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Use of a gel containing a phthalocyanine derivative in palatal wounds after gingival graft removal: case series

Uso de gel contendo derivado de ftalocianina em feridas palatinas após remoção de enxerto gengival: série de casos

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ABSTRACT

Background: Gingival grafts are used to correct mucogingival defects around teeth and implants, but post-operative morbidity, including pain and discomfort, still represents a clinical challenge. Studies using phthalocyanine derivatives (PHY) demonstrated antimicrobial effects, but these substances also seem to present beneficial properties in wound healing. **Objective:** This case series aimed to evaluate the use of a gel containing 0.1% PHY in the post-operative healing of gingival graft donor sites, with a focus on reducing discomfort and promoting healing. **Material and Methods:** Five healthy patients were submitted to standardized surgical procedures for root coverage with connective tissue grafts (de-epithelialization technique) and coronal advanced flap. After surgery, they received instructions to use 0.1% PHY gel in palatal donor sites. Clinical and somatosensory parameters were evaluated, as well as analysis of patient-centered outcomes (use of analgesics, difficulty of chewing and pain in the donor areas). Clinically, there was a progressive improvement in wound epithelialization over 30 days, reaching 100% of epithelialization. **Results:** There was a gradual reduction in the wound area, indicating a favorable trend towards complete healing. Somatosensory analysis revealed superior sensitivity in the donor areas after 60 days, with a decrease after 6 months. The use of analgesics was low, and pain scores were moderate. **Conclusion:** The use of 0.1% PHY gel seemed to be beneficial in promoting effective and rapid healing in palatal donor sites of gingival grafts. These results indicate that PHY gel may be a promising option for improving clinical results and patients' quality of life following gingival grafting procedures.

KEYWORDS

Connective tissue; Palate; Phthalocyanine; Quality of life; Wound healing.

RESUMO

Contexto: Os enxertos gengivais são utilizados para corrigir defeitos mucogengivais ao redor de dentes e implantes, mas a morbidade pós-operatória, incluindo dor e desconforto, ainda representa um desafio clínico. Estudos com derivados de ftalocianina (PHY) demonstraram efeitos antimicrobianos, mas essas substâncias também parecem apresentar propriedades benéficas na cicatrização de feridas. **Objetivo:** Esta série de casos teve como objetivo avaliar o uso de um gel contendo 0,1% de PHY na cicatrização pós-operatória de áreas doadoras de enxertos gengivais, com foco na redução do desconforto e na promoção da cicatrização. **Material e Métodos:** Cinco pacientes saudáveis foram submetidos a procedimentos cirúrgicos padronizados para recobrimento radicular com enxertos de tecido conjuntivo (técnica de desepitelização) e retalho avançado coronal. Após a cirurgia, receberam instruções para utilizar o gel de 0,1% de PHY nas áreas doadoras palatinas. Parâmetros clínicos e somatossensoriais foram avaliados, juntamente com resultados centrados no paciente (uso de analgésicos,

dificuldade de mastigação e dor nas áreas doadoras). **Resultados:** Houve melhora progressiva na epitelização das feridas ao longo de 30 dias, alcançando 100% de epitelização. A área da ferida reduziu gradualmente, indicando uma tendência favorável à cicatrização completa. A análise somatossensorial revelou maior sensibilidade nas áreas doadoras após 60 dias, com redução após 6 meses. O uso de analgésicos foi baixo e os escores de dor foram moderados. **Conclusão:** O gel de 0,1% de PHY mostrou-se benéfico na cicatrização eficaz e rápida das áreas doadoras palatinas, sendo uma opção promissora para melhorar os resultados clínicos e a qualidade de vida dos pacientes submetidos a enxertos gengivais.

PALAVRAS-CHAVE

Enxerto de tecido conjuntivo; Palato; Ftalocianina; Qualidade de vida; Cicatrização de feridas.

INTRODUCTION

Gingival grafts have been widely used to correct mucogingival defects around teeth and implants [1]. Considering root coverage procedures, subepithelial connective tissue graft (SCTG) associated with coronal advanced flap (CAF) is the gold standard treatment [2,3]. However, one of the most challenging aspects of techniques using autogenous grafts is the postoperative morbidity and discomfort following their removal from the palatal area. These symptoms may also be related to necrosis and bleeding [4]. Therefore, to improve patients' quality of life during the postoperative period, the use of agents that can minimize the effects of removing this type of graft is essential.

There are several methods of protecting the palatal wound, such as surgical dressing [5], modified Hawley plate [6], collagen sponge with cyanoacrylate [7], photobiostimulation with low-power laser [8], fibrin-rich plasma [9], hyaluronic acid, herbal extracts [10], tilapia skin [11], and others. The most commonly used methods promotes mechanical protection at donor areas, acting as a barrier (surgical dressing and modified Hawley plate). However, burning sensation, discomfort, bad breath and phonetic difficulties are common negative reports. Therefore, protective agents with biological effects such as platelet derivatives, hyaluronic acid and herbal extracts can enhance healing and reduce post-operative morbidity. Alternative agents to chlorhexidine have been investigated to improve healing outcomes in periodontal surgical sites, showing promising potential. The limitations of chlorhexidine, including its propensity to cause tooth and tongue staining with prolonged use and alterations in taste, have prompted increased interest in exploring alternative solutions [12].

Currently, there is a lack of consensus about the ideal protection, but it is expected mechanical protection and also bioactive properties capable of favoring regenerative process of palatal wound [13,14].

Phthalocyanine derivatives (PHY) are chemical compounds associated with metal ions, widely used as photosensitizing dyes in antimicrobial photodynamic therapy (aPDT). The PHY molecule is activated by visible light absorption, triggering electronic reactions from its excited state, and demonstrates good tissue penetration depth, resulting in an enhanced aPDT response [15]. Another less explored class of PHY in the literature includes self-activated derivatives, characterized by a broad spectrum of action based on self-activation and continuous, localized production of reactive oxygen species in the absence of light, chemicals, or electricity, requiring only molecular oxygen [16,17].

In vitro studies showed that self-activated PHY has antibacterial [16-18], antifungal [18], antibiofilm [16], antiviral [19,20] and low toxicity properties, without negative effects on wound healing [17,19]. Clinical studies demonstrated positive effects on periodontal treatment [21] and ulcer healing [22].

Aiming to enhance donor site healing and reduce post-operative morbidity, this case series proposed the use of a gel containing 0.1% PHY to promote healing of the donor area and reduce post-operative morbidity after root coverage procedures with SCTG plus CAF.

MATERIAL AND METHODS

Five healthy patients (42- to 58-year-old) were treated at Periodontics clinic of the Bauru

School of Dentistry- University of São Paulo (FOB-USP). This case series is part of a project approved by the Ethics Committee for Human Research of FOB-USP (CAAE: 19692019.1.0000.5417) and registered in Brazilian Registry of Clinical Trials (REBEC- RBR-93ccq38). Inclusion criteria were: patients with healthy palatal area, clinical diagnosis of multiple gingival recessions RT1 or RT2 with at least 1 of the gingival recessions (GR) ≥ 2 mm, including canines, premolars and molars. Exclusion criteria were: use of prostheses with palatal coverage, previous palatal graft removal, teeth with mobility, smokers, pregnant and lactating women, history of periodontal disease or recurrent abscess formation, use of medication (anticonvulsants, antihypertensives, contraceptives or immunosuppressants) or drugs that influence wound healing, poor oral hygiene (plaque index and bleeding index >20%).

Patients were submitted to scaling, root planing, coronal polishing and oral hygiene instructions before surgical procedures. Surgeries were performed under magnification (3.5x) by the same professional (RSC). Patients received written instructions to standardize home treatment. Oral rinse containing PHY (0.12%) and application of PHY gel in palatal wound (0.1%) were used during the first 14 post-operative days. Patients were also instructed to floss and brush the non-operated area with fluoride toothpaste three times a day (after breakfast, lunch and dinner). Mouthwashes with PHY rinse were performed twice a day (after lunch and dinner), for 60 seconds, 30 minutes after brushing. Patients applied a standardized amount of (size of a pea) PHY gel in palatal wound areas, using their fingertip to avoid injury on surgical site, 3 times a day (after breakfast, lunch and dinner). They were instructed to refrain from eating or drinking for approximately 1 hour after gel application. The application was performed after rinsing with mouthwash.

Consent statement

All patients received and signed a written informed consent form before undergoing the treatment.

Surgical procedure

GRs were treated with CAF [23] plus SCTG harvested by de-epithelialized technique [24,25]. Grafts were standardized with 5 mm width, two teeth mid-distal length, 1.5 mm thickness and palatal gingival margin preservation of 2 mm. SCTG was positioned and stabilized at cementum-enamel junction (CEJ) with 5-0 nylon monofilament sutures (Techsuture, Bauru/SP, Brazil). Flap was coronally positioned over CEJ with suspensory sutures. X-shaped sutures were made in palatal donor sites and removed after 7 days. Sutures in recipient areas were removed after 14 days. Patients received 8mg of dexamethasone 1 hour before surgical procedure. Postoperatively, participants used 200mg of nimesulide 2x/day on first and second days and 100mg of nimesulide 2x/day on third and fourth days. They were instructed to use paracetamol 750mg every 6 hours in case of pain.

Wound assessments

Clinical parameters of the palatal remaining wound area (RWA), wound epithelialization (WE) [26-28] and remaining remodeling area (RRA) were recorded after 7, 14 and 30 postoperative days. Standardized photographs (brightness, distance and angle) were taken and exported to Image J software (NIH, Bethesda, USA) for measurement of the areas (mm2) by a trained and calibrated professional (CAS). The RRA and RWA (Figures 1, 2 and 3) results were presented in mm2; WE was presented as percentage.

Quantitative evaluation of somatosensory profile (Von Frey) of donor areas was determined by Mechanical Detection Threshold (MDT) and Mechanical Pain Threshold (MPT) tests. Both tests were applied at baseline and after 2 and 6 months. MDT uses nylon monofilaments adapted by Semmes-Weinstein to determine patients' tactile threshold [29]. The force applied by the monofilament can vary from 0.008 g/mm^2 to 300 g/mm^2. Before the test, participants were instructed, with their eyes closed, to verbally report when they felt a "light touch" on the contact area of the monofilaments. The palatal contact area was defined at 1-1.5mm from gingival margin of premolars (SCTG donor area). MDT test began with the thinnest filament (0.008 g/mm^2), and sequentially thicker filaments were applied until the participant verbally reported feeling a light touch (positive stimulus (+)). After this positive report, the order was reversed for the next filament with the lowest value, until the participant no longer felt the application of the tactile stimulus (light touch) (negative stimulus

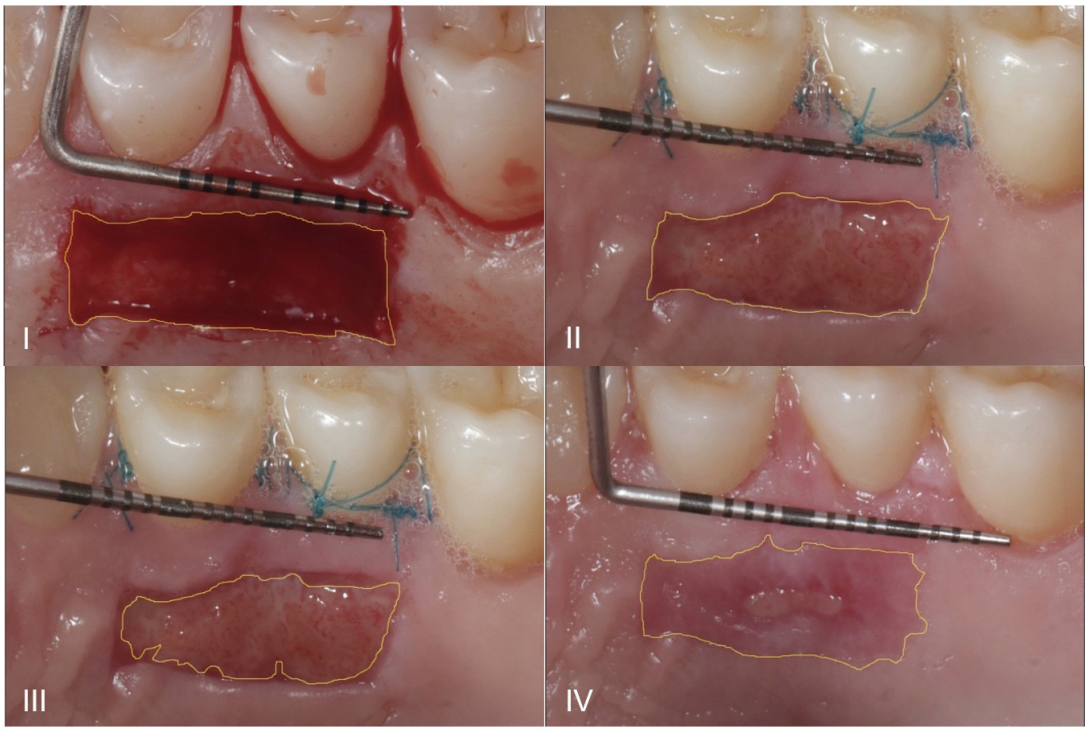

Figure 1 - Example of measurements performed in ImageJ software. (I) Wound area immediately after graft removal; (II) Delineation of the RWA at 7 days post-surgery; (III) Delineation of the RWA by the difference in color between the edges and the center of the wound; (IV) Delineation of the RWA 14 days after surgery.

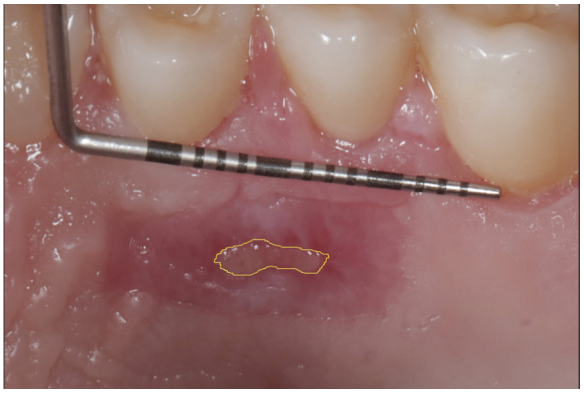

Figure 2 - Delimitation of the remaining wound area (RWA), considering the area in the center of the wound that has not yet epithelialized.

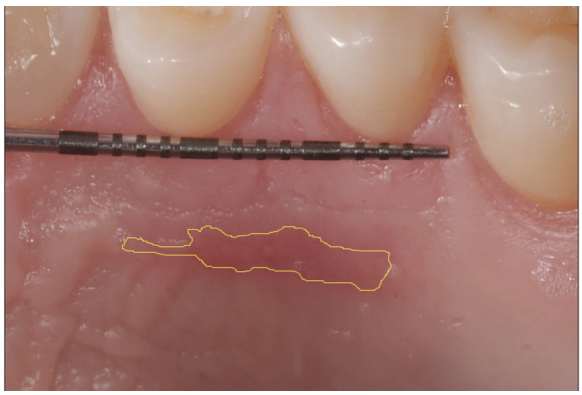

Figure 3 - Delimitation of the remaining remodeling area (RRA) after 30 days.

(-)). This measurement was made until 5 negative stimuli (downward) and 5 positive stimuli (upward) were obtained and the geometric mean of these repetitions was calculated [30-32].

The MPT also used the adapted monofilaments but assessed mechanical pain threshold. In the same way, the participant was instructed to verbally report when they felt a sensation of "needling, pinpricking or a slightly painful sting". The method of applying the filaments and measure the pain stimuli in MPT were the same described for MDT [31].

Patient-centered outcomes

Patients completed a diary during 14 days after surgery [33] to record treatments perceptions and spontaneously describe any PHY adverse effects. This diary was developed to assess patient's recovery in four main areas - post-surgical sequelae, pain and discomfort, oral function and interference with daily activities. Questions were answered using visual analog scales (VAS). In addition, questionnaire included a compliance table to ensure PHY use, filled in by the patient with "YES" or "NO", recording number of times of brushing, rinsing and topical applications each day.

RESULTS

Wound assessments

Table I shows the outcomes of palatal healing assessment at the different post-operative periods (7 days, 14 days and 30 days). Remarkable progress in wound epithelialization was observed over time, with all patients achieving 100% epithelialization within 30 days of surgery. In addition, there was a gradual reduction in wound area during the follow-up period, indicating a positive trend towards complete healing. At 60 days post-surgery, in all five cases, there was no visible wound (Figures 3 to 7).

Somatosensory evaluation

The analysis of somatosensory profile (Table II) demonstrated that at 60 days postoperatively, palatal areas showed superior sensitivity compared to baseline. However, after 6 months, although still more sensitive than baseline, this sensitivity decreased compared to 60 days. This suggests that the palate becomes more sensitive to touch and less resistant to pain after graft removal, during a follow-up of 6 months. In one patient, pain resistance after 6 months was higher than pre-surgery, while in two patients, pain resistance after 6 months was lower than 2 months after surgery.

Table I - RWA values in mm^2, RRA in mm^2 and WE in percentage, in the postoperative period

		BL	7	14	30
Patient 1	RWA	91.061	51.355	2.714	0
	RRA	-	74.937	67.223	53.106
	WE (%)	-	43.60	97.01	100
Patient 2	RWA	64.784	45.582	0.261	0
	RRA	-	55.404	42.001	26.374
	WE (%)	-	32.75	99.59	100
Patient 3	RWA	59.961	45.570	4.470	0
	RRA	-	52.331	41.140	2.609
	WE (%)	-	24	92.54	100
Patient 4	RWA	84.273	54.209	14.817	0
	RRA	-	74.231	54.105	25.052
	WE (%)	-	35.67	82.41	100
Patient 5	RWA	68.801	39.585	3.524	0
	RRA	-	56.592	44.663	15.551
	WE (%)	-	42.46	94.87	100

BL (baseline), RWA (remaining wound area), RRA (remaining remodeling area), WE (wound epithelization).

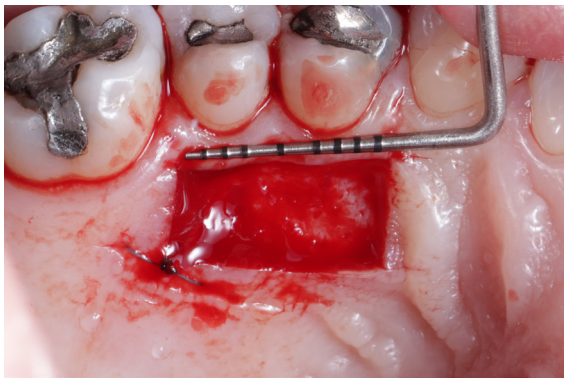

Figure 4 - Appearance of the palate immediately after free gingival graft removal.

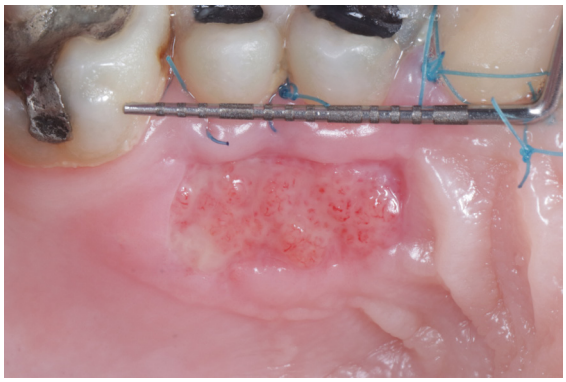

Figure 5 - Appearance of the palate after 7 days, possible to identify RRA and RWA.

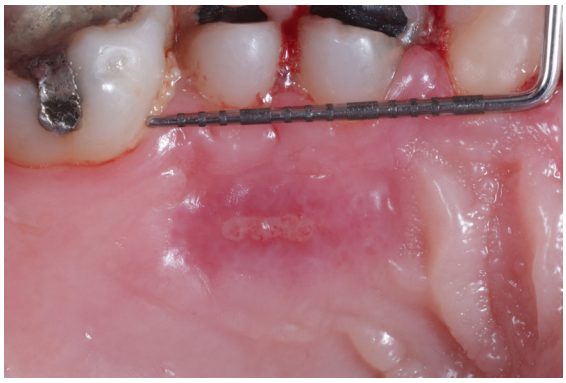

Figure 6 - Appearance of the palate after 14 days, predominantly RRA area.

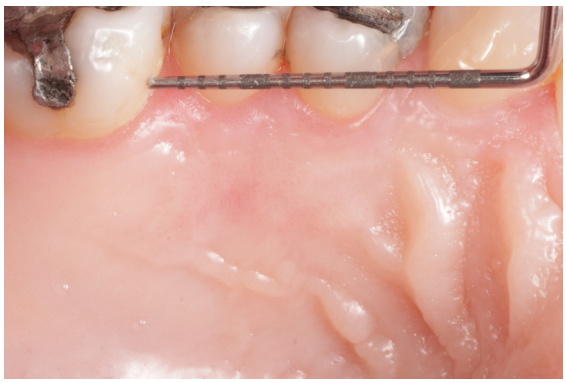

Figure 7 - Aspect of the palate after 30 days, 100% epithelialized area.

Table II - Results of the somatosensory profile tests (expressed in g/mm²) at three time points, BL (baseline), 2 months and 6 months.

	BL	2	6	Test
Patient 1	3.03	0.72	1.09	MDT
	32.54	9.61	11.81	MPT
Patient 2	1.50	0.39	1.18	MDT
	328.63	19.75	1.68	MPT
Patient 3	8.69	7.71	5.19	MDT
	109.54	50.05	77.46	MPT
Patient 4	0.27	0.05	0.09	MDT
	26.60	19.75	41.57	MPT
Patient 5	0.79	0.20	1.51	MDT
	29.58	10.93	9.05	MPT

MDT (mechanical detection threshold) and MPT (mechanical pain threshold) tests.

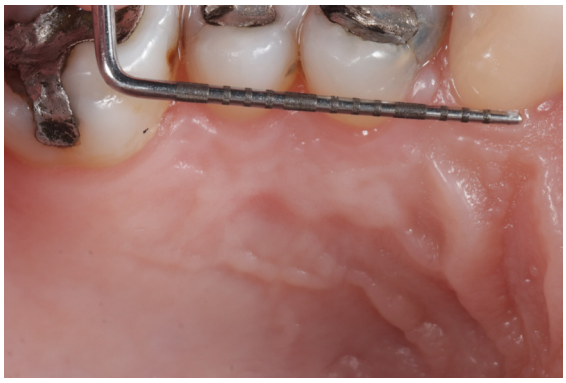

Figure 8 - Appearance of the palate after 60 days, no visible wound.

Patient-centered outcomes

Daily adapted questionnaire [33] reported that chewing difficulty was more inconvenient than palatal pain, reaching higher scores on the day of surgery (Figures 8 and 9). Palatal pain peaked on the sixth day (44), the same day of the highest mean of analgesic consumption (1.6) (Figure 10). VAS mean during 14 postoperative days were: Difficulty chewing - 28; Palate pain - 20.7; Number of analgesics - 0.57 (Figure 11). No adverse effects of PHY were reported.

DISCUSSION

In periodontal plastic surgeries, the use of gingival grafts harvested from different donor sites may lead to increased postoperative morbidity, such as pain, bleeding, and other complications that impact patients' quality of life. Considering these factors, the literature has highlighted important evidence on methods for protecting and managing the donor site, aiming to minimize postoperative complications and improve patients' postoperative experience. There is a lack of consensus about the best method of palatal protection for gingival graft donor sites. However, mechanical protection and bioactive

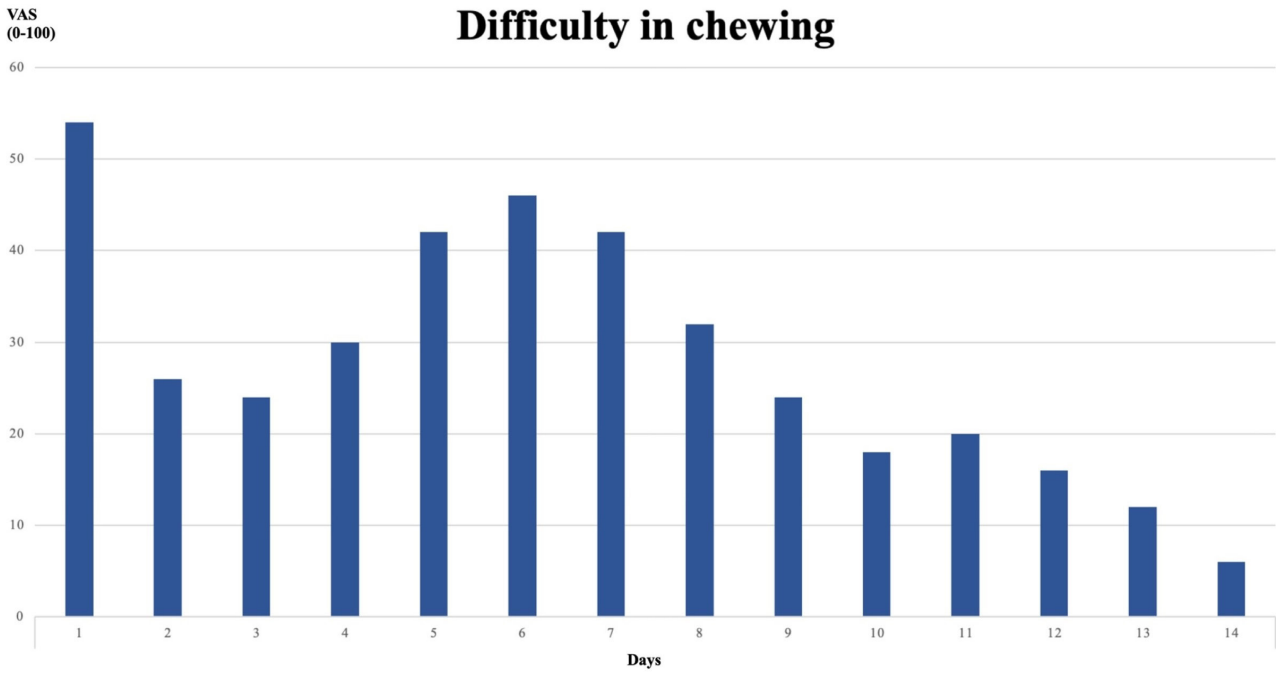

Figure 9 - Graph showing the mean Visual Analogue Scale (VAS) scale values of the five patients according to each of the 14 postoperative days. "Difficulty chewing" peaked on the first postoperative day.

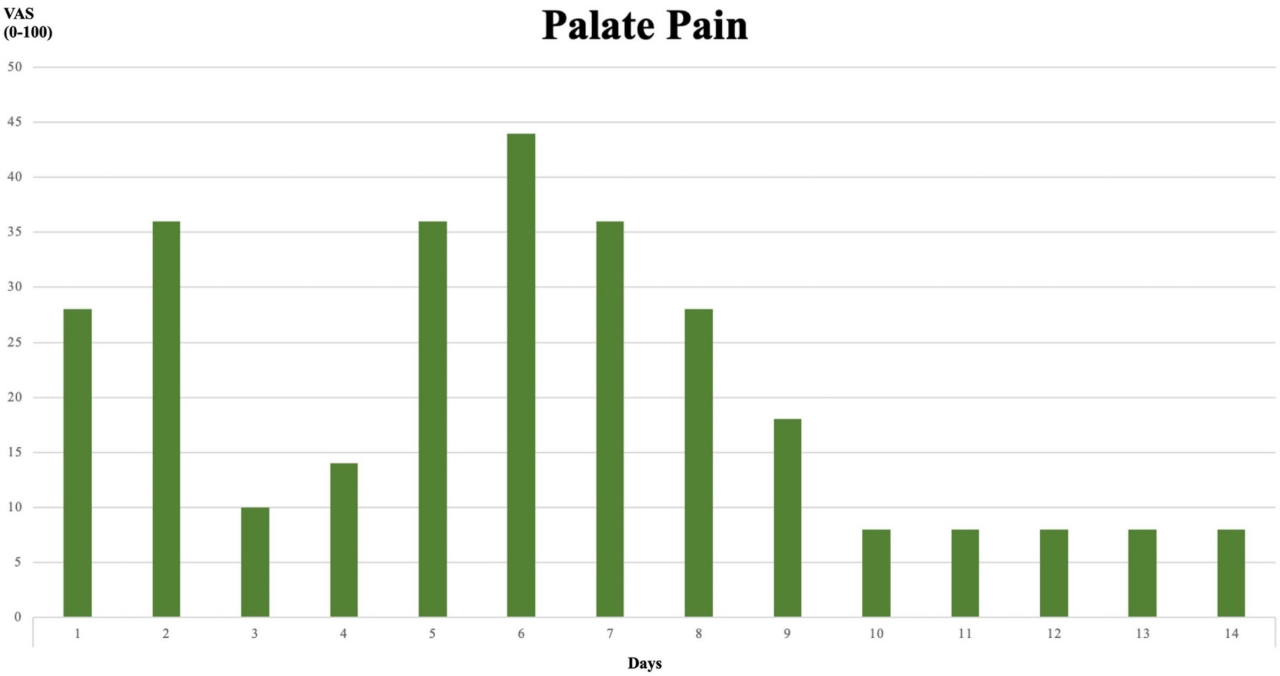

Figure 10 - Average VAS scale values for "palate pain", peaking on the sixth postoperative day.

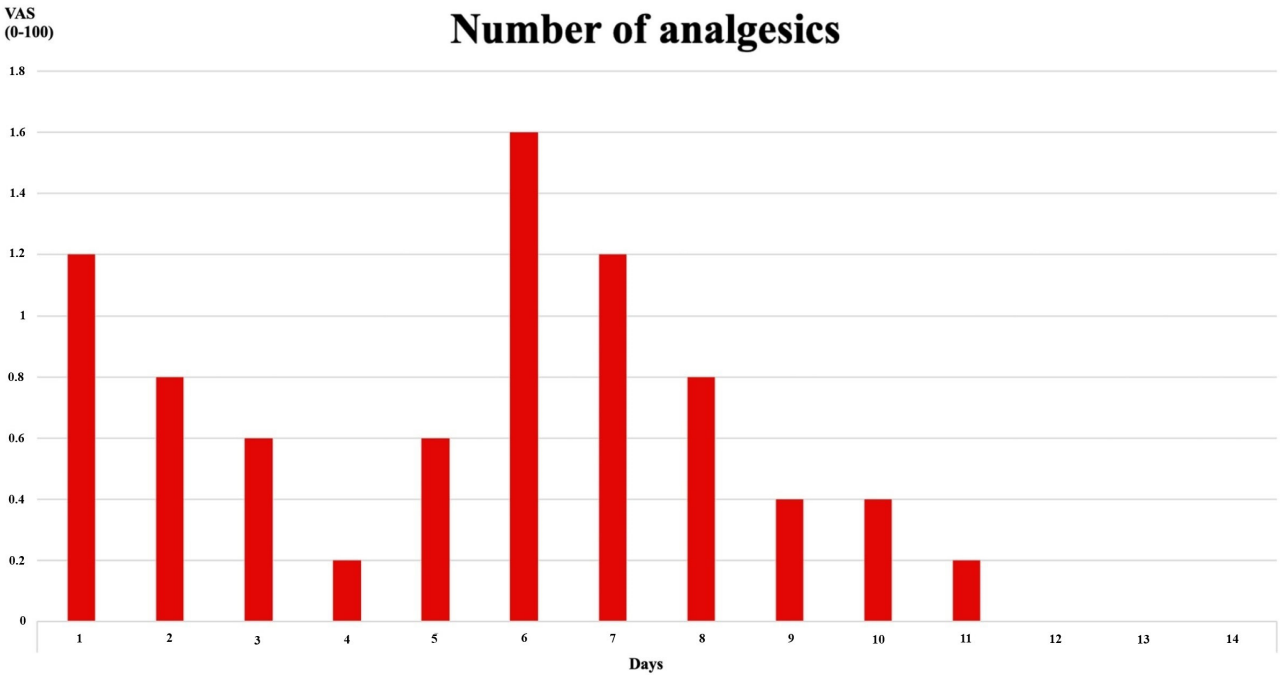

Figure 11 - Average VAS scale values for "number of analgesics" peaked on the sixth day, in line with the highest average reported for "palate pain".

properties favoring wound healing process are essential [34,35].

The present case series demonstrated that the use of PHY gel on palatal donor sites for 14 days post-operatively resulted in progressive reduction of RWA. WE of over 80% occurred within two weeks of follow-up and RRA was not visible after 60 days. Somatosensory profile showed that palatal sensitivity increased at 60 days and 6 months compared to baseline, with less resistance to pain. Difficulty of chewing presented superior impact compared to palatal pain and mean analgesic consumption was 0.88 and 0.57 at 7 and 14 days, respectively.

Randomized clinical trials have been conducted to evaluate agents with easy clinical application and cost-effectiveness, also favoring healing process [36]. Periodontal surgical dressing are the most used materials for palatal mechanical protection after harvesting gingival grafts. However, they can delay the healing process, cause biofilm accumulation, painful symptoms, bad breath and discomfort when speaking and chewing [5].

When evaluating mean of WE, this case series presented 35.7% in 7 days and 93.3% in 14 days. Similarly, Miguel et al. [28] obtained 38.4% and 90.0% WE after 7 and 14 days, respectively, with the application of low-intensity electrotherapy protocol on palatal wounds. The results were superior to control group (22.2% and 86.2%, respectively). In another investigation, topical application of ozone therapy and laser therapy on palatal wounds presented 33% and 25% of the palates with complete epithelialization after 14 days [37]. Another study conducted by the same group demonstrated that topical use of oral flurbiprofen spray reduced postoperative morbidity but presented negative effects on epithelialization of secondary palatal wound healing [38]. In the present case series, topical application of PHY gel positively influenced epithelialization and allowed complete healing of the palatal wound with no visible RRA after 60-day of follow-up.

The effect of a statin/chitosan gel on the palatal wounds healing after free gingival graft removal was assessed using a scale of 0 to 4, according to the color and appearance of the area with significant reduction between the seventh and fourteenth day [39]. Palatal wounds after Bruno's technique grafts removal were assessed considering the wound area after 7 days. Authors observed reduced wound areas in photobiomodulation group (60J/cm^2) after 14 days [27]. In another study with similar methodology, the wound area was also considered only after 7 days, using Bruno's technique and showed similar results of reduction of WA after 14 days [40]. Another study similarly to the present case series considered the time of free gingival graft harvesting for wound area analysis. Superior reduction in this parameter was observed in electrotherapy group, which was zero at 21 days [28]. However, no differentiation was made between RWA and RRA.

The technique of harvesting a free gingival graft [24] results in secondary wound closure, with exposure of connective tissue, which can lead to postoperative morbidity [41,42]. Thus, the search for a protective or regenerative agent for palatal wound that provides a more comfortable postoperative period for the patient is necessary. The analysis of self-reported patient-centered outcomes [33] proved to be accurate and reliable. The highest scores were for "difficulty chewing", which is to be expected as it involves the painful sensation (donor area pain) and also from recipient area. Authors evaluated patient-reported postoperative discomfort (VAS) after applying air spray to graft donor area at 7, 14, 30, 45 and 60-day follow-ups. Patients presented moderate discomfort on days 7 and 14, after 45 days, no reports of discomfort were observed [26,27]. Other study using the same questionnaire[30] reported that self-reported pain in postoperative diaries was generally low [28].

The evaluation of somatosensory profile revealed hypersensitivity in palatal donor area, i.e. less pressure (g/mm^2) was necessary for the patient to report sensitivity to touch (MDT); likewise, the region was more sensitive to pain (MPT). Only one patient (5) had a higher MDT value, and one patient (4) had a higher MPT value after 6 months compared to baseline. These results do not corroborate with the findings of another study [43]. The tactile sensitivity of donor area was checked with a periodontal probe and, after 2 months, patients reported normal sensitivity similar to baseline. In the present case series, after 2 months, all the patients had a palatal wound that was more sensitive to touch using the Von Frey filaments. Other researchers [44] reported that sensory changes can occur after palate graft removal, giving that two patients described persistent numbness or rough palatal surface at 20 and 51 months post-operatively. The main difference and novelty of the somatosensory tests used in the present study was that a measurement reported by the patient is obtained in numerical values, expressed in g/mm^2, and can be accurately compared to the baseline values.

Considering the limitations of the study's own nature (case series), phthalocyanine demonstrated safety and positive clinical applicability in gingival graft donor sites. The topical application of PHY gel twice a day for 14 days seems to have favored epithelialization

with complete healing of the palatal wound. No adverse effects were reported, and the post-operative period consisted of a low number of analgesics and no major complications. In addition, somatosensory analysis suggested that the palatal region after removal of gingival grafts may be more hypersensitive and less resistant to pain.

With the promising clinical results presented, safety and facility of topical application, randomized clinical studies are suggested to confirm the effects of PHY gel on palatal wounds.

CONCLUSION

The use of 0.1% PHY gel may promote healing in gingival graft donor sites, supporting complete epithelialization and wound reduction, making it a promising option for postoperative management in periodontal plastic surgeries.

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Author's Contributions

RSC: Investigation, Formal Analysis, Data Curation, Writing - Original Draft Preparation. CAS: Investigation, Formal Analysis, Data Curation, Writing - Original Draft Preparation. ACPS: Conceptualization, Methodology. CAD: Conceptualization, Methodology. FVV: Conceptualization, Methodology, Funding Acquisition, Resources. MSRZ: Conceptualization, Methodology, Supervision, Project Administration, Writing - Review & Editing, Validation, Visualization.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subject's oversight committee guidelines and policies of: Ethics Committee for Human Research of FOB-USP (CAAE: 19692019.1.0000.5417) and registred in Brazilian Registry of Clinical Trials (REBEC- RBR-93ccq38).

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