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ORIGINAL ARTICLE

Pain perception following epithelialized gingival graft harvesting: a randomized clinical trial

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Abstract

Objectives The aim of this study was to compare the effects of a hemostatic collagen sponge and a collagen sponge sealed with a bio-adhesive material on the palatal donor sites with the purpose of minimizing postoperative pain after epithelialized gingival graft (EGG) harvesting.

Material and methods The present study consisted of 44 EGGs harvested in 44 patients. In the control group, a hemostatic collagen sponge was applied over the palatal wound, while the test group was treated with additional cyanoacrylate. Patients were observed for 14 days, evaluating the pain level by using the visual analogic scale. The consumption of analgesic during the postoperative period, the willingness for retreatment and the characteristic of the graft were also analyzed.

Results Statistically significant differences in pain perception were found between test and control groups in each of the studied days ($p < 0.01$). Analgesic consumption was lower in the test group ($p < 0.01$). Graft width < 14 mm was found to be associated with lower discomfort ($p < 0.01$).

Conclusions Adding an additional layer of cyanoacrylate over a hemostatic collagen sponge on the palatal wound following EGG harvesting was found to be successful in minimizing the postoperative discomfort and the need for analgesics.

Clinical relevance Postoperative pain after palatal tissue harvesting can be successfully minimized if the donor site open wound is protected with an external layer of cyanoacrylate over a collagen sponge.

Keywords Pain management · Autografts · Free soft tissue graft · Wound healing

Introduction

Periodontal plastic surgery has long been successfully performed for the treatment of gingival recessions and mucogingival deformities [1–3]. Numerous techniques have been proposed in an attempt to obtain predictable root coverage outcomes. However, the results do not only depend on the technique selected but also on a variety of factors including but not limited to patient- and site-related factors [4]. Evaluation of the keratinized tissue (KT) around the recession defects is crucial to determine whether soft tissue augmentation together with a root coverage procedure is required [5, 6]. Also, when the gingiva is relatively thin (< 1 mm), the utilization of connective tissue graft (CTG) harvested from the palate underneath the primary flap has been suggested to restore an adequate amount of the KT and tissue thickness, together with better esthetic outcomes [7, 8]. A CTG, with or without epithelium, was also found to be effective around implants for several purposes including increase of the KT [9], for the treatment of implant mid-facial recession defects [10], in interimplant papilla reconstruction [11], and for soft tissue thickening purposes [12]. Edel in 1974 was the first to describe the "trap-door" technique allowing the harvesting of a CTG from the palate together with the wound healing by primary intention [13]. Langer and Langer in 1985 proposed a

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modification of this technique aiming at achieving a connective tissue graft characterized by the presence of a thin epithelial margin [14]. Thereafter, Harris in 1997 developed a technique based on a special scalpel for including an epithelial margin into the harvested CTG [15]. Years later, several variations for CTG harvesting were described aiming at reducing the postoperative morbidity by ensuring healing by primary intention [16, 17]. However, these techniques required a certain amount of palatal thickness in order to avoid desquamation of the undermined superficial flap due to compromised vascularization [18]. Indeed, as highlighted by Zucchelli and colleagues, a common complication of these harvesting techniques is the dehiscence or the necrosis of the primary flap if it was too thin or if sutures failed to secure it over the palatal wound [13, 14, 19, 20]. To avoid the necrosis of the primary flap, a certain amount of the sub-epithelial connective tissue should be preserved and because of this, the deeper connective tissue harvested is less dense, less stable, richer in fatty and glandular tissue, and more prone to shrinkage [20, 21].

Some clinical studies have reported higher postoperative pain and morbidity following EGG [18, 22, 23] when compared to CTG. Hence, several attempts were undertaken to control the palatal pain following EGG harvesting techniques, such as irradiating the palatal wound using lasers [24, 25], the addition of platelet-rich fibrin [26], or a collagen matrix over the donor wound site [27]. These techniques reported different levels of success. In a randomized clinical trial, Zucchelli and colleagues demonstrated that there was no difference between the self-perceived pain on the palatal wound resulting from the traditional trap-door technique and the EGG harvesting technique if the open wound was sealed with an absorbable hemostatic material [20]. Recently, bio-adhesive materials, such as cyanoacrylate surgical glue, have been successfully introduced in ophthalmology [28], in the treatment of massive hemoptysis [29], in embolization [30, 31], and for wound closure in dermatology [32] due to their strong sealing, bacteriostatic, and hemostatic properties [33]. Among the advantages of bio-adhesive materials, their high tissue compatibility and long half-life have also been described [34]. Consequently, due to its sealing, hemostatic, and antibacterial properties [33], cyanoacrylate may be applied for proper protection of the palatal wound during the secondary intention healing after EGG in order to reduce the postoperative morbidity related to this technique [18, 22, 23]. Our clinical experience suggested that cyanoacrylate alone on the palatal wound does not improve patient discomfort so the investigation was completed to see if using it in conjunction with a collagen sponge had better results than sponge alone.

This randomized clinical comparative study evaluated the postoperative pain following the EGG technique with two different methods for coverage of the palatal donor site. The control group was protected with an absorbable hemostatic collagen sponge while the test group consisted of collagen protection with the additional layer of cyanoacrylate surgical glue. Patient discomfort was assessed each day for 2 weeks along with different parameters with regard to dimensions and fibromucosa thickness on donor site.

Materials and methods

Participants

This study was a prospective controlled randomized clinical trial with a parallel design, performed to evaluate patients' morbidity following EGG harvesting from the palate, according to the CONSORT statement [35]. The wound was treated with a hemostatic porcine absorbable sponge (Spongostan; Ethicon, Somerville, USA) in the control group or with the same hemostatic product combined by an adhesive (PeriAcryl 90 HV; Glustitch, Delta, Canada) in the test group. The flow chart of the study is presented in Fig. 1.

Forty-four (15 males and 29 females) subjects between the ages 32 and 73 years old (mean age 51.7 ± 11) in need of a mucogingival procedure involving EGG harvesting—either free gingival graft or de-epithelialized gingival graft—were consecutively selected for this study. Six subjects were smokers (3, test group; 3, control group).

Only voluntary participants were involved in the study after giving verbal and written informed consents. The study protocol was in accordance with the Declaration of Helsinki of 1975, revised in Tokyo in 2004.

All patients were informed and understood the objectives of the study and signed informed consents. The study was performed in private practice (Sondrio, Italy) between October 2016 and May 2017.

Participants satisfying the following inclusion criteria were enrolled in the present study: (i) 18 years of age or greater; (ii) patients with no reported systemic diseases; (iii) healthy periodontium or demonstrating stable periodontal condition following conventional periodontal therapy; (iv) full mouth plaque score (FMPS) and full mouth bleeding score (FMBS) of < 15%; (v) clinical indication for periodontal plastic surgery utilizing de-epithelialized gingival grafts (DGGs) to treat either single or multiple recession defects (Miller classes I, II, III) around natural teeth or dental implants, located in the mandible or in the anterior maxilla (from canine to canine); (vi) no history of previous palatal harvesting.

The exclusion criteria were the following: (i) pregnancy, (ii) reporting the use of medications that would adversely affect periodontal tissues, and (iii) inadequate endodontic treatment or tooth mobility at site of surgery.

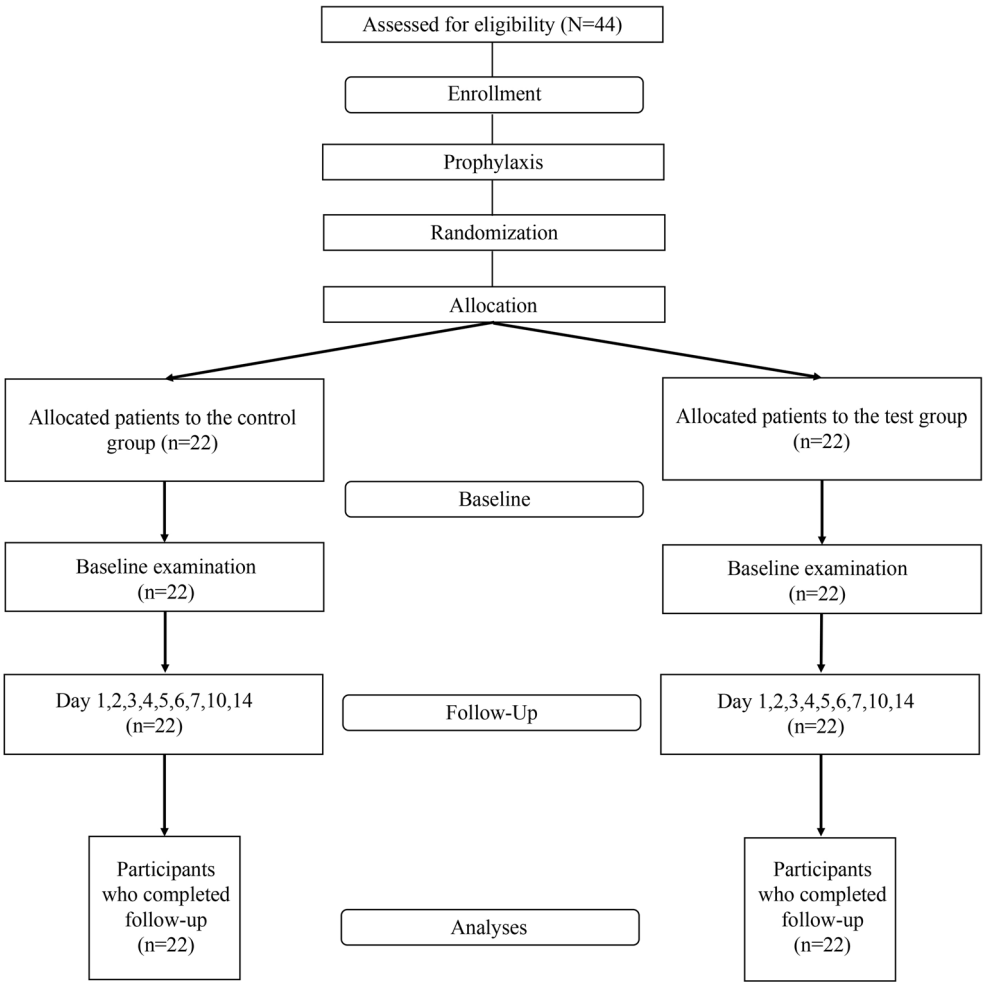

Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) flowchart showing the study design

Clinical measurements

The following measurements were collected before the palatal harvesting after performing the local anesthesia of the palate.

- PD: pocket depth of the palatal side of canine, premolars, and molars
- REC: recession depth of the palatal side of canine, premolars, and molars
- CAL: clinical attachment level of the palatal side of canine, premolars, and molars, which was obtained by adding PD and REC
- CHI: coronal horizontal incision of the EGG harvesting technique, which was performed about 2–3 mm apical to the gingival margin, according to the palatal PD of the teeth
- PT: palatal thickness, which was measured in the mesial, central, and distal parts of the designated area for graft harvesting by using the same anesthesia needle with an adjustable silicon disk stop

The following measurements were collected after the palatal harvesting.

- GH: graft height
- GW: graft width
- GT: graft thickness measured before de-epithelializing (if a connective tissue graft was required)

Demographic data and patient questionnaires

Before the surgery, age, gender, and smoking habits were registered. Smokers were considered patients who smoked ≥ 10 cigarettes per day.

To evaluate the postoperative pain, patients were instructed to complete a 100-mm VAS and classify the level of pain experienced on the palatal site from 0 to 10, with 10 being the worst pain ever experienced [36]. Each measurement was performed on days 1, 2, 3, 4, 5, 6, 7, 10, and 14 postoperative at the same time each day. The patients after each visit also answered the following questions: (a) "Did you take any more painkillers due to the palatal pain since the procedure was completed?" (b) "If necessary, would you repeat the palatal harvesting procedure?"

Sample size and randomization

Patients were randomly assigned to the test and control groups using a computer-generated randomization table. The group assignment for each patient was communicated to the operator through a sealed envelope that was opened during the surgery immediately after the graft harvesting procedure was completed. Patients were not aware of which one palatal protection they received. Sub-group analyses were also done by dividing the soft tissue graft measurements into two groups: height (≤ 4 mm and > 4 mm), width (< 14 mm and ≥ 14 mm), thickness (≤ 1.5 mm and > 1.5), and palatal tissue thickness (≤ 4 mm and > 4 mm).

Presurgical treatment

Each study participant received full mouth supragingival scaling, polishing, and oral hygiene instructions at least 3 weeks before the scheduled surgery. The patients were instructed on optimal toothbrush, dental floss, and/or interdental brush use. Each patient was given 600 mg of ibuprofen immediately before the surgery and was instructed to take another single same dose of ibuprofen after 6 h.

Surgical procedure

All surgical procedures were performed by the same clinician (C.T.) with extensive clinical experience to minimize the influence in the surgical technique.

The recipient site for the grafting technique, which was not in close proximity to the palatal donor site, dictated the size of grafts that were harvested. On the day of the surgery, 2% lidocaine with 1:100,000 epinephrine was administered for a greater palatine nerve block; palatal tissue thickness was measured in the mesial, central, and distal parts of the designated area for graft harvesting by using the same anesthesia needle with an adjustable silicon disk stop. These measurements were taken about 2–3 mm apical to the gingival margin of the adjacent tooth. The needle was inserted carefully, perpendicular to the mucosal surface until the palatal bone was contacted. At this point, palatal thickness was measured by fixing the silicon stop with cyanoacrylate (PeriAcryl 90 HV; Glustitch, Delta, Canada). Needle-penetration depth was then measured with an endodontic ruler. Both sides of the palate were included as donor sites for graft harvesting purposes.

An EGG was harvested by applying the same surgical technique previously described by Zucchelli and colleagues [20]. Briefly, the graft dimensions were outlined using a foil template in order to match the recipient bed. A coronal horizontal incision (CHI) was placed using a 15C blade apical to the gingival margin of the adjacent teeth followed by two vertical incisions perpendicular to the horizontal one. On the horizontal incision, the blade was moved perpendicular to the palatal bone reaching the depth of the desired soft tissue thickness. Afterwards, the blade was re-positioned, becoming parallel to the superficial surface. The blade was moved carefully to reach the apical part, after which a horizontal incision was made on the outer surface, perpendicular to the vertical ones, in order to free the graft from the palatal surface. The harvested graft was carefully de-epithelialized using a new blade extraorally.

For all of the harvested grafts, a UNC (University of North Carolina) periodontal probe (Hu-Friedy, Chicago, IL) was used to measure the height, width, and thickness of the graft before de-epithelialization and removal of fatty tissue. In the control group, the palatal wound was sealed with a porcine-derived collagen hemostatic absorbable sponge (Spongostan; Ethicon, Somerville, USA), which was kept in place by a 5-0 non-absorbable monofilament (Seralon; Serag Wiessner, Naila, Germany) sling crossed sutures anchored to the soft tissue apical to the palatal wound area. In the test group, in addition to the sling crossed sutures and the same collagen sponge, several drops of high-viscosity cyanoacrylate were applied along the wound borders and then throughout the whole collagen sponge in order to have a uniform superficial layer of the acrylic adhesive. In case of missing teeth, several simple interrupted sutures were used to secure the collagen sponge (Figs. 2 and 3).

Postsurgical instruction

Patients were asked not to brush the palatal surface of the maxillary teeth until the protection material and the sutures

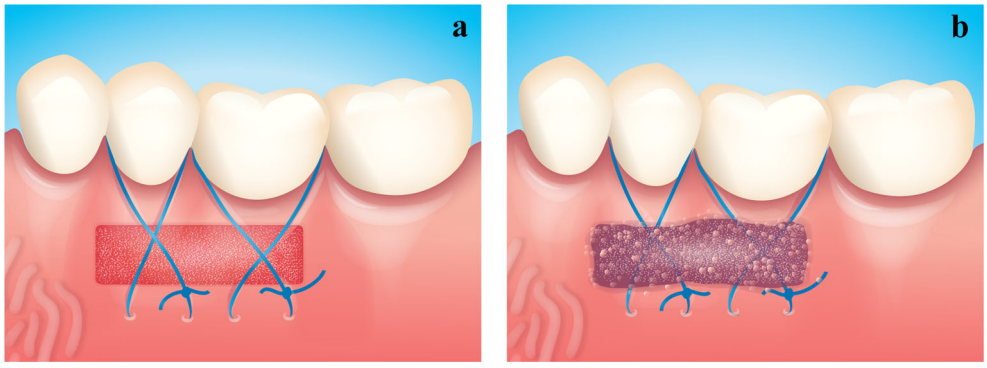

Fig. 2 Protection of the open wound by applying the following: **a** hemostatic collagen sponge (control group) and **b** cyanoacrylate layer on the underlying hemostatic collagen sponge (test group). In both groups, two sling crossed sutures were performed around the teeth in order to stabilize the collagen sponge

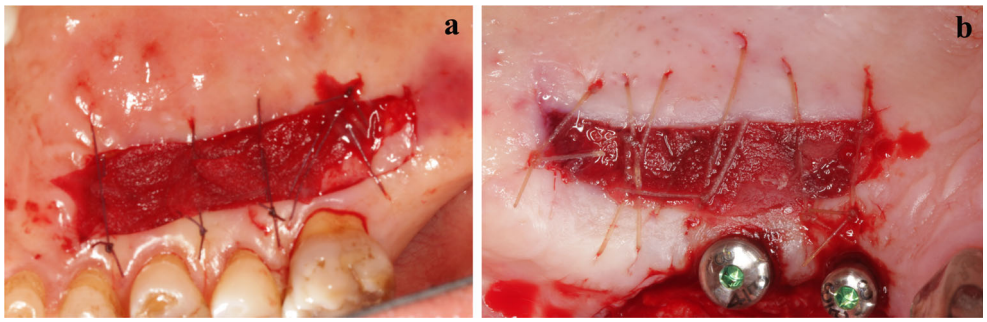

Fig. 3 Protection of the open wound by applying the following: **a** hemostatic collagen sponge (control group) and **b** cyanoacrylate layer on the underlying hemostatic collagen sponge (test group). In these cases, single interrupted sutures were used to stabilize the collagen sponge

were removed (14 days) and were instructed to take ibuprofen 600 mg 6 h after the surgery. During the following days, no ibuprofen was prescribed unless clearly necessary. No antibiotics were prescribed. Chlorhexidine rinses were prescribed twice a day until suture removal. Patients were also reminded to describe only the pain perceived from the palate during the VAS recording.

Statistical analysis

Statistical analysis was conducted by using the SPSS program 15.0 for Windows (SPSS) statistical software (IBM Corp, Armonk, NY, USA). Student's *t* test was performed in order to evaluate the mean difference between the harvested test and control soft tissue graft. Pairwise multiple comparisons (Bonferroni post hoc) after a multi-factor ANOVA were done to analyze if the VAS mean differences among the study days were statistically significant ($p < 0.05$). A general regression linear model was fitted relating test and control groups, smoking, sex, age, palatal thickness, graft thickness, graft width, and graft height with the VAS results. Finally, the 2 × 2 contingency chi-square was used for evaluating differences in patient painkiller consumption and willingness to repeat the surgery in the future.

Results

Forty-four patients were randomly distributed into two groups of 22 patients. Among them, three patients (two in the test group and one in the control group) presented with multiple implants in the posterior maxillary segment where the palatal graft was harvested. Demographic data of study participants are shown in (Table 1). Table 2 shows the dimensions of harvested grafts in the control and test groups. Throughout the duration of the study, no subjects dropped out and no postoperative complications were observed. The FMPS and FMBS remained < 15% during the whole study, without significant differences between groups. There was no significant difference between test and control group graft sizes ($p > 0.05$).

Statistically significant differences in pain perception were found between test and control groups in each of the studied days ($p < 0.01$). The greatest difference in VAS values between the two groups was on day 7, where the control group registered 1.8 higher VAS values. The lowest difference in VAS values was on day 14, where the control group registered 0.4 higher values than the test group (Fig. 4). Furthermore, a regression linear model showed no correlation between smoking habits, sex, and age with pain during the studied period ($p > 0.05$).

A similar trend was shown when the thickness of the palate and the dimensions of the harvested graft (height, thickness, and width) were correlated with the results of the VAS scale ($p > 0.05$). Comparing the width of the harvested graft in the two groups, it was statistically significant ($p < 0.05$) to have less pain (during days 3, 4, 6, 7, 10, 14) when the width was less than 14 mm. In general, height and thickness did not show significant difference for perceived pain. Results of the subanalyses are represented in Fig. 5. Throughout the study, 2 patients in the test group and 10 in the control group took 600 mg of ibuprofen ($p < 0.01$) at some point for pain on the palatal donor site.

When evaluating the willingness of patients to participate in future surgical procedures involving harvesting of the palatal tissue, 21 patients in the test group and 18 in the control were willing to repeat treatment if needed ($p > 0.05$). The differences in VAS scores among the studied days are depicted in Table 3.

Discussion

Coronally advanced flap in combination with sub-epithelial CTG has been extensively demonstrated as the gold standard

Table 1 Demographic characteristics of study participants

Characteristics	Control	Test
Age (years)	52.6 ± 9.3	50.86 ± 12.55
Gender	11 M, 11 F	4 M, 18 F
Smokers	3	3

Table 2 Dimensions of harvested grafts in the control and test groups

	Control	Test	*p* value
Graft height	4.63 ± 1.22	4.68 ± 0.84	> 0.05
Graft width	13.32 ± 4.32	13.87 ± 4.12	> 0.05
Graft thickness	1.59 ± 0.33	1.70 ± 0.33	> 0.05
Palatal thickness	4.27 ± 1.24	4.25 ± 0.84	> 0.05

for root coverage procedures [3, 37]. Alternatively, several authors have experimented with different graft substitutes or biologic agents [38] aiming at decreasing patient discomfort and pain perception. CTG harvesting techniques were designed to harvest an autologous sub-epithelial connective tissue while minimizing the postoperative pain by ensuring healing by primary intention [13–15, 17]. The open palatal wound and healing by secondary intention that characterizes the EGG harvesting techniques has led many clinicians to avoid this harvesting approach [39, 40]. However, as demonstrated by Zucchelli and coworkers in 2010, patient morbidity and discomfort following EGG harvesting techniques can be successfully controlled if properly managed [20].

The results of the present study demonstrated that the use of cyanoacrylate bio-adhesive in addition to a collagen sponge over the palatal wound results in significantly decreasing pain perception when compared to a collagen sponge alone after EGG surgery ($p < 0.01$). In addition, addition of cyanoacrylate bio-adhesive leads to better patient acceptance for re-treatment, if needed, and less tendency to consume analgesics ($p < 0.01$) compared to the control group.

Several advantages can be attributed to the EGG harvesting technique. Being a relatively faster procedure, it also provides a higher quality graft with less glandular and fatty tissue and more uniform thickness, and it can be performed in cases with thin palatal fibromucosa [20]. The EGG technique allows clinicians to use the graft with or without the epithelium and provides a graft that is dense, stable, and less prone to shrinkage than classic techniques for harvesting CTGs [10, 21].

In 2010, Zucchelli concluded that EGG harvesting technique does not cause more postoperative discomfort than conventional CTG harvesting technique [20], demonstrating that if the palatal wound is maintained and protected during the healing period with a hemostatic collagen sponge, no differences could be found between CTG and EGG groups in terms of pain and morbidity. Hence, the utilization of a hemostatic agent seems to be critical for minimization of postoperative pain.

Cyanoacrylate has been applied intraorally with multitude of different purposes including but not limited to the following: as periodontal dressing [41], for sealing sinus membrane perforations [42], for stabilizing bone fragments during fracture fixation, and in closing peripheral nerve anastomosis [43]. Cyanoacrylates seem promising in the intraoral field due to their strong sealing, bacteriostatic, and hemostatic properties [33]. Multiple studies examined the use of cyanoacrylate glues as an alternative to suturing intraoral and extraoral wounds concluding that cyanoacrylates are faster, more reliable [44], and less painful [45] and cause better hemostasis [46, 47]. In the present investigation, the use of cyanoacrylate resulted in less patient discomfort and a lower tendency to use analgesics compared with control patients. When comparing the VAS

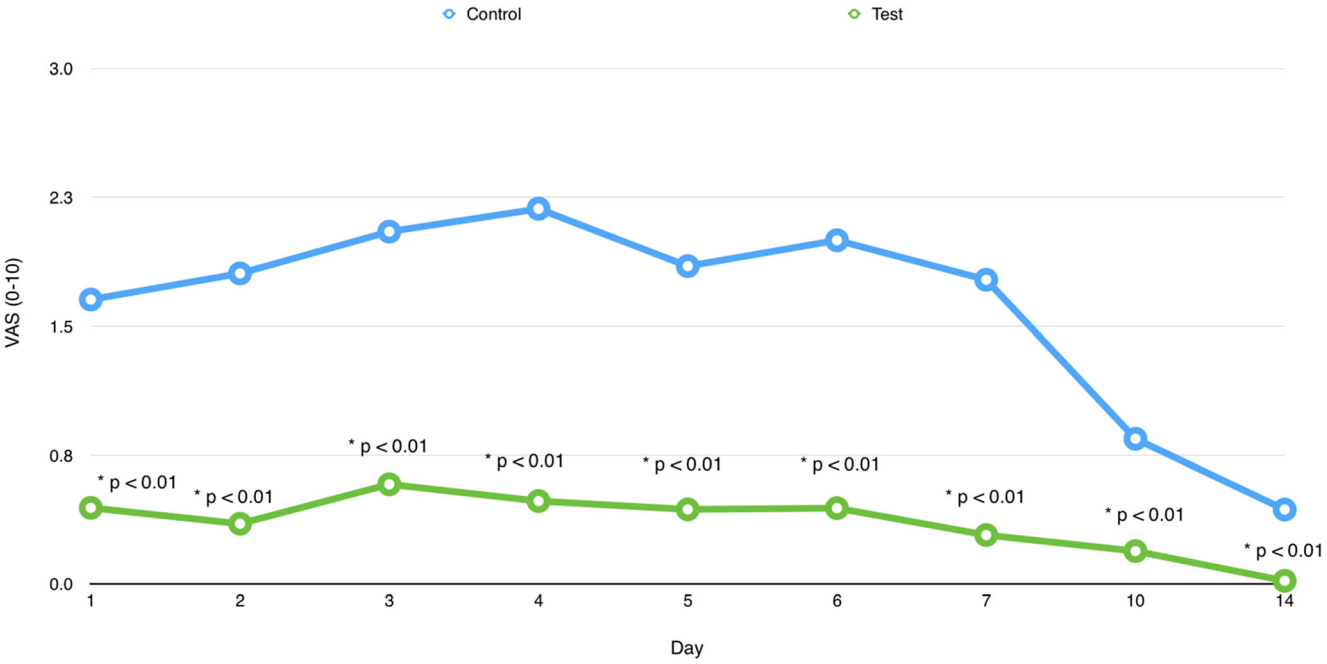

Fig. 4 Self-perceived pain between control and test groups for the entire follow-up period

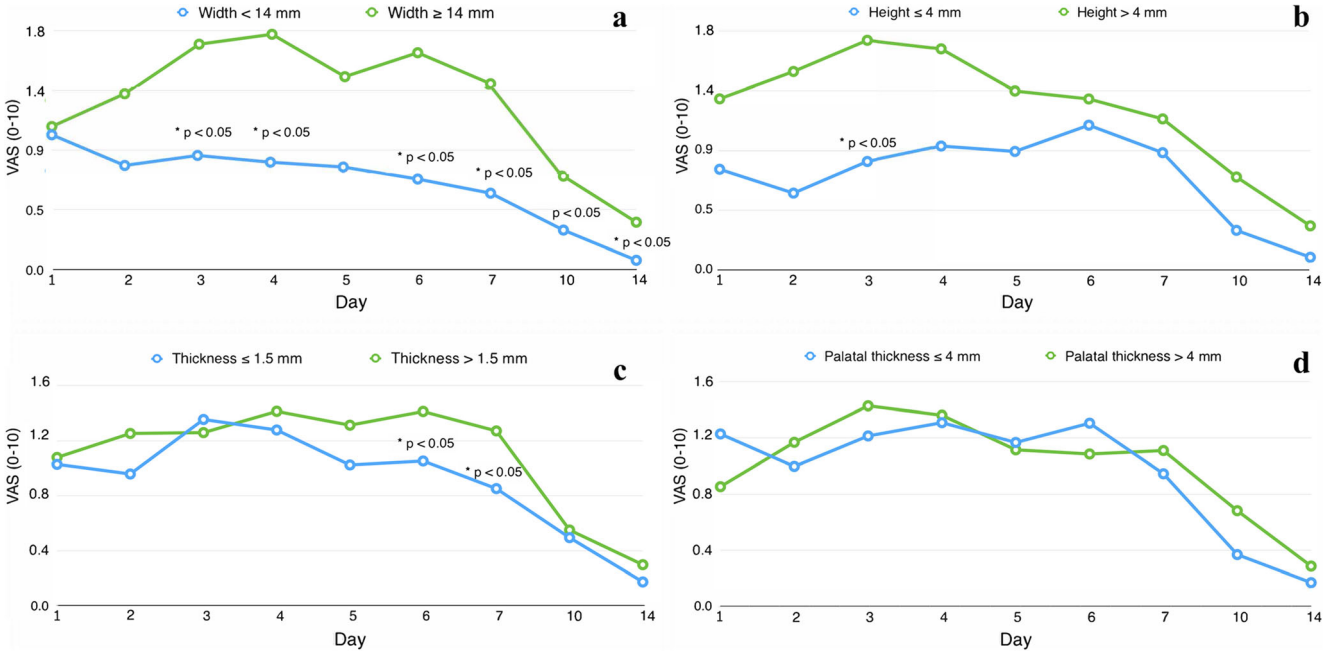

Fig. 5 Self-perceived pain in relation to the following: **a** graft width, **b** graft height, **c** graft thickness, **d** palatal thickness

scores from the test group of the current study to those from similar previous randomized controlled trials using collagen sponge [20] or platelet-rich fibrin [26], it is observed that test patients in the current investigation experienced overall less discomfort.

Contrary to the results obtained in the present study, Burkhardt and colleagues in 2015 reported a positive association between increased patient's morbidity and thickness of harvested graft [48]. This could be due to the fact that Burkhardt showed increased postoperative pain in cases of graft thickness > 2 mm, while in the present study no graft was thicker than 2 mm. Although it has been shown that the height of the graft may positively affect patient morbidity [20], our results failed to confirm this correlation. A possible explanation may be the smaller height of the graft harvested in the present study, 4.64 mm on average, compared to the study of Zucchelli et al. that reported a graft height of more than 6 mm in both test and control groups [20]. In agreement with the study of Zucchelli [20], the patient's palatal thickness did not seem to affect the morbidity. In the present investigation however, a graft width of > 14 mm was related to increased self-perceived pain during days 3, 4, 6, 7, 10, and 14.

In addition, Burkhardt and colleagues reported greater pain during the first postoperative day decreasing during the following days [48]. On the other hand, the current study found the peak of pain experience during the 3rd (test group) and 4th day (control group). This difference could be due to the lack of palatal protection in the study of Burkhardt, which could have induced pain because of the direct contact with the wound.

In a recent randomized clinical trial, Femminella et al. claimed that platelet-rich plasma was able to enhance palatal healing and reduce morbidity compared to gelatin sponge, reporting also a

Table 3 Comparison of the experienced pain among the studied days

	Day									
Day	0	1	2	3	4	5	6	7	10	14
	1	–	1.00	1.00	1.00	1.00	1.00	1.00	*0.05**	*0.001**
	2	1.00	–	1.00	1.00	1.00	1.00	1.00	0.121	*0.011**
	3	1.00	1.00	–	1.00	1.00	1.00	1.00	*0.002*	*0.000**
	4	1.00	1.00	1.00	–	1.00	1.00	1.00	*0.012**	*0.002**
	5	1.00	1.00	1.00	1.00	–	1.00	1.00	0.064	*0.004**
	6	1.00	1.00	1.00	1.00	1.00	–	1.00	0.163	*0.017**
	7	1.00	1.00	1.00	1.00	1.00	1.00	–	0.536	*0.052**
	10	*0.05**	0.121	*0.002**	*0.012**	0.064	0.163	0.536	–	*0.011**
	14	*0.001**	*0.011*	*0.000**	*0.002**	*0.004**	*0.017**	0.052	*0.011**	–

Italicized entries were statistically significant to $p = < 0.05$

lower mean discomfort VAS score (2.4 ± 0.88) compared to that of Zucchelli et al. (3.1 ± 1.99) [20, 26]. On the other hand, without sealing the palatal wound, Burkhardt et al. reported peaks of VAS pain at days 1 and 3, respectively, of 4.10 and 3.33 on average [48]. Our results, indeed, highlighted that the combination of collagen sponge and cyanoacrylate was related to VAS values always lower than 0.6, where the peak of pain was reached during the 3rd day (0.58 ± 0.92). It can be speculated that the sealing, bacteriostatic, and hemostatic properties together with the formation of a protective layer that isolates the wound from the oral cavity make cyanoacrylate effective at minimizing palatal pain when combined with an underlying collagen sponge. It is reasonable to assume that the complete seal and protection of the wound is the main reason for the less postoperative morbidity of the test group compared to that of the control group.

Possible complications of the application of cyanoacrylate include its early detachment from the wound or patient discomfort for its additional volume on the palate. However, in this study, no patient reported such a discomfort and all the cyanoacrylate protection were found in place at the day of suture (and protection) removal.

Authors are aware of the limitations of the present study. First, males and females were not homogeneous in the test group and that may have affected the postoperative pain perception.

Within the limit of this study, the following conclusions can be drafted: (i) patient morbidity following EGG harvesting technique can be managed by protecting the palatal open wound during healing; (ii) applying a layer of cyanoacrylate to a collagen hemostatic sponge stabilized to the palatal wound was more effective in reducing postoperative pain and drug consumption than a collagen sponge alone; (iii) graft height, graft thickness, and palatal thickness did not seem to affect the patient morbidity; (iv) graft width ≥ 14 mm was related to higher pain during the first 14 days.

New clinical studies comparing CTG harvesting technique and EGG combined with the described collagen and cyanoacrylate protection are needed to validate our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this article.

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