis

Meta-analyses using a random effects model were performed with RevMan 5.4 (RevMan 5.4, The Nordic Cochrane Centre, Copenhagen). Heterogeneity was assessed using the Q test and quantified with I^2 statistics. Data on means and standard deviations and event frequency and total sample size were obtained from the selected studies. For analyses, if the test showed substantial heterogeneity ($I^2 > 50\%$), a random effects model was applied; otherwise, if $I^2 \leq 50\%$, a fixed effects model was used.

RESULT

Synthesis Of Results

A narrative synthesis was provided for the findings from the included studies, focusing on intervention details, characteristics of participants (age, gender), inclusion criteria, exclusion criteria, study designs, outcome, and summaries of intervention effects for studies were provided by calculating mean and standardized mean difference (for continuous outcomes).

The heterogeneity of previously mentioned characteristics was assessed using chi-square test (significance 0.1) and I^2 statistics. If a high level of heterogeneity exists (I^2=50% or $p \leq 0.1$), a random effects model was used. The characteristics of the

included trials were analyzed and sources of heterogeneity might be explained by subgroup analysis or sensitivity analysis.

Literature search

The systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a rigorous and transparent selection process. Initially, 362 records were identified through comprehensive database searches (PubMed=142, Embase=103, Cochrane=45, Web of Science=37) and additional sources (Google Scholar=23, manual searches=12). After removing 35 duplicates, 327 unique records underwent title and abstract screening, during which 285 records were excluded primarily for focusing on irrelevant populations (n=120), non-VSP interventions (n=90), being review articles (n=50), or animal studies (n=25). The remaining 42 full-text articles were assessed for eligibility, with 35 excluded due to lack of comparative data (n=15), small sample sizes (n=8), non-English language (n=5), being conference abstracts (n=4), or duplicate data (n=3). Ultimately, 7 studies met all inclusion criteria and were included in the qualitative and quantitative synthesis. This multi-stage screening process, documented with explicit exclusion criteria, ensured only the most relevant and methodologically sound studies were incorporated into the final analysis. The process of study selection is documented in the PRISMA flowchart in Figure 1 and Table 5.

Table 5; study selection process.

	Identification, Screening, Eligibility, and Included Studies process
Records Identified	Database Searches: PubMed: 142 Embase: 103 Cochrane Library: 45 Web of Science: 37 Other Sources: Google Scholar: 23 Manual Search (Reference Lists): 12 Total Records Identified: 362
Screening	Records After Duplicates Removed: 327 Screening (Title/Abstract) Records Screened: 327 Records Excluded: 285 Reasons: Irrelevant population (n=120), Non-VSP interventions (n=90), Review articles (n=50), Animal studies (n=25)
Eligibility Assessment	Eligibility (Full-Text) Full-Text Articles Assessed: 42 Full-Text Excluded: 35 Reasons: No comparative data (n=15) Sample size <10 (n=8) Non-English language (n=5) Conference abstracts (n=4) Duplicate data (n=3)
Final inclusion	Studies Included in Review: 7

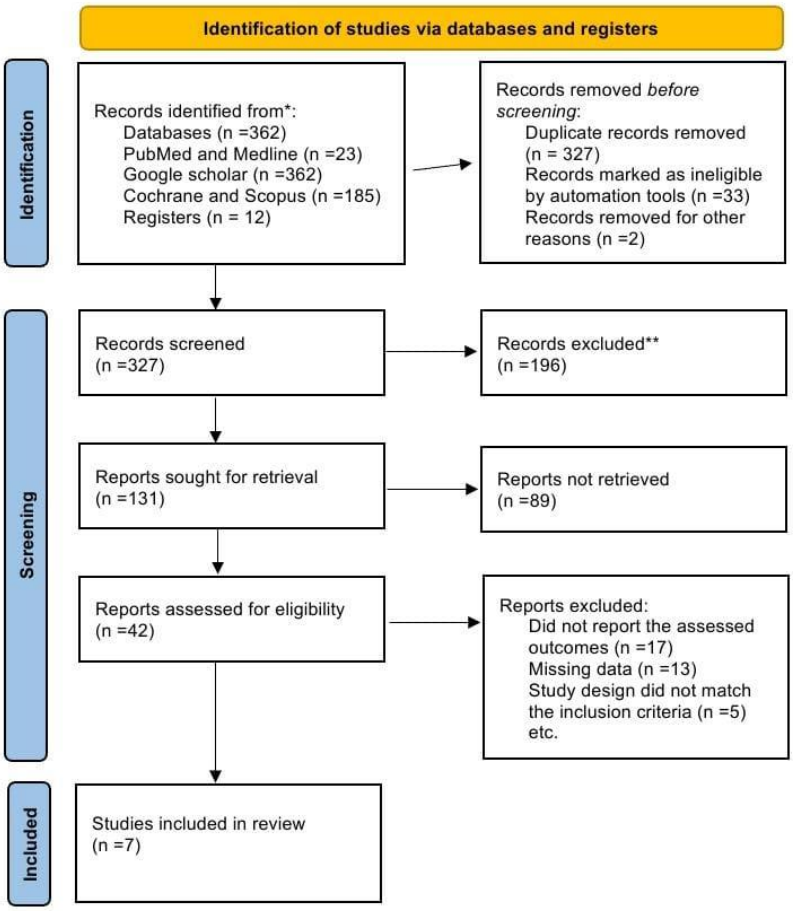


Figure 1; process of study selection.

Characteristics of included studies

A total of seven studies were included in the review. The characteristics of the included studies are summarised in table 6, 7, and 8.

Table 6: Characteristics of Included Studies (PICOS Framework).

Sno	Author name, year and country	Study design	Sample population	Group allocation	Follow up
1	Kulkarni et al 2006 [24] India	Randomised controlled Split mouth design	24 patients	Group A - 7th day group; Group B - 21st day group; Group C - 6th weekday group.	21st day
2	Khurana et al 2016 [21] India	Randomised controlled Split mouth design	20 patients with 40 sites	Group A Suture sites (SS): closed with 3-0 silk suture. N=20 Group B Cyanoacrylate sites (CS): closed with N-butyl cyanoacrylate N=20	2 weeks, 6 weeks, and 3 months
3	Abullais Saquib et al 2018 [20] India	Randomised controlled Split mouth design	30 patients with 60 sites	Group A Suture sites (SS): closed with 3-0 silk suture. N=30 Group B Cyanoacrylate sites (CS): closed with N-butyl cyanoacrylate N=30	Seventh, 21st and 42nd day
4	Lorenzo Tavelli et al 2018 [26]	Randomized Controlled	Fifty patients who	five groups: (1) a control group in which only sutures were applied; (2) a	2 weeks

	Sweden.	Clinical Study	needed a mucogingival surgery	cyanoacrylate group; (3) a periodontal dressing material group; (4) a haemostatic gelatin sponge group; and (5) a group in which the gelatin sponge and cyanoacrylate were combined	
5	Alhourani et al 2021 [23] Syria	Randomised controlled Split mouth design	12 patients with 24 sites male 3 female 9	Group A Cyanoacrylate sites (CS): closed with N-butyl cyanoacrylate N=20 Group B Suture sites (SS): closed with 3-0 silk suture. N=20	1 week, 2 weeks, 1 month, and 2 months
6	Hussein S. Basma et al 2022 [25] USA	four-arm randomized controlled clinical trial	72 patients,	four groups. Control: collagen plug + sutures (CPS); test: collagen plug with cyano-acrylate (CPC), platelet rich fibrin (PRF) + sutures, or palatal stent only (PS)	14 days
7	Gautam et al 2024 [22] India	Randomised controlled Split mouth design	20 patients with 40 sites	Group A Cyanoacrylate sites (CS): closed with N-butyl cyanoacrylate N=20 Group B Suture sites (SS): closed with 3-0 silk suture. N=20	third, fifth, seventh, and 14th days.

Table 7: outcomes assessed in the included studies.

So	Author name year and country	Wound healing	Pain	Other outcomes
1	Kulkarni et al 2006 [24] India	**A group** Suture 11.48 Cyanoacrylate 9.00 **B group** Suture 9.137 Cyanoacrylate 9.329 **Group C** Suture 8.625 Cyanoacrylate 8.500		**plaque scores** **Group A** Suture 1.576 Cyanoacrylate 1.149 **Group B** Suture 1.311 Cyanoacrylate 1.118 **Group C** Suture 1.218 Cyanoacrylate 0.995
2	Khurana et al 2016 [21] India	**SS** 1 week- 1.44 2 week-1.00 **CS** 1 week- 1.09 2 week-1.00	**SS** 1 week- 65 **CS** 1 week- 0	**Plaque index improvement** SS-53.9% CS-56% **Bleeding index improvement** SS-99.2% CS-100% **Probing depth improvement** SS-68.9% CS-71.1%
3	Abullais Saquib et al 2018 [20] India	**SS Group** 7 days 1.5867±0.1685 21 days 1.2933±0.1335 42 days 1.0 **CS group** 7 das-1.1933±0.0594 21 days-1.0867±0.0916 42 days 1.0	-	**Plaque index** **SS Group** Baseline - 0.713±0.145 7 days 2.613±0.2134 21 days 1.087±0.1522 42 days 0.743±0.0985 **CS group** Baseline-0.733±0.1543 7 days-1.753±0.1302 21 days-1.04±0.0986 42 days -0.74±0.091 **gingival index** **SS Group**

				Baseline - 0.667±0.0816 7 days 1.6067±0.096 21 days 0.866±0.134 42 days 0.693±0.099 **CS group** Baseline-00.6867±0.0743 7 days-1.313±0.064 21 days-0.946±0.130 42 days -0.693±0.070
4	Lorenzo Tavelli et al 2018 [26] Sweden.	-	**Day 1** Control-2.8 Periacryl-1.7 Spongostan-1.3 peripac-1.7 Spongostan+ periacryl- 0.3 **Day 5** Control-1.6 Periacryl-1.3 Spongostan-1.3 peripac-1 Spongostan+ periacryl- 0.3 **Day 14** Control-0.5 Periacryl-0 Spongostan-0.4 peripac-0.2 Spongostan+ periacryl- 0	-
5	Alhourani et al 2021 [23] Syria	**Group I (CS)** after 1 week 1.000 after 2 weeks 0.007 after 1 month 0.002 after 2 months 0.002 **Group II (SS)** after 1 week 1.000 after 2 weeks 0.020 after 1 month after 2 months 0.002	**Group I (CS)** Day 3 - 2.80 Day 5 - 1.50 Day 7 - 0.70 Day 14 - 0.20 **Group II (SS)** Day 3 - 2.90 Day 5 - 0.80 Day 7 - 0.30 Day 14 - 0.10	Graft size [mm2] Group I (CS) During surgery-43.25 ±7.03 After 2 months-28.83 ±6.37 After 3 months-25.08 ±5.12 After 6 months-19.08 ±4.78 **Group II (SS)** During surgery-43.25 ±7.03 After 2 months-28.00 ±5.83 After 3 months-21.08 ±3.92 After 6 months-16.83 ±4.84
6	Hussein S. Basma et al 2022 [25] USA		2.1 (±2.5), 2.2 (±2.8), 2.0 (±2.6), and 1.5 (±1.8) for CPS, CPC, PRF, and PS, respectively.	Pills consumed CPS-21.5 (10-29) CPC - 15 (0-62) PRF 11.5 (0-23) PF 7.5 (0-12)
7	Gautam et al 2024 [22] India	**Group I (CS)** Day 3 - 1.80 Day 5 - 2.40 Day 7 - 3.20 Day 14 - 3.80 **Group II (SS)** Day 3 - 2.30 Day 5 - 2.80	**Group I (CS)** Day 3 - 2.80 Day 5 - 1.50 Day 7 - 0.70 Day 14 - 0.20 **Group II (SS)** Day 3 - 2.90 Day 5 - 0.80	**Use of analgesics** **Group I (CS)** Day 3 - 5.300 Day 5 - 2.000 Day 7 - 0 Day 14 - 0 **Group II (SS)** Day 3 - 3.200

		Day 7 - 3.40 Day 14 - 4.20	Day 7 - 0.30 Day 14 - 0.10	Day 5 - 0 Day 7 - 0 Day 14 - 0

Table 8: key findings of the included studies.

So	Author name year and country	Key findings	Conclusion
1	Kulkarni et al 2006 [24] India	Plaque index scores of the suture and the cyanoacrylate sites in the 7th day group (Group A) were significantly different (P < 0.01) The gingival index scores of sutures and cyanoacrylates were compared; the scores showed statistically significant difference in Group A (P < 0.01) The epithelium did not show any signs of atrophy, hypertrophy or dysplasia. Connective tissue appeared disorganized, with high amount of inflammatory cells at 7 days on both the suture and cyanoacrylate sides. But on the 21st day and 6th weekday, the gingival connective tissue had more organized connective tissue fibres, with less number of inflammatory cells. The chronic inflammatory cells were present on all the three observation days in both the sites. Statistically significant (P < 0.01) difference between the suture and cyanoacrylate sites was detected only in Group A	Cyanoacrylate aids in early initial healing
2	Khurana et al 2016 [21] India	The relative improvement in plaque index is not significantly different between Group A and Group B The early healing index is not significantly different between Group A and Group B in the 2nd week There is no significant difference in bleeding index is Group A and Group B There is no statistically significant difference in improvement in probing depth between Group A and Group B None of the cases from Group A and Group B had burning/itching sensation Group B showed esthetical acceptability The incidence of pain/discomfort is significantly higher in Group A compared to Group B, the difference being statistically significant with P = 0.001. The incidence of redness did not differ significantly between Group A and Group B with P = 0.147. Absence of crater formation at the tip of papillae and absence of loss of sutures in both the groups	Cyanoacrylate aids in early initial healing.
3	Abullais Saquib et al 2018 [20] India	Plaque index score observed at cyanoacrylate sites was lesser as compared to suture sites with statistical significance at seventh day indicating that plaque control was better when flaps were closed with cyanoacrylate as compared to silk sutures Gingival index score observed at cyanoacrylate sites was lesser as compared to suture sites with statistical significance at seventh day indicating that gingival inflammation was lesser when flaps were closed with cyanoacrylate as compared to silk suture Wound Healing index score observed at cyanoacrylate sites was also lesser as compared to suture sites with statistical significance at seventh day Inflammatory cells at cyanoacrylate sites were lesser as compared to suture sites with statistical significance on the seventh day Connective tissue fibres observed at cyanoacrylate sites were more as compared to suture sites with statistically significance on seventh day	The closure of periodontal flaps with cyanoacrylate results in better initial post-operative healing as compared to closure with silk suture and that this method of closure can be advocated in a routine surgical periodontal practice.
4	Lorenzo Tavelli et al 2018 [26]	The overall difference in postoperative palatal pain was statistically significant between the DLP and the control group (P < .01). In particular, during the first and second days after the harvesting, this	The use of a gelatin sponge and cyanoacrylate might reduce pain and postoperative

	Sweden.	difference between the DLP group and the control group was statistically significant (P < .05). The apicocoronal dimension of the graft (graft height) contributed to the perception of pain during the first 7 days following the surgery: the higher the graft, the more pain was experienced by the patients (0.4 VAS points per 1 mm on aver-age; P < .05) The age was inversely correlated with pain, with statistically significant differences during postoperative days 3 through 7 (–0.03 VAS points per 10 years on average, P < .05).	discomfort. Pain was correlated with graft height and inversely correlated with age.
5	Alhourani et al 2021 [23] Syria	There were no significant differences between the 2 sites after 1 week, 2 weeks, 1 month, and 2 months. However, the healing process was completed 1 month postoperatively in the tissue adhesive group, whereas in the suture group, it lasted up to 2 months The VAS score at the recipient site decreased from day 1 and reached minimum at day 3 in the tissue adhesive group, while the same pain minimum level was achieved on day 4 in the suture group The size of the graft reduced significantly within the 2 groups at 2, 3 and 6 months after the surgery ($p < 0.05$). After 2 and 6 months, there were no significant differences between the 2 groups. However, after 3 months, the cyanoacrylate group showed significantly less shrinkage as compared to the other group	A tissue adhesive could be a reliable alternative material to sutures in stabilizing FGG at the recipient site. It reduced postoperative pain and improved the healing of the recipient site.
6	Hussein S. Basma et al 2022 [25] USA	The VAS values were only statistically significant for days 7 and 8 when comparing the collagen plug and platelet rich fibrin groups. After 10 days, the difference in VAS values diminished among groups Amount of swelling - The average daily mean scores were 2.2 (±2.4), 1.4 (±2.0), 1.3 (±1.9),and 1.3 (±2.0) for CPS, CPC, PRF, and PS, respectively. The Activity tolerance test were 2.4 (±2.4), 1.8 (±2.4), 1.5(±2.1), and 1.3 (±1.8) for CPS, CPC, PRF, and PS, respectively The average daily mean scores were 2.1 (±2.5), 2.2(±2.8), 2.0 (±2.6), and 1.5 (±1.8) for CPS, CPC, PRF, and PS, respectively. There was a difference in graft thickness that was found to be statistically significant (P = 0.0472) among groups;	The use of a palatal stent seemed to be associated with less overall pain, pain pills consumed, and higher willingness of doing the same procedure again.
7	Gautam et al 2024 [22] India	The mean score of the verbal rating scale and wound healing index differ significantly at different intervals of time ($p < 0.001$). The mean difference of the analgesics between Group 1 and Group 2, the mean score statistically differed from each other on days three and five, respectively, but the p-value was not calculated in the case of days seven and 14 because the mean difference is zero in this case No statistically significant difference between the verbal rating scale and wound healing index at different levels of intervals during the intergroup comparison	Isoamyl 2-cyanoacrylate can be used as an alternative to conventional silk sutures as it decreases post-operative pain and discomfort.

Characteristics of the individual studies

Kulkarni et al 2006[24] performed a study to assess the healing of the periodontal flaps when closed with the conventional silk sutures and N-butyl cyanoacrylate. 24 patients who needed flap surgical procedure for pocket therapy were included in the study. It was found that healing with the cyanoacrylate is associated with less amount of inflammation during the first week when compared with silk. However, over a period of 21 days to 6 weeks, the sites treated with both the materials showed similar healing patterns. The authors concluded that cyanoacrylate aids in early initial healing.

Khurana et al 2016[21] performed a study with split mouth design on 20 patients to compare healing after periodontal flap surgery using isoamyl 2-cyanoacrylate (bioadhesive material) and silk sutures. One side was closed with 3-0 black silk sutures and N-butyl cyanoacrylate adhesive on the other side. The results showed that there is a relative improvement in plaque index is not significantly different between Group A and Group B The early healing index is not significantly different between Group A and Group B in the 2nd week There is no significant difference in bleeding index is Group A and Group B. There is no statistically significant difference in improvement in probing depth

between Group A and Group B. None of the cases from Group A and Group B had burning/itching sensation. Group B showed esthetical acceptability. The incidence of pain/discomfort is significantly higher in Group A compared to Group B, the difference being statistically significant with P = 0.001. The incidence of redness did not differ significantly between Group A and Group B with P = 0.147. Absence of crater formation at the tip of papillae and absence of loss of sutures in both the groups. The authors concluded that cyanoacrylate aids in early initial healing.

Abullais Saquib et al 2018[20] **pe**rformed a study on 30 patients undergoing bilateral flap surgery to compare effectiveness of the black silk suture with cyanoacrylate adhesives in closing reflected periodontal flap. One side was closed with 3-0 black silk sutures and N-butyl cyanoacrylate adhesive on the other side. The authors observed that the amount of inflammation was less during the first week of healing when cyanoacrylate was compared with silk. Plaque index score and gingival index was lesser at cyanoacrylate sites than suture sites. Wound Healing index score observed at cyanoacrylate sites was also lesser as compared to suture sites. The authors concluded that the closure of periodontal flaps results in better initial post-operative healing as compared to closure with silk suture and that this method of closure can be advocated in a routine surgical periodontal practice.

Lorenzo Tavelli et al 2018[26] performed a study to evaluate the impact of different haemostatic treatments following palatal gingival harvesting on patient discomfort. Fifty patients who needed a mucogingival surgery requiring gingival graft harvesting were enrolled and randomly assigned to one of five groups: (1) a control group in which only sutures were applied; (2) a cyanoacrylate group; (3) a periodontal dressing material group; (4) a haemostatic gelatin sponge group; and (5) a group in which the gelatin sponge and cyanoacrylate were combined. In the 2 weeks following the procedures, perception of pain, healing, consumption of drugs, and willingness to repeat the procedure were recorded through visual analog scale (VAS) by patients. Over the 2 weeks, lower pain (VAS) was found in all test groups compared to the control group (P < .01, value for time-group interaction). Notably, the gelatin sponge combined with cyanoacrylate group had very low pain (VAS ≤ 0.5 points) throughout the 14 days. The lowest healing scores at day 10 were associated with the control group (6.8 VAS points) in contrast to the four test groups (8.2 to 9.0 VAS points, P = .0001). Pain was inversely correlated with age (P < .05). Pain also depended on the apicocoronal dimension of the graft: the higher the graft, the more pain was experienced by the participants (0.4 VAS points per 1 mm, P < .05). Within the limitations of this study, palatal coverage appears to result in better outcomes when compared to suture alone. In particular, a double-layered protection of the palatal wound with a gelatin sponge combined with cyanoacrylate appeared to be the best option in reducing pain and postoperative discomfort.

Alhourani et al 2021[23] performed a study to compare the use of the tissue adhesive N-butyl cyanoacrylate + octyl cyanoacrylate (N-BCA + OCA; Iceberg-glue®) and surgical sutures to evaluate the stabilization and fixation of FGG, which is indicated to increase the width of the keratinized attached gingiva. A total of 24 cases – 12 patients aged 18–45 years with gingival recession and the absence of the keratinized gingiva underwent FGG surgery at 2 parallel sites at the same time. A long piece of FGG was taken from the palate, from the area adjacent to a canine to a second molar, and divided into 2 equal pieces. The bed of the graft was prepared at each side with a 15C blade. One piece was applied to each bed; one graft was sutured using 0/5 nylon sutures and the other one was stabilized using the tissue adhesive. The data analysis showed that the postoperative pain ended after 3 days at the tissue adhesive site, but it continued up to 4 days at the suture site. The healing index was significantly better after 2 months at the tissue adhesive site. Graft shrinkage was significantly lower after 3 months at the tissue adhesive site, whereas there was no significant difference in graft shrinkage between the 2 methods at 6 months after the surgery. The authors concluded that the Iceberg-glue tissue adhesive proved to be a reliable alternative material to sutures in stabilizing the free gingival graft at the recipient site. It reduced postoperative pain and improved the healing of the recipient site.

Hussein S. Basma et al 2022[25] performed a study to compare the effects of four different commonly used wound dressings in improving patient reported outcomes (PROMS) after free epithelialized mucosal grafts (FEGs) harvesting. Following 72 FEGs harvesting from 72 patients, patients were assigned into four groups. Control: collagen plug + sutures (CPS); test: collagen plug with cyano-acrylate (CPC), platelet rich fibrin (PRF) + sutures, or palatal stent only (PS). Compared to the control group all test groups indicated significant lower pain perception (P < 0.0001), lower analgesic consumption (P < 0.0001), and higher willingness for retreatment (P < 0.0001), while no statistically significant differences among test groups were observed. There were no statistically significant differences in amount of day-by-day swelling, bleeding, and activity tolerance among four groups. Compared to other groups, the PS had the lowest overall pain scores (over the 14-day period). Palatal thickness, graft length, graft width, and graft thickness did not appear to affect patient morbidity (P > 0.05). The authors concluded that all interventions significantly decreased pain perception compared to a hemostatic collagen sponge alone over the palatal donor site after FEG.

Gautam et al 2024[22] performed a study to assess clinical outcomes by comparing the healing after periodontal flap surgery when secured with 3-0 braided

silk suture versus cyanoacrylate. Twenty surgical sites from 10 patients with moderate to severe periodontitis were selected and randomly divided into two groups after phase-1 therapy: the test group (isoamyl 2-cyanoacrylate) and the control group (3-0 silk braided suture). The results showed that the mean score of the verbal rating scale and wound healing index differ significantly at different intervals of time ($p < 0.001$)..The mean difference of the analgesics between Group 1 and Group 2, the mean score statistically differed from each other on days three and five, respectively, but the p-value was not calculated in the case of days seven and 14 because the mean difference is zero in this case. No statistically significant difference between the verbal rating scale and wound healing index at different levels of intervals during the intergroup comparison. The authors concluded that isoamyl 2-cyanoacrylate can be used as an alternative to conventional silk sutures as it decreases postoperative pain and discomfort.

Risk of bias assessment

To determine the validity of the included RCTs, a tool developed by the Cochrane Collaboration was used to assess the risk of bias in clinical trials. Random sequence generation was reported adequately only in two studies by Basma et al and Tavelli et al. In other studies, the method of randomization was not mentioned. Therefore, the domain of random sequence generation was categorized as having an unclear risk. Allocation concealment was reported adequately only in two studies by Alhourani et al and Tavelli et al and was categorized as high risk. The nature of the interventions did not allow participant and examiner blinding; however, knowledge of interventions to the investigator could have resulted in bias and hence it was categorized as high risk. Blinding of outcome assessment was reported adequately only in two studies by Alhourani et al and Tavelli et al and was categorized as high risk. There were drop-outs in all studies; however, drop-outs were compensated by increasing the sample size before the start of the study and hence termed as low risk. Selective reporting was rated as having an unclear risk since the protocol was available for only one study by Alhourani et al. Other unspecified types of bias were also considered as associated with the lack of information on sample size estimation, examiner calibration, etc. Sample size estimation was reported in only two studies by Alhourani et al and Basma et al.

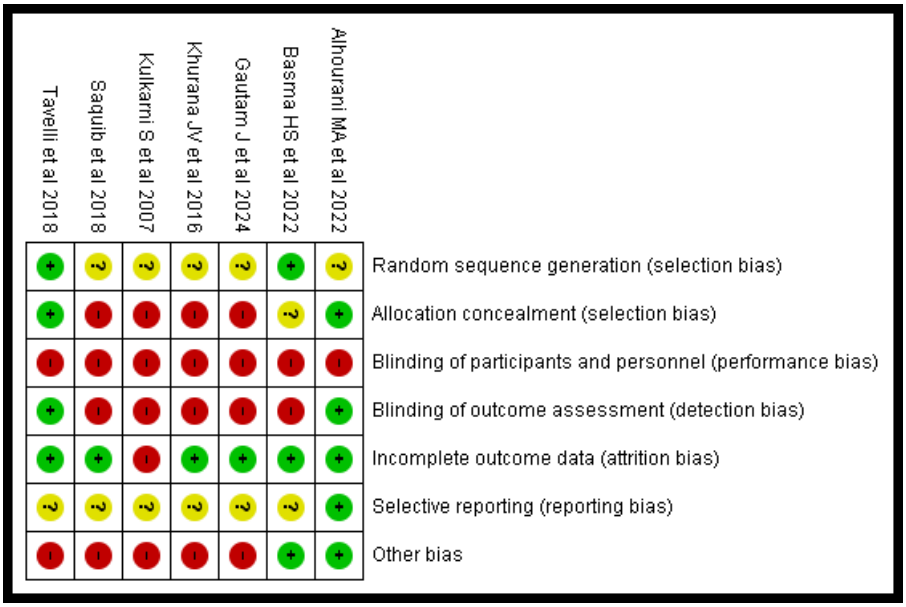


Figure 2; Risk of bias assessment for the included studies with RoB 2 tool; a)Risk of bias domains: Traffic-light plot of individual studies.

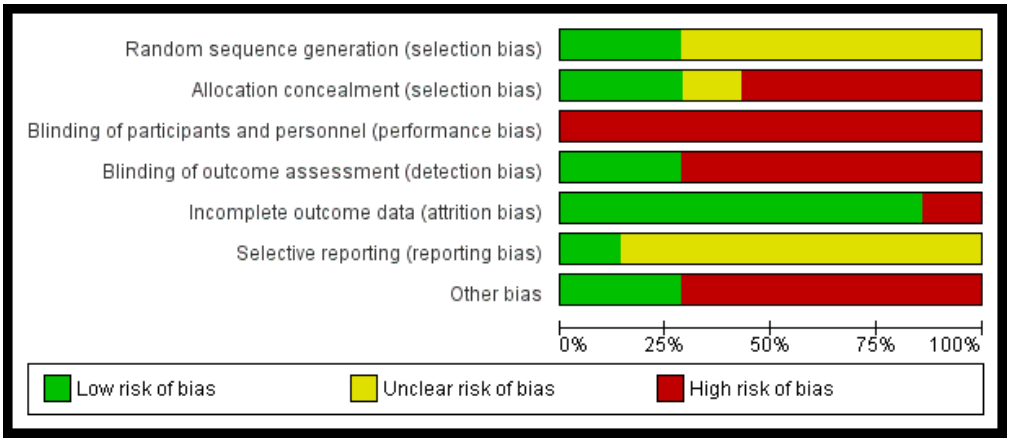


Figure 3; Summary Plot: Review authors' judgements about each risk of bias item for each included study.

Meta-analysis: **Comparison of healing after 7-10 days between cyanoacrylate adhesive and sutures**

Meta-analysis was performed on three studies that qualified with the required data outcome that could be analyzed quantitatively. The results of the overall comparison have been depicted as a forest plot. With the meta-analysis conducted for selected studies, heterogeneity was more than 50% (I2 = 97%); hence, a random effects model was applied. The mean healing index score did not differ significantly between the cyanoacrylate adhesive and suture groups with a standardized mean difference of –0.26 (95% CI = -3.25 to 2.72; Z value = 0.17; p=0.86). (fig 4)

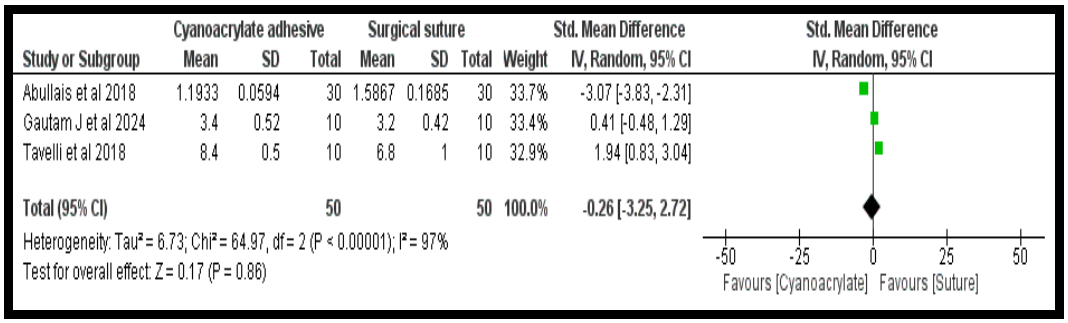


Figure 4: forest plot depicting Comparison of healing after 7-10 days between cyanoacrylate adhesive and sutures.

DISCUSSION

Cyanoacrylates, particularly n-butyl and isoamyl derivatives, are increasingly used in periodontal surgery as alternatives to traditional sutures.[15] The use of cyanoacrylate adhesive (CA) is used in medicine for the same goal to achieve closing traumatic and surgical incisions.[27,28-31]

This adhesive is maintained in a liquid state by an acidic stabilizer, is partially ionized molecules of water, and has the action of neutralizing the inhibitor. Once applied the adhesive in the tissue it gradually polymerizes to a solid state in 10 seconds for the contact with blood or saliva.[32]

The cyanoacrylate has become the most popular and common adhesive tissue that offers several clinical advantages. These tissue adhesives provide a combination of hemostatic, bacteriostatic, and wound-stabilizing properties.[33,34] Additionally, This material has good bonding properties. The bond strength to hold the tissue margins together, simplifying surgical procedures and enhancing patient comfort. It also has good working properties like the flow and fast setting i.e. within 5 to 10 seconds.[35-38]

The present study aims to evaluate and compare the effectiveness of cyanoacrylates as a tissue adhesive to conventional suturing in terms of healing and post-operative pain by systematic review and meta-analysis. A total of 7 studies were included in the present review. All the 7 studies were randomised controlled trials and evaluated the effectiveness of cyanoacrylates in split mouth design.

Wound Healing

The Meta-analysis in the present study indicates that the mean healing index score did not differ significantly between the cyanoacrylate adhesive and suture groups. Saquib et al[19] reported that on seventh day WHI scores between the suture and the cyanoacrylate sites showed a significant difference with suture sites exhibiting increased score. A better healing response was exhibited at cyanoacrylate sites in comparison to suture sites. As healing progressed at 42nd day no statistically significant

difference was reported in scores between suture and cyanoacrylate sites.

Similarly, Khurana, et al.[21] reported that the statistically significant difference was seen when redness, crater formation at tip of papillae, loss of suture, and accumulation of materia alba were assessed after 1 week between the sutured site and the site where isoamyl 2-cyanoacrylate was applied. The absence of redness, absence of crater formation at the tip of papilla and absence of Materia alba were seen in the site where isoamyl 2-cyanoacrylate was applied. Gautam et al[22] reported that there is no statistically significant difference between the verbal rating scale and wound healing index at different intervals during intergroup comparison, but the number of analgesics consumed post-operatively was less in the cyanoacrylate group as compared to the control group.

Alhourani et al[23] reported that there were no significant differences between the cyanoacrylates and suture group after 1 week, 2 weeks, 1 month, and 2 months. However, the healing process was completed 1 month postoperatively in the tissue adhesive group, whereas in the suture group, it lasted up to 2 months.

Sadatmansouri et al[43] in 2020, evaluated early healing using cyanoacrylate tissue adhesive. They found no statistically significant difference between sutures and the cyanoacrylate group. The better wound healing results may be increased connective tissue fibers in Cyanoacrylate sites in comparison to suture sites on the seventh day.[19] Kulkarni et al.[24] conducted a clinical and histological study to compare healing after periodontal flap surgery. The results of their study depicted better healing in the cyanoacrylate group both clinically and histologically.

Similarly, Paknejad et al.[48] found a significant difference between the 2 groups in the healing process after 10 days, though there were no significant differences in the healing process after 20 and 90 days.

Pain

The results of Khurana, et al.[21] study reported that Isoamyl 2-cyanoacrylate showed the absence of pain/discomfort, absence of burning/itching and was found to be aesthetically acceptable by all subjects. Alhourani et al[23], Giray et al.[39], Gautam et al[22], and Lorenzo Tavelli et al[26] in their study found that the pain scores were lesser in the Cyanoacrylate group but were not statistically significant. Alhourani et al[23] reported that the VAS score at the recipient site decreased from day 1 and reached a nadir at day 3 in the tissue adhesive group, while the same pain nadir level was achieved on day 4 in the suture group. In contrast, Paknejad et al.[48] found no significant differences in pain levels between the 2 groups.

Basma et al[25] reported that the collagen + cyanoacrylates group had statistically significant less for needing analgesics, willingness to have another FEG surgery performed, and postoperative pain ($P < 0.0001$). CPC also had less postoperative swelling compared to CPS, and less bleeding through the first 5 postoperative days. Patients that were in the CPC group also performed the Activity Tolerance test better for the first 10 days compared to the control group.

Other Outcomes

Gautam et al[22] reported that the duration of surgery, patient comfort, post-operative pain, and number of analgesics taken were less in isoamyl 2-cyanoacrylate group. Similarly, Padhye and Pol[40] stated that cyanoacrylate has an added advantage with respect to time and methodology of diminishing the two-step procedure of suturing followed by dressing to just one step of application of the material.

Time taken during surgical procedures using cyanoacrylate is crucial because it lessens trauma to the patient, fatigue to the surgeon, reduces postoperative swelling and operating time, easier to apply than suture, and more comfort to the patient. Other advantages are, in cyanoacrylate tissue adaptation is better, and healing is faster. Sadatmansouri et al[43] concluded that patient compliance was better in the cyanoacrylate group. Therefore, it can be used as an alternative for wound closure.

Forrest[41] reported that the tissue adaptation is better as it provides fixation of the flap to the whole surface, while sutures provide only marginal fixation. Moreover, cyanoacrylate also saves cost of preparing, sterilization, and storing instruments at the time of suture removal. Advantages of cyanoacrylate from subjects' point of view: removal of sutures is annoying/painful for some patients and there is less discomfort on sutureless sites in the days after surgery.

These advantages overcome the limitations of the Suturing method. The wound suture by suturing is a gold standard technique for post-operative flap closure yet it is technique-sensitive, time consuming procedure and shows wicking action that increases the bacterial infiltration of tissue.[42]

Despite these advantages, it is necessary to consider the toxicity issues regarding the cyanoacrylate's usage. Leggat et al.,[28] reported that cyanoacrylate tissue adhesives pose occupational hazards for workers and are safer for patients. Excessive exposure may lead to respiratory and dermatological ailments.

In periodontal graft surgery, graft shrinkage noticed during the healing period is a major concern that decreases the success rate. The adequate blood supply of the graft affects graft shrinkage; there must not be any factors that disrupt the continuity of graft nutrition.[44,45]

Sullivan and Atkins stated that number of sutures should be decreased to minimum, since every suture induces a localized hematoma under the graft, which may increase graft shrinkage.[46] Alhourani et al[23] reported that the graft shrinkage was significantly lower in Cyanoacrylate group than suture group. Similarly, Gümüş and Buduneli[47] observed that graft shrinkage was significantly lesser at the cyanoacrylate site than at the other two.

In conclusion from the above findings, tissue adhesive could be a reliable alternative material to sutures in periodontal regeneration surgery as cyanoacrylates have benefits of reduced postoperative pain, improved the healing of the recipient site, and ensures improved surgical outcomes.

LIMITATIONS

The present study has few limitations;

- There is a wide heterogeneity among the sample population, type of periodontal surgery, duration of follow up.
- Only seven studies were included in the review and relatively only small sample size was included which may limit the generalizability of the findings to other populations.
- The duration of the outcome assessment in the included studies may have been insufficient to capture long-term outcomes or potential complications associated with the two different methods of wound closure.
- Different chemical composition of the tissue adhesives were used among the studies which may hinder the reliability of the results.
- Since the data was not quantifiable, only one metaanalysis was performed.

CONCLUSION

The main objective for the use of sutures in surgical procedures is to close the wound, bringing together the edges of the incision so that the wound can heal properly. In periodontal regenerative surgery, minimal suturing has suggested to close wounds and additionally reduce the graft shrinkage. The results of the present meta-analysis indicate that the mean healing index score did not differ significantly between the cyanoacrylate adhesive and suture groups.

The present systematic review findings suggest that the cyanoacrylate can be used as an alternative to conventional silk sutures as it decreases postoperative pain and discomfort, shortens the duration of surgery, and better wound healing properties. Thereby, tissue adhesive could be a reliable alternative material to sutures in stabilizing periodontal graft surgery at the recipient site.

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