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HUMAN RANDOMIZED CONTROLLED TRIAL

A randomized clinical trial of cyanoacrylate tissue adhesives in donor site of connective tissue grafts

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Abstract

Background: The purpose was to compare patient-centered outcomes, early wound healing, and postoperative complications at palatal donor area of subepithelial connective tissue grafts (CTG) between cyanoacrylates tissue adhesives and polytetrafluoroethylene (PTFE) sutures.

Methods: Thirty-six patients who required harvesting of CTG were enrolled in this randomized clinical trial and assigned to one of two groups. In the "suture" group, wound closure was achieved with standardized continuous interlocking 6-0 PTFE sutures, while in the "cyanoacrylate" group, a high viscosity blend of n-butyl and 2-octyl cyanoacrylate was applied until hemostasis was achieved. The primary outcome was the discomfort (eating, speaking, etc.) from the donor site during the first postoperative week; this was self-reported on a visual analog scale questionnaire. Secondary outcomes were the time required for suture placement or cyanoacrylate application, patient self-reported pain on the first day and the first week after surgery, the analgesic intake and the modified early-wound healing index (MEHI).

Results: The median value of discomfort was 1.49 in the "suture" group and 1.86 in the "cyanoacrylate" ($P = 0.56$). The mean time required for suture placement was 7.31 minutes and for cyanoacrylate application 2.16 minutes ($P < 0.0001$). No statistically significant differences were found between the two methods in reported pain level, analgesic intake, and MEHI.

Conclusions: Cyanoacrylate performs similarly to sutures and can be used for wound closure of the donor site of CTG. The application was about 5 minutes faster than conventional suture placement, reducing the total time of the surgical procedure.

KEYWORDS
cyanoacrylates, pain, sutures, tissue adhesives, wound healing

1 | INTRODUCTION

Subepithelial connective tissue grafts (CTG) are considered the "gold standard" treatment in periodontal plastic surgery.[1] CTG procedures require harvesting tissue from a donor area, usually the palate.[2] This addition of another surgical site extends the complexity of the procedure and increases patient discomfort.[2] Horizontal suspension[3] or continuous interlocking[2] sutures are the most common method of wound closure.[4] The difficulty with suturing and the need for suture removal are major challenges; therefore, research has focused on more effective wound closure methods with better

efficiency and fewer complications.[4] Biomaterials such as staples, adhesive tapes, cyanoacrylate tissue adhesives, and fibrin sealants have been used generally to accelerate healing.[5–7]

Cyanoacrylate adhesives are synthesized as monomers by condensation of a cyanoacetate with formaldehyde in the presence of catalysts and the adhesive film develops by fast polymerization triggered by hydroxyl groups on the surfaces to be glued.[8] The reaction of polymerization is exothermic; does not require catalysts, solvents, or application pressure; and leads to strong and flexible bonds.[8,9] Water can act as a catalyst to activate this anionic polymerization.[10] Cyanoacrylate adhesives retain their adhesive qualities even in the presence of moisture, and have the added benefits of being bacteriostatic and hemostatic.[10] Their general chemical formula is CH2 = C(CN)-COOR, where R can be substituted for any alkyl group, ranging from methyl to decyl.[5,8,9,11] Methyl cyanoacrylate, the shortest-chain derivative, was the first glue developed, but tissue toxicity precluded its use.[5,12] Longer-chain derivatives such as ethyl-2-cyanoacrylate, isobutyl-2-cyanoacrylate, butyl-2-cyanoacrylate, n-butyl cyanoacrylate and 2-octyl-cyanoacrylate have subsequently been developed.[11] Changing the type of alkyl chains in the compound to one with a longer molecular chain can reduce tissue toxicity.[11] The properties of cyanoacrylate tissue adhesives with the greatest interest in the surgical field are the reported excellent hemostasis, rapid adhesion of tissues, and possible bacteriostatic qualities.[8] Their use in dentistry is restricted to superficial application.[9]

Few studies are focused on evaluating wound healing and assessing patient-centered outcomes on the palatal donor area following different harvesting techniques.[2,13] To the best of our knowledge, there is no study that compares different methods of wound closure of the donor site in CTG procedures. The purpose of this study was to compare patient-centered outcomes, postoperative complications, and early wound healing at palatal donor areas between those receiving sutures and cyanoacrylate tissue adhesives.

2 | MATERIALS AND METHODS

2.1 | Patient population and enrollment

The parallel randomized clinical trial was approved by the University of Manitoba's Biomedical Research Ethics Board (HS20114 (B2016:092) and registered on ClinicalTrials.gov (NCT02935426). Patients included in the study attended the Dr. Sam Borden Periodontology Clinic, Dr. Gerald Niznick College of Dentistry, University of Manitoba, Winnipeg, Manitoba and required harvesting of CTG from the palate from January 2017 to April 2018. All participants signed an informed consent form. Patients received an initial periodontal examination and treatment, if necessary. Full-mouth plaque score and full-mouth bleeding score needed to be <20% to be eligible. Patients with coagulation disorders (e.g. Hemophilia a/b, von Willebrand disease, liver disease, anticoagulative therapy), patients on corticosteroids, with uncontrolled diabetes, or with any systemic disease that precluded periodontal surgery, as well as patients with a history of contact dermatitis to formaldehyde were excluded.

2.2 | Surgical protocol

Surgical procedures were performed by one of three calibrated periodontics residents (CS, JB, DR). The three surgeons were calibrated in a calibration meeting using the detailed parameters from the study protocol and clinical pictures. For all measurements the same periodontal probe* was used.

At the donor site, anesthesia was achieved with greater palatine block anesthesia and palatal local infiltrations, if needed, with 1.8 mL lidocaine 2% 1:100,000 epinephrine. The thickness of the palatal gingiva at the donor site was measured with bone sounding. The CTG was harvested with the single incision technique.[14] Once the graft was harvested, pressure was applied to the palate until hemostasis was achieved. The thickness, length, and height of the harvested graft were measured and recorded.

2.3 | Wound closure groups

Patients were then randomly assigned to one of two groups, the suture or the cyanoacrylate group (Fig. 1). Randomization was achieved using computerized randomization scheme with allocation ratio 1:1 and was communicated to the surgeon during the surgery by an independent examiner (AC). Patients were block-randomized for each of the three operators for balance, maintaining the 1:1 allocation ratio. In the suture group, continuous interlocking 6-0 polytetrafluoroethylene (PTFE) sutures† were placed 4 mm apart[2] leaving 3- to 4-mm tails. In the cyanoacrylate group, thin layers of a high viscosity blend of n-butyl and 2-octyl – cyanoacrylate tissue adhesive‡ were applied and rinsed with saline at least three times with an interval of at least 30 seconds[15] to allow for complete polymerization, until hemostasis was achieved. The number of sutures placed and the number of layers of cyanoacrylate applied to achieve hemostasis were recorded. The time required for suture placement or for cyanoacrylate application was also recorded with a timer.

* Hu-Friedy PCPUNC 15 mm, Hu-Friedy, Chicago, IL.

† Omnia 6/0, 75 cm PTFE Surgical Suture with 1/2 circle Diamond Tip needle, Omnia, Abbottstown, PA.

‡ PeriAcryl 90 High Viscosity, GluStitch, Delta, BC.

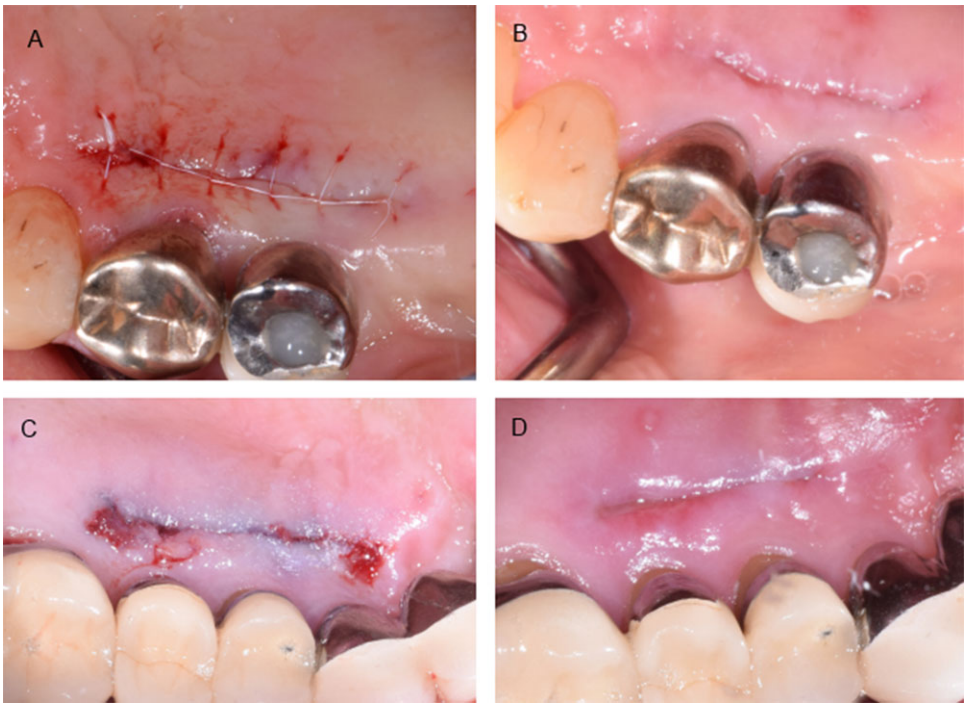

FIGURE 1 Clinical photographs of treatment groups; 1A. Baseline clinical photograph from suture group; 1B. Clinical photograph of case in 1A at 1-week follow-up appointment; 1C. Baseline clinical photograph from cyanoacrylate group; 1D. Clinical photograph of case in 1C at 1-week follow-up appointment

2.4 | Postoperative care and records

All patients received a loading dose of amoxicillin 2 g or clindamycin 600 mg, in case of allergy to penicillin, and ibuprofen 400 mg immediately after the surgery. All patients received the same postoperative instructions. Soft diet was recommended for all patients. Chlorhexidine 0.12% mouth rinse was prescribed to each patient for use twice daily. Ibuprofen 200 mg, 20 tablets were also dispensed for the patients to consume 1 to 2 tablets orally every 4 to 6 hours as needed. Patients were asked to return the unused tablets for recording of analgesic-intake at the 1-week follow-up appointment. A 0 to 10 pain visual analog scale (VAS) questionnaire was given to the patients to note the level of pain from the palatal site on the first postoperative day, before the consumption of analgesics.

At the 1-week follow-up appointment, analgesic-intake during the first postoperative week was recorded. Patients were asked to report any self-medication for pain. A 0 to 10 VAS questionnaire was also given to participants to fill in. The participants were asked to note the level of pain from the donor and recipient sites, and the level of discomfort (eating, speaking, etc.) from the donor site during the first postoperative week. Discomfort was defined as irritating sensation and difficulty in eating, speaking, etc. and pain as inability to function requiring analgesics. Sutures were removed in the suture group. The length and height of the wound at the palatal site were measured. Based on the clinical presentation and the presence of fibrin and necrosis, the modified early-wound healing index (MEHI)[2] (Fig. 2) was recorded. Finally, the presence of normal or abnormal inflammation was also recorded.

Postoperative complications like severe bleeding for >20 minutes, infection, abnormal pain, root exposure of the teeth adjacent to the donor site, and sloughing were recorded for 1-month postoperatively.

2.5 | Statistical analysis

According to the sample size calculation for discomfort level, 32 patients with 16 patients in each group were required, anticipating standard deviation 1 on the VAS.[2] In total, 36 patients were recruited in the trial to allow for 10% dropouts or losses to follow-up and for balance among the operators. The primary outcome was the discomfort from the donor site during the first postoperative week. Secondary outcomes were the time required for suture placement or cyanoacrylate application, the level of pain from the palatal site on the first postoperative day and during the first postoperative week, the analgesic intake, and the MEHI. The study was masked at the level of data assessment.

Descriptive statistics include means, standard deviations, and frequencies. For comparing continuous outcomes between the two methods of wound closure, the Wilcoxon-rank sum test was used. For the discrete outcome of MEHI, the Fisher exact test was used. MEHI categories 1, 2, 4, and 5

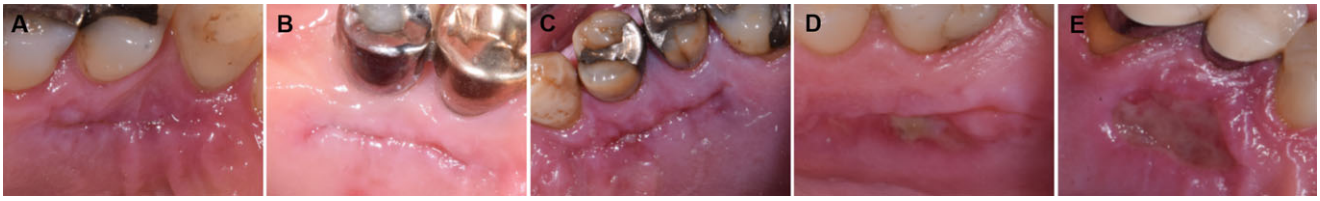

FIGURE 2 Modified early wound healing index (MEHI); 2A. MEHI 1: complete flap closure without fibrin line at the palate; 2B. MEHI 2: complete flap closure with fibrin line at the palate; 2C. MEHI 3: complete flap closure with small fibrin clot at the palate; 2D. MEHI 4: incomplete flap closure with partial necrosis of the palatal tissue; 2E. MEHI 5: incomplete flap closure with complete necrosis of the palatal tissue (> 50% of former flap)

were combined due to the small cell sizes. Values 1 and 2 were regarded as primary closure, values 4 and 5 as secondary closure, and value 3 as intermediate. The level of significance was established at $P \leq 0.05$. Program R version 3.5.1 was used for the analysis.*

3 | RESULTS

3.1 | Patients' characteristics

Data from 35 patients, 18 patients in the suture group and 17 patients in the cyanoacrylate group, were available at the end for analysis. One patient from the cyanoacrylate group failed to attend on the day of the surgery for unknown reasons and no records were collected. One patient in the cyanoacrylate group was a smoker and one patient in the suture group reported smoking cannabis. Both participants were encouraged to cease smoking during the healing period. One patient was allergic to ibuprofen and received acetaminophen 1 g and 20 tablets of acetaminophen 500 mg to consume as needed during the first postoperative week. Twelve patients were American Society of Anesthesiologists (ASA) score 1 and 23 were ASA 2. There were 10 males and 25 females, aged 23 to 81 years, included in the study. The demographic characteristics of the patients appear in Table 1. Data on the thickness of the palate, the length of the incision, the thickness, height and length of CTG, and the number of sutures placed or the number of cyanoacrylate coats applied are also presented in Table 1.

There were no major imbalances between the two wound closure methods with respect to age, thickness of palate, length of incision, thickness of graft, height of graft, or length of graft. However, groups were noticeably different in their sex profiles. The donor area was always unilateral, extending from the lateral incisor to the second molar with the majority of the grafts being harvested from the premolar region in both groups.

* R Foundation for Statistical Computing, Vienna, Austria.

3.2 | Outcomes

Regarding the primary outcome, the level of discomfort from the palate during the first postoperative week, the mean value for the cyanoacrylate group was 1.86 ± 2.25 on the VAS and 1.49 ± 1.96 in the suture group (Table 2), which was not statistically significant ($P = 0.56$).

For the level of pain reported from the palate on the first postoperative day, the mean value for the cyanoacrylate group was 1.27 ± 1.92 and for the suture group 1.42 ± 1.88 ($P = 0.96$) (Table 2). As far as the level of pain from the palate during the first postoperative week, the mean value for the cyanoacrylate group was 1.55 ± 2.32 and for the suture group 1.07 ± 1.87 ($P = 0.28$) (Table 2). For the analgesic-intake during the first postoperative week, the median value for the cyanoacrylate and the suture group was four tablets of ibuprofen 200 mg ($P = 0.94$). The cyanoacrylate group demonstrated a bimodal distribution, comprised of two distinct groups, whereas the suture group was more of a single continuum. Self-medication was reported by 11 of 35 patients, five from the suture group and six from the cyanoacrylate group. Three of these patients reported ibuprofen intake and the number of tablets consumed were added to the analgesic intake. For the remainder of the patients, there were no records on the type and the number of analgesics consumed.

With regards to the time required for suturing or application of the cyanoacrylate adhesive, the mean value for the cyanoacrylate group was 2.16 ± 1.21 minutes and 7.31 ± 2.19 minutes for the suture group (Table 2). The difference between the two methods of wound closure was 5.15 minutes ($P < 0.0001$). The mean value for surgery time for the more experienced operator (CS) was 3.7 ± 2.22 minutes and for the less experienced operators (DR and BJ) 5 ± 4.42 minutes and 5.6 ± 2.34, respectively.

The results for the MEHI are presented in Table 3. The difference between the two methods of wound closure was not statistically significant ($P = 0.91$).

3.3 | Complications

Postoperative bleeding was reported from two patients in the cyanoacrylate group. In the first patient, the bleeding

TABLE 1 Summary of results for age, sex, thickness of palate, length of incision, thickness, height and length of graft, and number of sutures or layers of cyanoacrylate

	Sutures		Cyanoacrylate	
Parameters	**Mean***	**Min – Max†**	**Mean**	**Min – Max**
Age (years)	58.5 ± 13.52	23 – 74	53.18 ± 20.2	27 – 81
Sex				
Female (%)	9 (50%)		16 (94.1%)	
Male (%)	9 (50%)		1 (5.9%)	
Thickness palate (mm)	3.44 ± 0.77	2 – 5	3.38 ± 0.78	2 – 5
Length incision (mm)	18.94 ± 2.78	15 – 25	17.06 ± 5.51	10 – 31
Thickness graft (mm)	2.14 ± 0.36	1.5 – 3	2.41 ± 0.51	2 – 3
Height graft (mm)	7.03 ± 4.83	3 – 20	6.41 ± 2.67	4 – 14
Length graft (mm)	15.06 ± 4.26	4 – 24	13.76 ± 6.42	6 – 27
Sutures/layers number	6.67 ± 0.97	5 – 8	4.41 ± 1.23	3 – 8

*Data are presented as mean ± SD.
†Data are presented as minimum and maximum (min – max) value.

TABLE 2 Summary of results for discomfort, time, pain, and analgesic-intake

Outcomes	Mean sutures*	Median sutures†	Mean cyanoacrylate*	Median cyanoacrylate†	*P* value
Discomfort (0 to 10 VAS‡)	1.49 ± 1.96	0.75 (1.75)	1.87 ± 2.25	0.80 (2.6)	0.56
Pain_first day (0 to 10 VAS)	1.42 ± 1.88	0.5 (2.2)	1.27 ± 1.92	0.3 (1.925)	0.96
Pain_first week (0 to 10 VAS)	1.07 ± 1.87	0.2 (1.2)	1.55 ± 2.32	0.5 (1.5)	0.28
Analgesic intake	6.12 ± 6.79	4 (10)	5.24 ± 6.30	4 (5)	0.94
Time (minutes)	7.31 ± 2.19	6.59 (2.41)	2.16 ± 1.21	2.00 (1.12)	<0.0001

*Data are presented as mean ± SD.
†Data are presented as median value (interquartile range).
‡VAS, visual analog scale.

TABLE 3 Summary of results for the modified-early wound healing index (MEHI)

Category	Sutures	Cyanoacrylate	*P* value
MEHI 1 or 2	44.4%	35.3%	0.91
MEHI 3	16.7%	23.5%	
MEHI 4 or 5	38.9%	41.2%	

occurred during the second postoperative week and lasted 15 minutes and was managed with tongue pressure. In the second patient, the bleeding occurred during the first postoperative week after consumption of fruits and lasted about 4 minutes. The patient was reassured and no further management was required.

Abnormal inflammation was recorded only for one patient from the cyanoacrylate group. Necrosis and edema at the palatal site were noted without signs of infection at the 1-week follow-up appointment. No specific management was required. MEHI 5 was assigned to this patient. The healing was completed uneventfully. The level of pain and discomfort reported from the patient was at the area of 0.5 on the VAS, and the patient took only one tablet of ibuprofen during the first week of healing.

3.4 | Additional analyses

Because of the imbalance between the groups in the sex profile, we tested for associations between sex and each of the following outcomes; patient discomfort, time, pain on the first postoperative day and during the first postoperative week, analgesic intake and MEHI. None of them were significant, except for sex and time. However, time is the only outcome that differs between the two methods. In multivariable regression models (data not included), the relationship between method of wound closure and time remained highly significant upon adjustment for sex, and both the magnitude and direction of the relationship were largely unchanged.

From additional analyses with Kruskal-Wallis rank sum test and Fisher exact test, it was found that the MEHI did not correlate with the dimensions of the graft (length; $P = 0.11$, height; $P = 0.57$, or thickness; $P = 0.68$). As tested with Wilcoxon rank sum test and Spearman rank correlation, the dimensions of the graft were also not related to the analgesic intake ($P = 0.52$ for length, $P = 0.26$ for height and $P = 0.25$ for thickness) or to the level of reported 1-week pain ($P = 0.53$ for length, $P = 0.78$ for height, and $P = 0.69$ for thickness). Finally, after testing with Kruskal-Wallis rank sum test, no significant relationship was found between the

MEHI and analgesic intake ($P = 0.56$) or the reported pain ($P = 0.11$).

4 | DISCUSSION

In this randomized clinical trial, clinical outcomes from two different methods of wound closure of the palatal donor site of CTG were compared. Continuous interlocking 6-0 PTFE sutures or application of a high viscosity blend of n-butyl and 2-octyl–cyanoacrylate tissue adhesive was randomly selected as a wound closure method in 35 patients after harvesting CTG with the single-incision technique.[14] No significant differences were found between the two methods in terms of patient discomfort and postoperative pain. The two methods also demonstrated similar wound healing short-term, as evaluated with the MEHI at the 1-week follow-up appointment. A significant difference between the two groups was found only in the time required for suture placement or cyanoacrylate application.

The application of cyanoacrylate tissue adhesive in the donor palatal site of CTG was found to be >3 times faster than suture placement. Soni et al. found that the time savings increased for cyanoacrylate as the length of the incisions increased, because the application time, unlike that of sutures, does not increase significantly with incision size.[16] The time saving could decrease intraoperative patient discomfort increasing patient acceptance and practice productivity.

The single-incision technique for harvesting of CTG results in less secondary wound healing, minimum patient discomfort, and limited postoperative complications compared with other techniques.[2,3,14] For these reasons, this technique was chosen in our study.

Continuous interlocking 6-0 PTFE sutures were selected for wound closure in the suture group as used from Fickl et al.[2] As a monofilament, PTFE does not accumulate plaque enhancing wound healing. It is also non-resorbable, minimizing the risk of early loss and postoperative bleeding.

There were no major imbalances between the two methods of wound closure with respect to age, thickness of the palatal gingiva, length of the incision, thickness of the harvested graft, height or length of the graft. Therefore, these are unlikely to confound the association between method of wound closure and the outcomes of pain, MEHI, and time. However, the groups were noticeably different in their sex profile. The increased total number of females in the study is in agreement with the results of Furuta et al.[17] However, randomization should have brought sex balance between the two groups. The imbalance may be due to the small sample size. If sex is associated with any of the outcomes, this may bias the results. However, in multivariable regression models, the relationship between method of wound closure and time remained highly significant upon adjustment for sex, and both the magnitude and direction of the relationship were largely unchanged.

The 0–10 VAS questionnaires were elected to evaluate the level of pain and discomfort in our study. Because pain is a subjective, personal, and private experience, recording pain has limitations.[18] The VAS is considered to be an efficacious tool to evaluate clinical parameters, such as pain,[4,16] especially for pain assessment after surgery.[18]

Postoperative bleeding was reported by two participants in this study. The first incident occurred during the second postoperative week. The patient did not notify the operator of the incident and just reported it at the second follow-up appointment. The incident may be related to the incorrect application of the adhesive. The second incident occurred after consumption of food. This is in agreement with Griffin et al., that bleeding is associated with postoperative irritation or trauma, rather than the surgical procedure.[19] Both bleeding complications occurred in the test group but were not considered "major" as they lasted <20 minutes and did not require any special management.

The cyanoacrylate tissue adhesive used in the study was a blend of n-butyl cyanoacrylate and 2-octyl cyanoacrylate. Butyl cyanoacrylate is a bacteriostatic, biodegradable, hemostatic cyanoacrylate with a long half-life and good tissue compatibility.[12] It sets within 5 to 10 seconds by polymerization in the presence of moisture and even blood, with release of heat.[12] Before the application of cyanoacrylate, the tissue surfaces should be cleaned and dried as much as possible. Careful application drop by drop is better than rapid massive application, to minimize heat production during polymerization.[11]

The adhesive is sloughed from the surface by 5 days, and the remnants of cyanoacrylate are phagocytosed.[20] The histotoxic effect is related to the heat of polymerization, the byproducts of the polymer degradation such as formaldehyde and alkyl cyanoacetate, the length of the alkyl group of cyanoacrylate derivatives and the rate at which degradation occurs.[9,11,16] Foreign body reaction with histiocytic proliferation[21] and formation of giant cells in tissues[22] has been reported histologically on cyanoacrylate sites. Kulkarni et al. reported less inflammation clinically and histologically at 7 days after the use of cyanoacrylate tissue adhesive for closure of periodontal flap as compared with sutures.[12] The difference disappeared at 21 days and at 6 weeks.[12] Giant cell proliferation or histiocytes were not reported in either of the sites of that study.[12] Bhasker and Frisch said that there would be giant cell reaction and phagocytosis if the cyanoacrylate material were to be implanted deep into the tissue.[23] Thus, the cyanoacrylate adhesives should be topically applied after the edges of the incision are brought together to avoid entrapment of adhesive within the wound.[5] If the polymer was accidentally swallowed, degradation and assimilation of a significant percentage of the polymer occurred in an animal model with

rats.[24] There is no evidence of carcinogenesis of isobutyl- and butyl-2-cyanoacrylate.[16]

Dermatologic reactions, such as urticarial reactions and irritant dermatitis and other non-dermatologic reactions (reversible eye and upper airway irritation) have been reported from cyanoacrylate adhesives.[25] Outbreaks of asthma and irritant dermatitis in dental staff were observed where the environmental humidity was low.[25] The high levels of humidity are thought to induce polymerization of free monomers of cyanoacrylates, thereby reducing their volatility reactions.[25] Dental staff should take care to avoid direct contact with cyanoacrylate, use cyanoacrylate in a well-ventilated area, and wear appropriate personal protective equipment.[25]

Similar wound healing was found between sutures and cyanoacrylate tissue adhesives in this study. However, cyanoacrylates have been shown to speed wound healing in partial-thickness wounds in an animal model.[26] In contrast with our results, cyanoacrylate adhesives were found to aid in early initial healing and cause less intraoperative and postoperative discomfort to patients after application on intraoral wounds, as compared with standard suture wound closure.[5] Perez et al. found high patient acceptance of tissue adhesives because of pain relief and less eating discomfort.[27]

No signs of infection were noted on any of the participants. Cyanoacrylate adhesives have antimicrobial properties against Gram-positive organisms and may decrease wound infections.[28] The antibacterial effect is possibly caused by strong electronegative charge of the polymer.[29]

Ghoreishian et al. reported that the use of cyanoacrylate adhesives for wound closure after removal of impacted mandibular third molars was characterized by simplicity, higher speed, and better hemostasis.[4] However, they considered the cost of tissue adhesive to be a limitation.[4] In our study, it was calculated that the PTFE sutures were three times more expensive than the cyanoacrylate adhesive. Other disadvantages reported are the occasional difficulty of application at posterior sites, especially palatally and lingually, and the ease with which the monomer will polymerize on exposure to small amounts of moisture.[8]

Potential limitations in this clinical trial include the lack of a negative control group for ethical reasons and to avoid excess postoperative bleeding, masking only occurred at the level of data analysis, and the noticeable imbalance in the sex profile of the two treatment groups. Moreover, the possible variation in the thickness of the overlying flap and the thickness of the graft, the varying amounts of areas harboring the palatal blood clot, the multiple surgeons and the second surgical site may be seen as limitations of this study. Even though the two groups were balanced and no significant relationship was found, it cannot be ruled out that the varying flap/graft dimensions and varying surgeons may have influenced the healing capacity, thus patient discomfort and pain postoperatively. Furthermore, the duration of the soft tissue grafting procedure is an important indicator for postoperative pain.[13] Also, differences in patient perception can also influence the levels of reported postoperative pain.[13,30] Thus, caution is needed in interpreting our results, as this clinical trial may be affected by an unintentional bias. Even though efforts were made to increase compliance with returning the pain questionnaires and unused tablets of ibuprofen during the first week of healing, a few patients returned them at the second follow-up appointment. This can be considered a limitation of this study. Finally, the amalgamation of the MEHI categories, due to the small sample size, might have limited our ability to detect any differences in healing between the two methods of wound closure.

5 | CONCLUSIONS

From this randomized clinical trial, it can be concluded that cyanoacrylate tissue adhesives perform similar to sutures for wound closure of the palatal donor site of CTG. The application of cyanoacrylate tissue adhesive was >3 times faster than the placement of sutures. No statistically significant differences were found between the two methods of wound closure in terms of patient discomfort and postoperative pain.

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REFERENCES

1. Chambrone L, Tatakis DN. Periodontal soft tissue root coverage procedures: a systematic review from the AAP Regeneration Workshop. *J Periodontol*. 2015;8:S8–S51.
2. Fickl S, Fisher K, Jockel-Schneider Y, et al. Early wound healing and patient morbidity after single-incision vs. trap-door graft harvesting from the palate—a clinical study. *Clin Oral Investig*. 2014;18:2213–2219.
3. Hurzeler W. A single-incision technique to harvest subepithelial connective tissue grafts from the palate. *Int J Periodontics Restorative Dent*. 1999;19:279–287.

4. Ghoreishian M, Gheisari R, Fayazi M. Tissue adhesive and suturing for closure of the surgical wound after removal of impacted mandibular third molars: a comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;108:e14–e16.
5. Vastani A, Maria A. Healing of intraoral wounds closed using silk sutures and isoamyl-2-cyanoacrylate glue: a comparative clinical and histologic study. *J Oral Maxillofac Surg*. 2013;71:241–248.
6. Banche G, Mandras N, Gallesio C, et al. Microbial adherence on various intraoral suture materials in patients undergoing dental surgery. *J Oral Maxillofac Surg*. 2007;65:1503–1507.
7. Yaman Z. Fibrin sealant fixation of a skin graft in mandibular vestibuloplasty. Case report. *Aust Dent J*. 1998;43:213–216.
8. Forrest JO. The use of cyanoacrylates in periodontal surgery. *J Periodontol*. 1974;45:225–229.
9. Herod EL. Cyanoacrylates in dentistry: a review of the literature. *J Can Dent Assoc*. 1990;56:331–334.
10. Leggat P, Kedjarune U, Smith DR. Toxicity of cyanoacrylate adhesives and their occupational impacts for dental staff. *Ind Health*. 2004;42:207–211.
11. Toriumi DM, Raslan WF, Friedman M, et al. Histotoxicity of cyanoacrylate tissue adhesives. *Arch Otolaryngol Head Neck Surg*. 1990;116:546–550.
12. Kulkarni S, Dodwad V, Chava V. Healing of periodontal flap when closed with silk sutures and N-butyl cyanoacrylate: a clinical and histological study. *Indian J Dent Res*. 2007;18:72–77.
13. Pandit N, Khasa M, Gugnani S, et al. Comparison of two techniques of harvesting connective tissue and its effects on healing pattern at palate and recession coverage at recipient site. *Contemp Clin Dent*. 2016;7:3–10.
14. Lorenzana E, Allen E. The single-incision palatal harvest technique: a strategy for esthetics and patient comfort. *Int J Periodontics Restorative Dent*. 2000;20:297–305.
15. Al-Belasy F, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg*. 2003;61:1405–1409.
16. Soni A, Narula R, Kumar A, et al. Comparing cyanoacrylate tissue adhesive and conventional subcutical skin sutures for maxillofacial incisions—a prospective randomized trial considering closure time, wound morbidity and cosmetic outcome. *J Oral Maxillofac Surg*. 2013;71:2152.e1–2152.e8.
17. Furuta M, Ekuni D, Irie K, et al. Gender differences in gingivitis relate to interaction of oral health behaviors in young people. *J Periodontol*. 2011;82:558–565.
18. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth*. 2008;101:17–24.
19. Griffin TJ, Cheung WS, Zarvas AI, et al. Postoperative complications following gingival augmentation procedures. *J Periodontol*. 2006;77:2070–2079.
20. Galil KA, Schofield ID, Wright GZ. Effect of n-butyl-2-cyanoacrylate (histoacryl blue) on the healing of skin wounds. *J Can Dent Assoc*. 1984;7:565–569.
21. Greer R. Studies concerning the histotoxicity of isobutyl-2-cyanoacrylate tissue adhesive when employed as an oral hemostat. *Oral Surg*. 1975;40:659–669.
22. Miller GM, Dannenbaum R, Cohen WD. A preliminary histologic study of the wound healing of mucogingival flaps when secured with cyanoacrylate tissue adhesives. *J Periodontol*. 1974;45:608–618.
23. Bhasker SN, Frisch J. Use of cyanoacrylate adhesives in dentistry. *J Am Dent Assoc*. 1968;77:831–817.
24. Ousterhout DK, Gladieux GV, Wade CW, et al. Digestive tract absorption of alkyl α-cyanoacrylate-β-14C. *Oral Surg Oral Med Oral Pathol*. 1969;27:410–416.
25. Yoo J, Chandarana S, Cosby R. Clinical application of tissue adhesives in soft-tissue surgery of the head and neck. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16:312–317.
26. Davis SC, Eaglestein WH, Cazzaniga AL, et al. An octyl-2-cyanoacrylate formulation speeds healing of partial-thickness wounds. *Dermatol Surg*. 2001;27:783–788.
27. Perez M, Fernandez I, Marquez D, et al. Use of n-butyl-2-cyanoacrylate (histoacryl blue) on the healing of skin wounds. *J Can Dent Assoc*. 1984;7:565–569.
28. Quinn JV, Ramotar K, Osmond MH. The antimicrobial effects of a new tissue adhesive. *Acad Emerg Med*. 1996;3:536–537.
29. Quinn J, Maw J, Ramotar K, et al. Octylacrylate tissue adhesive versus suture wound repair in a contaminated wound model. *Surgery*. 1997;122:69–72.
30. Gilman T. Wound outcomes: the utility of surface measures. *Int J Low Extrem Wounds*. 2004;3:125–132.

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