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REVIEW ARTICLE

Current status of split-mouth controlled clinical trials comparing cyanoacrylate *vs.* conventional suture after lower third molar surgeries: a systematic literature review

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ABSTRACT

Objetive. During the last few years, cyanoacrylate has been used for wound closure in oral and maxillofacial surgery with growing frequency. When comparing cyanoacrylate with sutures, some authors report similar experiences, while others have found differences. Some agree on the similar outcomes obtained between cyanoacrylate and sutures, others have registered better effects with cyanoacrylate, and others with sutures. Therefore, the aim of this systematic review (SR) was to evaluate postoperative parameters – pain, swelling, trismus, healing and complications (bleeding and infection) – after lower third molar (LTM) removal using cyanoacrylate compared with sutures. *Materials and methods*. Electronic and manual literature searches were conducted independently by two reviewers up to March 2022. *Results*. Four studies met the pre-established inclusion criteria and were included for descriptive analysis. These were controlled clinical trials comparing the effects of cyanoacrylate with sutures in 116 patients and 232 split-mouth cases. Pain and haemostasis were significantly reduced on the cyanoacrylate group, swelling showed the same results on two of the studies analysed, trismus and healing had no significant differences between both groups. *Conclusions*. Both techniques were found to be effective in terms of wound closure, proposing cyanoacrylate as an effective resource that should be investigated in future research. Nevertheless, the literature on cyanoacrylate is scarce and lacks comparative studies of its outcomes and effects.

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Suture; cyanoacrylate; third molar; dentistry; adhesive

Introduction

Lower third molar (LTM) extraction is the most common and demanded surgical procedure in oral and maxillofacial surgery [1–3]. The procedure may involve postoperative complications, such as swelling, pain, trismus, infection, or nerve injuries [4,5] which are determined by surgical/intraoperative time, trauma and the surgical complexity of the case [3]. Wound closure plays a very important role in the prevention of these complications [2].

Traditionally, the most commonly used closure method has been conventional sutures (Figure 1) because of the technique's ease of use, low cost and the closure security provided by knots [2,3].

Sutures are classified according to the type of material degradation in absorbable and non-absorbable, the latter being the most used. Although both may have some drawbacks, such as weakening or loss over time, dissolving too soon or remaining in the treated area longer than recommended, thereby causing infection due to biofilm accumulation, they are still the most widely used method in wound closure today. Taking into account these inconveniences and the constant evolution in dentistry, new wound closure techniques have been consequently investigated aimed at limiting these drawbacks [2].

One of these methods is cyanoacrylate (Figure 2), which however offers adhesive properties first described since the end of the 1950s. It was approved by the Food and Drug Administration (FDA) in 1964 [6]. Nevertheless, especially in recent years, cyanoacrylate has been used more and more as a tissue adhesive after the extraction of the LTM [7].

On the one hand and within the advantages of this material, cyanoacrylate benefits from the wet conditions provided by saliva [2], which favour traction resistance and adherence to tissues [3]. Polymerization takes 10–15 s and cyanoacrylate detaches from the mucosa and skin 7–10 d after application [2,3].

On the other hand, and within the limitations of cyanoacrylate, it should be noted that it is difficult to handle and involves a learning curve to acquire the necessary skills; A considerable amount of the material is needed for wound closure, so its price is higher. In addition, possible allergic reactions and a possible relationship with thrombotic events have been described as it has to be placed intravascularly in the wound [5]. In any case, the use of cyanoacrylate

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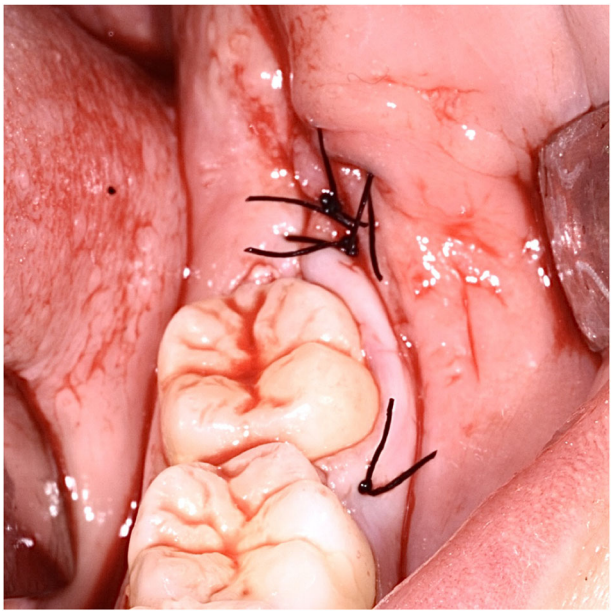

Figure 1. Clinical photo of the suture provided by Dr. Luis Sánchez-Labrador.

Figure 2. Clinical photo of the cyanoacrylate provided by Dr. Luis Sánchez-Labrador.

compared to conventional sutures remains a subject of controversy among professionals [8,9].

To our knowledge, no previous systematic review (SR) has evaluated the effectiveness of cyanoacrylate in comparison with traditional sutures. So, the objectives of this study were to compare postoperative parameters (pain, swelling, trismus and healing) and complications (bleeding and infection) after LTM removal between the two wound closure techniques.

Materials and methods

Development and PICO question review

This SR followed guidelines established in the (Preferred Reporting Items for SR and Meta-Analyses (PRISMA) statement and was registered in the International Prospective Register of Systematic Review (PROSPERO) (Reg. no. CRD42021288032).

Table 1. PICO question.

	PICO question
P	Patients with bilateral lower third molars to be extracted
I	Wound closed with cyanoacrylate
C	Wound closed with suture
O	Pain
	Swelling
	Trismus
	Healing
	Complications (bleeding, infection)

It set out to answer the following PICO (Population, Intervention, Comparison and Outcome) question: 'In patients undergoing bilateral LTM extraction, is the use of cyanoacrylate more effective for closing surgical wounds than sutures?' whereby Population (P) was healthy patients with bilateral LTMs that required extraction; Intervention (I) was third molar extraction and wound closed with cyanoacrylate; Comparison (C) was third molar extraction and wound closed with sutures; and the main outcomes (O) were evaluations of pain, swelling, trismus, healing and complications (bleeding and infection) as shown in Table 1.

Eligibility criteria

Inclusion criteria

- Randomized and controlled split-mouth clinical trials.
- Human clinical studies reporting any of the following data: pain, swelling, trismus, healing and complications (bleeding and infection).
- Patient population:
  - Patients aged 18–35 years with LTMs in similar positions.
  - Bilateral LTMs requiring extraction.
  - Non-smokers.
  - Good systemic and periodontal health, good oral hygiene.
  - No drug allergies.

Exclusion criteria

- Articles design:
  - Animal studies, case reports, editorials, posters, letters to the editor and *in vitro* laboratory studies.
- Studies without comparison between cyanoacrylate and sutures.
- Studies without extraction of third molars.
- Studies with multiple and different surgical procedures.
- Presence of different surgical procedures in addition to LTM.

Type of intervention and comparisons

The selected studies compared the use of cyanoacrylate *vs.* conventional sutures for wound closure after surgical LTM

extraction using a split-mouth model. All items use silk in the same way as does the repositioning of the flap.

On the test side, cyanoacrylate was used for wound closure and healing after LTM extraction. Patients were evaluated either on the first, second and seventh postoperative days; [10] on the first, third and seventh postoperative days; [11] or on the first five postoperative days [12,13].

On the control side, sutures knotted in simple stitches were used for wound closure and healing without any other material after LTM extraction. All studies used silk in the same way when repositioning the flap after LTM removal. Conditions and post-operative evaluations were identical on both sides.

Data collection

The primary outcome used to assess the efficacy of cyanoacrylate was the appearance of primary signs and symptoms (pain and bleeding), secondary signs and symptoms (trismus and healing) and complications (infection) after LTM extraction, on both the test (cyanoacrylate) and control (sutures) sides.

Pain and bleeding were analysed in all studies; not all the other parameters were evaluated in all the studies.

Sources and search strategy

An electronic search was conducted in four electronic databases: The National Library of Medicine (MEDLINE/PubMed); Web of Science; Scopus; and the Cochrane Central Register of Controlled Trials (Table 2).

The search identified studies published in English, Spanish or German with publication dates up to the end of March 2022. In addition, a manual search was made in oral surgery and oral implantology journals for articles published up to the end of March 2022. A manual search in the reference sections of the articles found was also carried out to identify other relevant studies that might have been overlooked. The search strategy was adapted to each of the search engines used as shown in Table 1 and Figure 3.

Study selection and screening methods

Two reviewers (A.O.P. and A.F.S.L.G.) conducted all steps of the selection process independently. Of 86 articles identified in the electronic and manual searches, 60 were excluded as these were duplicates or triplicates. The remaining 26 articles were selected on the basis of title and abstract, rejecting a further 13 after reading the full text (Figure 3). Subsequently, only four articles met all inclusion/exclusion criteria.

Clinical data extraction

The two reviewers performed data extraction in duplicate. When data was incomplete or missing from an article, the authors were contacted. If any doubt arose, data were temporarily excluded until clarification became available. Any disagreement was resolved through consultation with a third reviewer (L.S.L).

The following clinical data were extracted: author(s), year of publication, type of study, number of patients, mean patient age, type of suture and cyanoacrylate, number of third molars extracted, variables studied, variable measurements and study outcomes.

Risk of bias in individual studies

All the studies included were controlled clinical trials [10–13], and used a split-mouth model, evaluating the symptoms and signs listed above.

Risk of bias assessment for randomized clinical trials was performed using the method detailed in the Cochrane Handbook for Systematic Reviews and Interventions version 5.1.0. [14], which consists of seven domains: selection bias, allocation bias, blinding of participants and staff, blinding of outcome assessors, incomplete data, selective reporting of results and other biases. Each were classified as low risk, high risk, or uncertain risk (represented by a green (+), a red (−) or a yellow (?). So, studies were classified as low risk (the article achieved the conditions imposed); high risk (the article did not meet the conditions imposed); or uncertain risk (the article did not mention whether or not conditions were met).

Results

Study selection

Of a total of 86 articles identified in the initial electronic and manual searches, 60 were duplicates and triplicates and were discarded. After screening titles and abstracts the remaining 26 articles were selected for full-text reading, discarding a further 13. Applying inclusion and exclusion criteria, four articles were selected for review, as they evaluated both cyanoacrylate and sutures used for mucosa closure after LTM extraction in the same patient. The nine rejected studies and the reasons for their exclusion are shown in Table 3.

Table 2. Search strategy using different databases.

Search strategy	
Data base	Key words
PubMed/Medline	Suture AND cyanoacrylate AND oral surgery
Scopus	Suture AND cyanoacrylate AND third molar AND comparisons
Web of Science	Suture AND cyanoacrylate AND third molar AND evaluation AND clinical trials
Cochrane	Suture AND cyanoacrylate AND third molar AND evaluation
Manual search	Oral Surg Oral Med Oral Pathol Oral Radiol Endod, Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology, Journal of Cranio-Maxillo-Facial Surgery, BioMed Research International and Journal of Oral Implantology

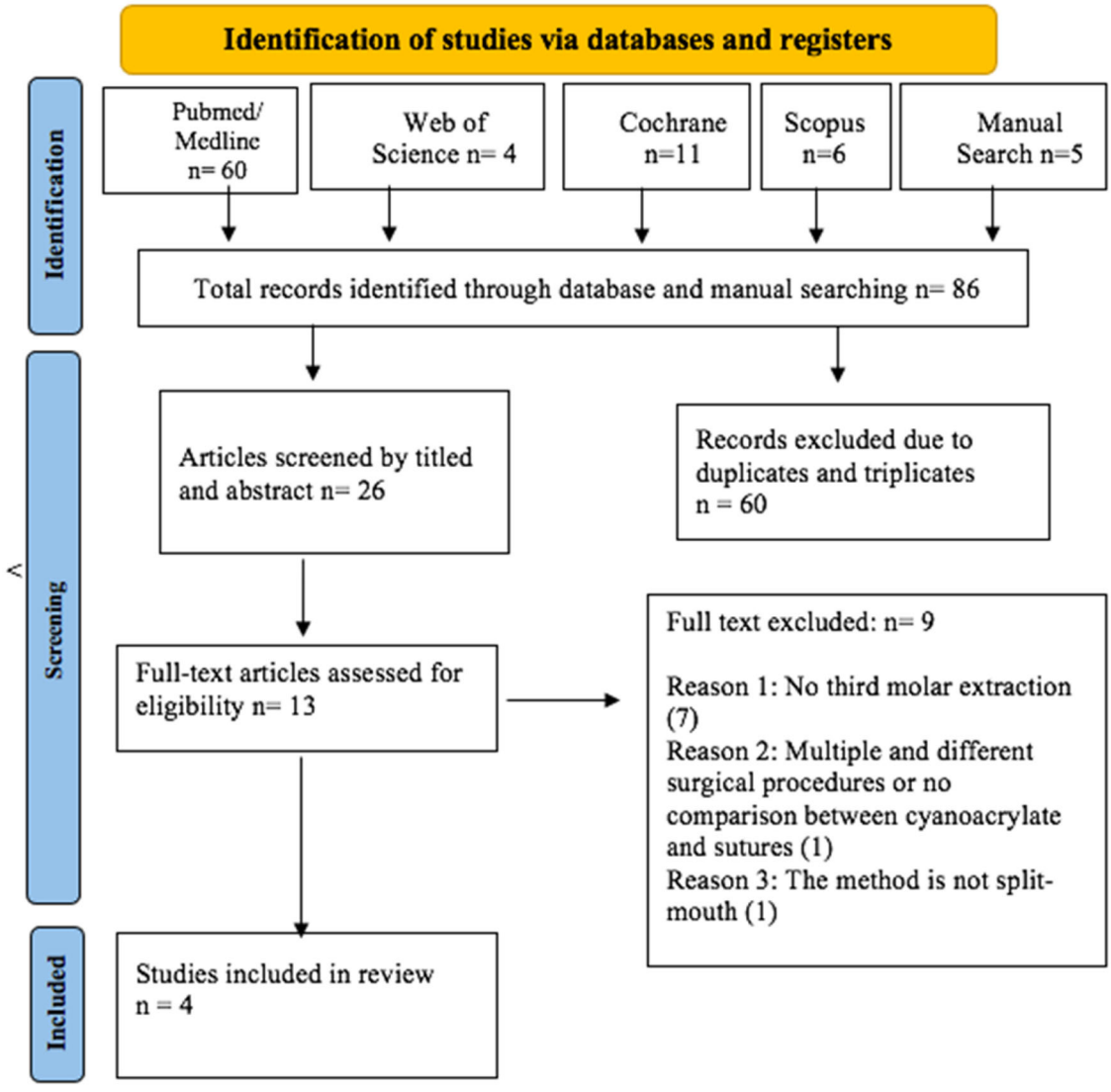

Figure 3. Flow chart outlining search and selection process.

Table 3. Excluded studies and reason for exclusion.

Excluded studies	
Author/journal/year of publication	Reason for exclusion
Sagar P. et al./Int J Biomater/2015 [7]	No third molar extraction Multiple and different surgical procedures
Vastani A. et al./J Oral Maxillofac Surg/2013 [8]	No third molar extraction
Suthar P. et al./Korean Assoc Oral Maxillofac Surg/2020 [15]	No third molar extraction
Sahu S. et al./J Oral Biol Craniofac Res/2019 [16]	No third molar extraction Extraoral maxillofacial incisions
Rezende ML. et al./J Contemp Dent Pract/2015 [17]	No third molar extraction No comparison between cyanoacrylate and sutures Guided tissue regeneration
Kulkarni S. et al./Indian J Dent Res/2007 [7]	No third molar extraction Treatment of periodontal flaps
Coulthard P. et al./Cochrane Database Syst Rev/2010 [18]	No third molar extraction Systematic review
Pérez M. et al./Artif Organs/2000 [19]	Presence of different surgical techniques besides third molar extraction
Oladega A et al./J C-Maxillofac/2019 [20]	The method is not split-mouth

Study characteristics

The most relevant information in the studies reviewed is shown in Tables 4 and 5. The types of study included are described above in Risk of bias in individual studies Section. Pain and bleeding were studied in all the articles [10–13], and some of them included additional variables: swelling [10,11], trismus [11], healing [10,11] and complications [11] (infection). Patients were aged 18 – 35 years.

All the articles reviewed were clinical trials; quality assessment is summarized in Table 6.

Table 4. Information about studies reviewed.

Study details								
Author/year	Type of study	N° patients/ third molars	Age/gender	Adhesive	Suture/ surgical time	Location/position	Type of patient	Type of extraction, anaesthesia and incision
Ghoreishian M et al./2009 [12]	Controlled clinical trial	16/32	18–24 years 9♀ 7♂	Ehil-cyanoacrylate (epiglu) 2 layers	Silk 3/0 NM	Lower third molars Similar inclination/position	ASA I No drug allergies Non smokers	NM 2% lidocaine/epinephrine 1:100,000 Envelope flap
Joshi A et al./2011 [13]	Controlled clinical trial	30/60	20–32 years NM	Isoamyl 2-Cyanoacrylate (Amcrylate) 2 layers/20sec	Silk 3/0 NM	Lower third molars Position B (Pell and Gregory classification)	ASA I No drug allergies Non smokers	Class II (Pell y Greg) difficult index-5 2% lidocaine/epinephrine 1:200,000 Ward's incision
Setiya S et al./2014 [10]	Controlled clinical trial	50/100	18–35 years 30♀20♂	Isoamyl 2-Cyanoacrylate (Amcrylate) 2 layers/20 s	Silk 3/0 NM	Lower third molars Similar inclination/position	ASA I No drug allergies Non smokers	George Winter Classification 2% lidocaine/epinephrine 1:200,000 Ward's incision
Rewainy M et al./2015 [11]	Controlled clinical trial	20/40	18–30 years 8♀12♂	N-butyl cyanoacrylate and 2-octyl cyanoacrylate (Periacryl 90) 2 layers/20 s	Silk 3/0 NM	Lower third molars Mesioangular/Position B (Pell y Gregory)	ASA I No drug allergies Non smokers	Class II (Pell and Gregory) 2% Mepivicaine/Adrenaline 1:80,000 Ward's incision

Synthesis of results

Inter-reviewer agreement

The inter-reviewer Kappa statistics between the two independent reviewers (A.O.P. and A.F.S.L.) was 0.8 with CI = 95%. The intervention of a third reviewer for consensus purposes was not needed.

Patient characteristics

The total of 116 patients was treated [10–13], extracting 232 LTMs. All studies specified patient sex and age. Ages ranged from 18 to 35 years.

All patients were non-smokers in good general health (ASA I), not taking any medication, and presenting no allergies.

All used a split-mouth model, closing the test side with Ethyl-cyanoacrylate [12], Iso-amyl 2-cyanoacrylate [10] or Iso-amyl-cyanoacrylate [11], while Joshi A et al. [10] did not specify the type of cyanoacrylate used. All used 3/0 silk suture on the control side.

Pain

Pain was evaluated in all studies by means of visual analogue scales (VASs). In three of them, the scale was completed by the patient [10,12,13] and in one by a professional, according to the expression on the patient's face [10]. All studies [10–13] showed that cyanoacrylate caused less pain, although only one study [10] reported a statistically significant difference ($p < .05$). The pain evaluations in individual studies are shown in Table 5, separating the cyanoacrylate adhesive group from the suture group.

Bleeding

All the works evaluated the incidence of bleeding, measured by a VAS completed by patients according to subjective sensation and the presence or absence of blood in saliva.

Ghoreisan M. et al. and Joshi S. et al. studied bleeding on the first three postoperative days, expressing data as medians and interquartiles. Setiya S. et al. and Rewainy M. et al. measured bleeding on the first, second and seventh postoperative days; the number of patients allotted to one or another group were expressed as whole numbers and percentiles. All studies [10–13] agreed that cyanoacrylate achieved better haemostasis with statistically significant difference. The exact data are shown in Table 5.

Swelling

Swelling was evaluated by Setiya S. et al. and Rewainy M. et al. by taking measurements at facial points: Eye-Gonion Ridge (angle mandible); Tragus-Labial Commissure; and Tragus-Pogonion.

Rewainy M et al. took post-operative measurements at 24 h, 3 and 7 d after surgery. Setiya S. et al. evaluated swelling on the first, second and seventh day post-operatively. Inferences were drawn with the equation: $EG + TM + TP = mm/3$, which means that the results were

Table 5. Information about selected studies.

Study results

Author/year	Variables studied	Variable measurement technique	Measurement times	Results
Ghoreishian M et al./2009 [12]	Pain S: 2.356 C: 2.48	VAS (0–5)	First five postoperative days	S less pain It is not statistically significant
	Bleeding S: 1.50* C: 1.00* *Median	VAS (0–4)		C better haemostasis Statistically significant
Joshi A et al./2011 [13]	Pain S: 1.304 C: 1.24	VAS (0–3)	First five postoperative days	C less pain Not statistically significant
	Bleeding S: 0.06 C: 0	VAS (0–3)		C better haemostasis Statistically significant
Setiya S et al./2014 [10]	Pain S: 1.55 C: 1.09	VAS (0–5)	First, second and seventh postoperative days	C less pain Statistically significant
	Bleeding S: 0.33 C: 0.006	VAS (0–4)		C better haemostasis Statistically significant
	Swelling S: 348.21 mm C: 344.01 mm	Evaluation with facial points (Eye-Go, Tg-Cm and Tg-Pg) in mm/3		C less swelling Statistically significant (Eye-Go) + (Tg-Cm) + (Tg-Pg) = __mm/3
	Healing S: 3.24 C: 3.36	Scoring scale (1–4)		C better healing It is not statistically significant
Rewainy M et al./2015 [11]	Pain S: 2.43 C: 1.47	VAS (0–4)	First, third and seventh postoperative days	C less pain It is not statistically significant
	Bleeding S: 1.33 C: 0.2	VAS (0–3)		C better haemostasis Statistically significant
	Swelling S: 441.4 mm C: 429.1 mm	Evaluation with one facial points (Tg-Cm) in cm expressed by 'edema'		C less swelling Statistically significant (Eye-Go) + (Tg-Cm) + (Tg-Pg) = cm
	Trismus S: 29.6 mm C: 36.6 mm	NM the evaluation, neither with facial points or scoring scale, only cm		C less trismus Statistically significant
	Infection S: 4 subjects C: 0 subjects	Presence/absence of suppuration		C less infection Statistically significant
	Healing S: 4 C: 1	Visual inspection of dehiscences		C better healing It is not statistically significant

VAS: visual analogue scale. C: cyanoacrylate. S: suture Tg: tragus; Pg: pogonion; Cm: commissure; Go: gonion.

divided by three to obtain the mean on each day and in each group. These results are shown in detail in Table 5.

Trismus

Trismus was only evaluated in one study [11], although no pre-treatment observations were recorded for comparison. Rewainy M. et al. reported that cyanoacrylate presented better recovery in comparison with sutures, finding statistically significant differences on the first and seventh days after surgery. Although the authors reported evaluating trismus, they did not explain the method used [11].

Infection

Infection was reported in only one of the studies [11]. This recorded infection according to the presence of suppuration in the wound. Cases of infection were observed in the suture group, 2 and 7 d after surgery (2 and 4 patients, respectively), while no cases of infection were observed in the cyanoacrylate group, with statistically significant difference between the groups ($p < .05$).

Healing

Two of the four studies analysed wound healing [10,11]. Setiya S et al. measured healing by means of a rating scale and did not find any statistically significant difference between cyanoacrylate and sutures on the first, second and seventh days after the surgery. The rating scale was as follows: 1 (Not healed); 2 (Gaping); 3 (Healed adequately); 4 (Satisfactory). Rewainy M et al. evaluated healing as positive or negative (dehiscence or not of the wound), finding no significant difference between the groups after 2, 3 and 7 d. Only one case of dehiscence was observed in the cyanoacrylate group, while four cases were found in the control group after one week.

Table 6. Quality assessment of included studies using the Cochrane bias assessment tool.

	Domains						
	Selection bias		Performance bias	Detection bias	Bias for incomplete follow-up	Bias per report other risks	Other bias
Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of risk
Ghoreishian M et al. [12]	-	?	+	?	?	+	-
Joshi A et al. [13]	-	?	+	+	?	-	?
Setiya S et al. [10]	-	?	+	+	?	?	?
Rewainy M et al. [11]	+	+	+	?	+	-	?

Discussion

This SR aimed to assess postoperative clinical parameters – pain, swelling, trismus, healing or complications (bleeding and infection) – after surgical extraction of LTM, comparing two different wound closure methods: cyanoacrylate and conventional sutures. The review included a total of 116 patients undergoing 232 LTM extractions.

Wound healing closure is considered an important factor in determining a successful outcome after oral surgery. To this day sutures are still considered the gold standard. Despite presenting many advantages, it also has shortcomings as it has been mentioned above [20–22]

Thus, alternative methods, such as tissue adhesives are being investigated in order to overcome these problems [2,15,23]. In this sense, it has been shown that cyanoacrylate has an immediate haemostatic effect on wounds that present excessive bleeding, being therefore useful as a local haemostatic material in anticoagulated patients [2,15]. This adhesive also has an antimicrobial effect due to its bacteriostatic properties and eliminates the patient's anxiety about suture removal [7,24]. Azevedo et al. [25] evaluated the cytotoxic effects of Histoacryl® and two other homologous ethyl cyanoacrylates (Super Bonder® and Ultrabond®), analysing in turn other variables, and obtaining results similar to those presented in this SR. These authors highlighted both its biocompatibility and its haemostatic efficacy, making it an also useful material in endodontic surgery [26–28].

Furthermore, applications in a range of procedures, within the field of oral and maxillofacial surgery, have been studied including alveolus closure after extraction, Schneider membrane perforation during maxillary sinus floor augmentations procedures with lateral approach, periodontal surgeries or biopsy closures [28–33].

Moreover, it has shown good properties in other medical fields (gastrointestinal fistulae [34], knee arthroplasty [35], for closing abdominal wounds [36] and so on). Nevertheless, and despite all these advantages, cyanoacrylate also suffers many drawbacks as aforementioned [31,32]. However, when compared with various gelatine derivatives (polyurethane, epoxy and resorcinol) it shows favourable results [33–35].

In the present SR, both cyanoacrylate and sutures were shown to be effective in achieving healing after LTM extraction, obtaining similar results, although with some differences. Lower values were obtained for pain and bleeding in the cyanoacrylate group, with statistically significant differences. Swelling and healing obtained controversial results between the articles analysed; the same occurred with the incidence of infections. Our results agree on those obtained by Ellis [37], who reported a reduction in pain after wound closure using cyanoacrylate instead of silk sutures for skin lesions, evaluating specimens from each group under light microscopy the 3rd, 7th, 14th and 21st post-operative days [38–40].

As for bleeding, all authors agreed on the cyanoacrylates' better haemostatic effect, as shown by Sagar P. et al. [7] and Amer et al. who also described the haemostatic effect of cyanoacrylate glue on warfarin-treated patients undergoing oral surgery [41–43]. Azevedo et al. [25] argued that blood coagulum filling the defect and protecting the wound is affected by the fibrinolytic effect of salivary secretion. But at cyanoacrylate sites the wound is isolated by the adhesive allowing healing without interference, so the healing pattern is faster, more uniform, and shows less inflammatory response [25]. This study reported a similar infection rate to this review.

Although cyanocrilate has shown better results in terms of pain and haemostasis, and other parameters, such as swelling, trismus and healing did not have differences, its use should be considered with caution, due to the small number of studies available in the literature, and the impossibility of blinding patients and professionals in research.

The studies included in this review have their own limitations. First, blinding process is not possible, maybe affecting the results. In the same manner, the way to establish the clinical parameters varied among studies, not allowing to perform a meta-analysis. In turn, although impacted LTM were in a similar position in all the included studies, not all the LTM had the same depth or angulation; the same occurred with LTM classification. While Ghoreisan M. et al. and Joshi A. et al. [10,13], described the situation as mesioangular or horizontal position, Setiya S. et al. [11], used

George Winter's classification and finally Rewainy M et al. [20], used Pell and Gregory's classification.

Despite all the limitations mentioned, these studies have many strengths. All of them explained in detail the section of material and methods; (the including and excluding criteria, the intervention technique and all the materials used in the process). They also illustrated the interventions and measures with pictures and diagrams, which helped the readers to better understand and find the relevant information about the effects of cyanoacrylate and sutures in an easy way.

In conclusion, cyanoacrylate has shown better results in terms of pain, bleeding and swelling in comparison with sutures. In addition, cyanoacrylate's bacteriostatic and haemostatic properties provide better healing and fewer complications, such as infection in comparison with traditional sutures. However, cyanoacrylate suffers a number of limitations: higher cost, the skill required to handle the adhesive and the limited size of the wound that may be treated. Nevertheless, cyanoacrylate would appear to be a safe substitute for suturing LTM wounds. Given the scarcity of published controlled clinical trials of cyanoacrylate, more studies are needed with adequate protocols and sufficient sample sizes in order to confirm the present findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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