Evaluation of palatal donor site haemostasis and wound healing after free gingival graft surgery


Abstract

Aim: Evaluating effectiveness of a medicinal plant extract (MPE) in achieving haemostasis and early wound healing at free gingival graft (FGG) donor site in a randomized controlled fashion.

Methods: Forty patients requiring FGG at lower anterior area were randomly assigned into two groups. FGG was performed to all patients and following graft procurement; wet gauze (WG) was applied alone (control: WG group) or with MPE (test: MPE + WG group) for haemostasis. Donor site working time, bleeding (BLE), colour match (CM), pain, epithelization (EP) and sensation loss (SL) were evaluated.

Results: Thirty-three participants completed a 6-month period study. In the test group, primary BLE was shorter \((p < 0.001)\) and fewer individuals showed secondary BLE during 3 days \((p < 0.001)\). During the 6 days, pain scores were higher in WG patients \((p < 0.05)\). Later on, no inter-group difference was observed. EP was relatively faster \((p < 0.001)\) and CM was slightly better \((p < 0.05)\) in MPE + WG group.

Conclusion: MPE provided faster and continuous haemostasis that made a positive contribution to the early soft tissue healing to some extent but due to limitations; further trials are needed to demonstrate the efficiency of this material.

Key words: donor site; free gingival graft; haemostasis; palatal healing; wound healing

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Due to its anatomic advantages and ideal tissue thickness, palatal keratinized mucosa has been proposed as optimal donor region for free gingival graft (FGG; Sanz et al. 2014). However, paresthesia, herpetic lesion, mucocele, arteriovenous shunt, excessive bleeding (BLE) and severe post-operative pain have been reported following FGG procedure (Brasher et al. 1975, Wang et al. 2001). Although haemostatics (Rossmann & Rees 1999, Kim et al. 2012), mechanical barriers (Farnoush 1978), bioactive materials (Carnio & Hallmon 2005, Yen et al. 2007, Shanmugam et al. 2010, Ayvazyan et al. 2011, Hammad et al. 2011, Thoma et al. 2012), antibacterial and antiseptic agents (Kozlovsky et al. 2007, Hammad et al. 2011, Patel et al. 2012), herbal products (Hammad et al. 2011, Verstappen et al. 2012) have been found effective in preventing such complications, an ideal support could not be specified for this purpose. Further, undesired side effects such as delayed wound healing/foreign body reaction (Petersen et al. 1984, Finn et al. 1992, Matthew et al. 1993) have been notified.

The medicinal plant extract (MPE) – Ankaferd Blood Stopper – is a haemostatic agent composed of plant extracts named *Alpinia officinarum, Vitis vinifera, Glycyrrhiza glabra, Urtica dioica* and *Thymus vulgaris*. Positive contributions of these plants on blood cells, microorganisms, cellular proliferation, cell mediators, endothelium, angiogenesis and inflammation have been demon-
Compressed MPE (Barka et al. 2000, Ait Barka et al. 2002, Testai et al. 2002, Lee et al. 2005, Matsuda et al. 2006, Sheela et al. 2006, Kukric et al. 2012). With MPE, it is possible to maintain physiological haemostasis by generation of organized protein structure acting as a harbour for erythrocyte aggregation without disturbing coagulation factor-associated mechanism (Goker et al. 2008). Several studies showing management of haemorrhage in various systems have been published (Aysan et al. 2010, Kandemir et al. 2010, Guler et al. 2011). Outside haemostasis, MPE have shown positive effects on early bone healing (Isler et al. 2010) and bacterial inhibition (Akkoc et al. 2008, Tasdelen Fisgin et al. 2009). Kaya et al. (2013) investigated impact of MPE on exposed experimental wounds in rats and demonstrated its promotional effect in healing. In dentistry, MPE have been suggested as an appropriate alternative for patients with haemostatic disorders (Ercetin et al. 2010, Cakar and et al. 2013). Further, it has been tested in endodontic (Yaman et al. 2012) and restorative (Arslan et al. 2012) procedures in terms of obviating blood contamination during bonding application or achieving haemostasis in the pulpotomy procedure. Although subjective symptoms occurring after free soft tissue graft procurement are acceptable by many patients, adverse effects such as BLE and pain are frequently being documented. However, an optimal method to prevent/reduce post-surgical symptoms and to improve early healing in donor area has not been defined yet. Therefore, it has been hypothesized that MPE enhances wound healing and reduces subjective post-operative complications in palatal donor area after harvesting FGG. The objectives of the study are to evaluate effectiveness of MPE in achieving donor site haemostasis and to compare wound healing with standardized wet gauze (WG) compression in a randomized controlled fashion.

Materials and Methods

Subjects and study design

An approval from the institutional ethics committee (Date: 10 May 2012, Number: 12/16) was achieved at the beginning of this single-centred, randomized, prospective and controlled study. Forty systemically healthy patients requiring gingival augmentation, specifically FGG, at lower anterior area were selected by one of the investigators (B.U.A.). Participants were recruited according to sequence of arrival among 618 individuals appealed to the Periodontology Department, Kirikkale University, Kirikkale, Turkey (Fig. 1). During selection, exclusion criteria including gagging reflex, smoking, allergy to impression material, history of periodontal surgery, presence of proximal bone loss, loss of sensation, mobility and/or occlusal trauma in corresponding area were accounted. It was decided to discard the participants not complying with post-operative suggestions and/or attending their visits irregularly. Trial was conducted between May 2012 and February 2013 and each attendant signed an informed consent after having detailed information about the technique and expected success or failures related to the procedure.

Following examination and completion of the initial periodontal treatment phase by the same author (B.U.A.), 40 participants having full mouth plaque score (FMPS) <20% and full mouth bleeding score (FMBS) <20% were transferred to surgical stage (Burkhardt & Lang 2014). Another author (S.K.) randomly assigned transferred patients into test (MPE + WG) and control (WG) groups with a 1:1 allocation ratio by admitting the first one with coin toss. Afterwards, the second patient was allocated to the other group and remaining part of the allocation was sustained systematically until the end of the study. No information was given to the patients and other investigators about which group the participants were assigned and extreme care was taken to preserve blinding during whole study period.

Surgical period

Before surgery, impression of palatal region was taken to prepare a surgical stent designed for the donor area protection. Surgical procedures were carried out by one of the authors (B.U.A.), not aware of the study groups, according to mostly used technique which was described by Sullivan & Atkins (1968) and developed by Miller (1985). At the time of graft harvesting, the area between distal finish line of the maxillary canine and first molar tooth was used in both groups (Song et al. 2008, Wennstrom et al. 2008). A rectangular shape incision with 1–1.5 mm thickness was made and care was taken to place most coronal part of the incision to at least 2 mm apical from gingival margins of the upper teeth. Width and length of the extracted tissue was measured by using a standardized caliper (Kohdent 7243; Kohdent Roland Kohler Medizintechnik, Stockach, Freiburg, Germany) to the nearest 0.1 mm to determine the dimensions of the wound. After removing the graft, WG was compressed to the donor site by the surgeon during 60 s with moderate finger pressure. While MPE was applied to the open wound before stent placement by dripping with a 2 cc needle in the test group, only gauze was kept in place to stop BLE in the control group. In addition, sterile saline was dripped over the wound surface to create a placebo effect. Both MPE and saline solutions were quickly removed with a surgical aspirator and patients were not allowed to get the taste of the solutions. A masked clinician (S.K.), who did not follow the surgical period, performed all experimental haemostatic interventions by concealing from the other investigators (the surgeon left the room during application). Immediately following haemostasis, stent was placed over the palatal area and surgical site was checked on every 5 min. with regard to any reactivated BLE.

Immediately after the operation, participants were instructed to avoid from eating and drinking acidic/hot. After stent removal at seventh day, the site was irrigated by sterile saline and period of routine periodontal care and professional plaque control was started.

Evaluation parameters

All evaluations were acquired by one of the authors (H.G.K.) unaware to the type of haemostatic agent used. During surgical period, primary BLE time (recorded just after achievement of the haemostasis and before stent
placement), donor site working time and duration of total procedure were detected with a stopwatch.

During 7 post-operative days, all patients were requested to fill up questionnaires containing following recordings: number of medication taken for pain relief, Visual Analog Scale (VAS) pain scores (between 0 and 10. 0: no pain, 1: minimal pain, 10: severe pain; Price et al. 1983) and presence of secondary BLE.

Epithelization (EP) was evaluated once a week until first month by means of bubble formation after dripping hydrogen peroxide (3%) to the wound surface and EP was ranked as total, partial or none (Marucha et al. 1998).

Until first month once a week and at 2, 3 and 6-month follow-up, four-point (apical, coronal, mesial, distal) discrimination scale was utilized around the donor site with a calibrated Michigan-O-periodontal probe for determination of sensation loss (SL; Del Pizzo et al. 2002). To objectively test SL, two different movements including pricking of the sharp ending of the probe and rubbing movement were made. As an identical assessment and reliable comparison, contra-lateral site was also examined. Participants were requested to rate their SL as severe, moderate or none (3-point verbal descriptor scale).

Colour match (CM) of the donor site was also identified at same visits with SL assessment by using VAS scores (between 0 and 10. 0: no CM, 10: excellent CM) in comparison with adjacent and contra-lateral palatal mucosa.

**Statistical analysis**

Power analysis was carried out by using G*Power software program (G*Power v.3.1.3, Heinrich Heine University, Düsseldorf, Germany). By considering the investigation as a superiority trial and “primary bleeding time” as primary outcome variable, 13 subjects for each group achieved 82% power to detect 1.5 s difference (0.3–1.8 s) with known standard deviations of 1.5 for both groups and with $\alpha = 0.05$ significance level, using a one-sided two-sample $t$-test. Because of the dropout possibility, it was decided to assign 40 patients (20 per group). Owing to the missing data from first week evaluation for seven subjects that failed to complete the study, a post hoc power analysis was performed according to the result based on primary BLE time and group sample sizes of 17 and 16 achieved 100% power to detect a difference of $-2.5$ s (0.4–2.9 s) with standard deviations of 0.2 and 1.1 and with a significance level of $\alpha = 0.05$ using a one-sided $t$-test.

Statistical analysis was performed by using IBM-SPSS Statistics (v.21; IBM, Chicago, IL, USA). Although dropouts were not intervention related and reasons (missing the appointment, fail to comply the suggestions) for dropouts were similar in both groups (Missing Completely at Random-MCAR, $p = 0.677$), a per-protocol analysis was conducted to be able to include all available data at each evaluation point. Significance level for rejection of the null hypothesis was set at $\alpha = 0.05$.

Descriptive statistics for all parametric variables were expressed as mean ± SD or frequency (percent). After normality analysis, $t$-test was performed for parametric variables and non-parametric variables were assessed by Mann–Whitney $U$-test. A Kaplan–Meier plot was also generated to show percentage of sites with ongoing BLE at a given time period. Repeated measures analysis of variance (ANOVA) was used for evaluating time-dependent change and post hoc testing was done when significant difference was found.

**Results**

The study started with 40 individuals but seven patients dropped out before first week evaluation due to start smoking, removing the stent early or not attending to the first control visit (Fig. 1). No complication was
experienced in recipient sites except ordinary post-operative complaints and a functional attached gingiva was obtained at all grafted regions. Trial was ended with completion of 6-month follow-up visits and data of 33 patients was analysed. Information pertaining to age, gender, surgical duration and graft dimensions is shown in Table 1. No difference was observed in terms of these variables between MPE + WG and WG groups. Mean working time in donor site was calculated as 14.28 ± 1.18 min.

Mean primary BLE duration was 2.91 ± 1.11 s for WG and 0.37 ± 0.23 s for MPE + WG groups respectively and values reached to statistical difference (p < 0.001; Table 1). Ongoing BLE fraction and number of patients reported secondary BLE are shown in Fig. 2 (Kaplan–Meier) and Table 2. While continued donor site BLE was reported more often by WG group through first 3 days of the surgery (10 versus 3 individuals), tendency of remission was noticed in both groups and almost all of the attendants showed similar secondary BLE symptoms as from fourth post-operative day (Fig. 3; Table 2).

According to the questionnaires, all patients reported pain at their donor site following graft surgery and mean medicine numbers taken for analgesia until third day visit were 4.94 ± 1.21 and 6.56 ± 1.73 for MPE + WG and WG groups respectively. As expected, analgesic use decreased gradually in both groups in the ongoing follow-up period with no inter-group difference (data not shown). Data related to VAS pain scores are shown in Table 3. During first 6 post-operative days, mean VAS pain scores were significantly higher in WG patients (p < 0.001). Then, no statistical difference was observed between MPE + WG and WG groups in first and second week control visits.

None of the patients showed total EP at first week and EP could be completed within 4 weeks at all donor sites. Compared to WG, higher number of participants showed partial EP in MPE + WG group at 2-week examination and the difference was statistically significant (p < 0.001; Table 4). At third week, almost half of the participants achieved total EP in MPE + WG group while the proportion of the patients showing total EP was approximately 8/20 (25%) in WG group (Table 4).

Three patients from MPE + WG group and two patients from WG group showed partial SL. However, sensation came back consecutively in all affected patients after 4 weeks healing period. VAS scores exhibiting CM were 0.56 ± 0.81 and 1.24 ± 0.83 (p < 0.001) and as expected, showed an increase towards third week and reached values of 4.75 ± 1.65 and 5.12 ± 1.41 (p < 0.001) for WG and MPE + WG groups respectively. However, a subjective mismatch was still present at the third week in both groups and did not disappear up to sixth month visit. Except a slight but significant difference at first four examinations (p < 0.05), study groups showed a similar course in terms of their CM assessment (Table S1).

### Discussion

The present randomized controlled clinical trial aimed to evaluate the effectiveness of a novel haemostatic agent on parameters related to donor site haemostasis and wound healing during 6 months following FGG. As a result, accelerated haemostasis and wound EP was detected in addition to slightly but significantly more effective post-surgical pain management compared to conventional gauze compress method.

Selection of palatal donor site as a healing assessment model based on permitting standard wound creation, accurate time measurement and easy access for clinical observation by means of being an open and shallow soft tissue healing model. Even though palatal molar area proximal to the tuberosity, with high quality of connective tissue and less variability in the amount of submucosal tissue, would have been a better area for grafting (Zuhr et al. 2014), the area between distal finish lines of canine and first molar tooth – one of the most suggested donor site (Wennström et al. 2008) – was selected for graft harvesting due to its anatomic advantages with regard to usual course of the greater palatine artery and also to be able to make a comparison with the results of main previous studies evaluating

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**Table 1. Demographics and surgical information**

<table>
<thead>
<tr>
<th></th>
<th>MPE + WG</th>
<th>WG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>33.06 ± 8.02</td>
<td>28.44 ± 9.07</td>
<td>30.82 ± 8.72</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>3 (17.00)</td>
<td>2 (12.50)</td>
<td>5 (15.20)</td>
</tr>
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<td>Female (%)</td>
<td>14 (82.40)</td>
<td>14 (87.50)</td>
<td>28 (84.80)</td>
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<tr>
<td>Primary bleeding time (s)</td>
<td>0.37 ± 0.23*</td>
<td>2.91 ± 1.11</td>
<td>1.60 ± 1.50</td>
</tr>
<tr>
<td>Graft dimensions</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Height</td>
<td>8.23 ± 2.06</td>
<td>7.75 ± 1.06</td>
<td>8.00 ± 1.60</td>
</tr>
<tr>
<td>Width</td>
<td>12.06 ± 2.52</td>
<td>11.76 ± 3.30</td>
<td>11.90 ± 2.90</td>
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<tr>
<td>Surgical duration (min.)</td>
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<td>14.31 ± 2.21</td>
<td>14.24 ± 1.88</td>
</tr>
<tr>
<td>Donor site</td>
<td>41.35 ± 4.25</td>
<td>39.75 ± 5.00</td>
<td>40.50 ± 4.60</td>
</tr>
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MPE + WG, medicinal plant extract + wet gauze.
*Statistically lower compared to WG (p < 0.001).

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MPE + WG, medicinal plant extract + wet gauze.
*Statistically lower compared to WG (p < 0.001).
In the present study, enhanced rate of FGG donor wound closure under the effect of MPE was determined. To our knowledge, this is the first randomized controlled clinical study evaluating the impact of MPE on this phenomenon and therefore, the exact underlying mechanism has not been ascertained, yet. The rate of palatal wound EP is determined by the relationship between proliferative and migratory activity of the peripheral keratinocytes and collagen synthesis of the exposed connective tissue (Sculean et al. 2014). Even though a direct influence of MPE on these cells or a related mechanism does not readily exist, the acceleration of EP and wound closure rate can be explained through positive contributions of MPE to cellular proliferation, vascular dynamics (Barka et al. 2000, Ait Barka et al. 2002, Testai et al. 2002, Lee et al. 2005, Matsuda et al. 2006, Sheela et al. 2006) and antimicrobial activity (Kukri et al. 2012). Moreover, rapid clot formation in MPE + WG group might have provided an extracellular matrix for earlier connective tissue healing affecting the closure rate of the wound.

Examination of clinical photographs, direct visualization (inspection), hydrogen peroxide utilization and various staining agents has been described to assess EP (Del Pizzo et al. 2002, Silva et al. 2010). Inspection alone is not strongly recommended owing to its subjectivity and compared to others; early EP results have been interpreted as ‘conflicting’ with this method (Rossmann & Rees 1999, Del Pizzo et al. 2002). Clinical photographs may need sophisticated environment settings to assess EP and achieving standardized shots from the same

**Table 2. Number of patients exhibiting secondary bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPE + WG, n (%)</td>
<td>17</td>
<td>6 (35.29)</td>
<td>6 (35.29)</td>
<td>3 (17.65)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>WG, n (%)</td>
<td>16</td>
<td>12 (75.00)</td>
<td>12 (75.00)</td>
<td>10 (62.50)</td>
<td>3 (18.75)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

MPE + WG, medicinal plant extract + wet gauze.

**Table 3. Visual Analog Scale pain scores (mean ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPE + WG</td>
<td>17</td>
<td>4.41 ± 1.58</td>
<td>2.94 ± 1.47</td>
<td>1.88 ± 1.61</td>
<td>1.06 ± 1.24</td>
<td>0.41 ± 0.79</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>WG</td>
<td>16</td>
<td>6.25 ± 1.80</td>
<td>4.87 ± 1.58</td>
<td>3.75 ± 2.40</td>
<td>2.43 ± 2.12</td>
<td>1.68 ± 1.81</td>
<td>1.06 ± 1.52</td>
<td>0.56 ± 1.03</td>
</tr>
<tr>
<td>p</td>
<td>–</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>0.058</td>
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</table>

MPE + WG, medicinal plant extract + wet gauze.

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Donor site haemostasis and wound healing

Table 4. Number of patients exhibiting partial or total EP

<table>
<thead>
<tr>
<th></th>
<th>Partial EP, n (%)</th>
<th>Total EP, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPE + WG</td>
<td>WG</td>
</tr>
<tr>
<td>1st week</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>2nd week</td>
<td>9 (52.94)*</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>3rd week</td>
<td>8 (47.06)</td>
<td>12 (75.00)</td>
</tr>
<tr>
<td>4th week</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

EP, epithelization; MPE + WG, medicinal plant extract + wet gauze.
*Higher than WG group at second week (p < 0.001).
†Higher than WG group at third week (p < 0.001).

involving histological, immunological and microbiological evaluations will be beneficial to manifest the efficiency of this material.

The common limitations, also goes for the present trial, encountered in clinical studies evaluating donor healing are subjective methods, absence of histologic assessment and the wide range and drawbacks in scoring systems. In these clinical trials, different devices/techniques such as custom metal template (Silva et al. 2010) and mucotome (Thoma et al. 2012) were used to leave a standardized wound area after graft harvesting. As a limitation, although supreme care was taken to obtain the graft in constant thickness (Zucchelli et al. 2014), the technique used in the present study might have impaired the standardization of wound depth, compared to those relevant studies. Moreover, absence of quantitative wound dimension measurements can be rendered as another limitation.

Based on the present results, MPE did provide a faster and continuous haemostasis, and make a positive contribution to the early soft tissue healing to some extent and thus, might be considered as a promising agent in accelerating the healing rate of the donor site and thus, developing post-operative comfort of the FGG harvested patients. However, some methodological aspects such as poor randomization process, inappropriate placebo selection and lack of additional tests evaluating the effects of MPE on microbial community, inflammation and histologic determinants of wound healing weakened the quality of the outcomes. Therefore, further, well-designed randomized controlled clinical trials

References


Finn, M. D., Schow, S. R. & Schneiderman, E. D. (1992) Osseous regeneration in the presence of patient at different visits is technically difficult. In the present trial, although a toxic reaction was possible (Tenovuo & Larjava 1984, Yu et al. 2012) and a thin layer of epitelium could have demonstrated an illusively complete EP scoring, hydrogen peroxide was selected by considering it as a well-defined, semi-objective and practical method to distinguish the areas of completed EP. During implementation, hydrogen peroxide was dripped over the wound to assess quality of epithelial bridging and presence of observable bubbles, originating from the interaction of diffused hydrogen peroxide and catalase inside the connective tissue, were monitored (Guglielmoni et al. 2001).

Medicinal plant extract has three commercial forms including ampoule, spray and patch. When the literature investigating donor site healing process was reviewed, it can be seen that many haemostatic agents are utilized in with sponges, matrices or dressings due to their ease of use. Protection of the agent from oral fluids and achievement of prolonged release are the other reported advantages (Yen et al. 2007, Shanmugam et al. 2010, Thoma et al. 2012). However, gel and liquid forms are also preferred for the same purpose (Kozlovsky et al. 2007, Hammad et al. 2011). In the light of this information, to use the ‘patch’ form of MPE could be suggested. However, the material might play a role as a scaffold for the bacteria and therefore, might increase the donor site infection risk. Moreover, absence of validity in its introral use and higher costs directed the authors to choose the ampoule form applied with a disposable injector. Although, in our study, there was a potential risk in achieving stabilization of the solution over the wound surface, quick clot formation and immediate placement of acrylic stent provided the stabilization of material.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:


Table S1. Visual Analog Scale (VAS) colour match (CM) scores (mean ± SD).

Video S1. Application of medicinal plant extract to palatal wound.

Clinical Relevance

Scientific rationale for the study: The present randomized controlled trial tests a medicinal plant extract (MPE) – wet gauze compress combination by comparing with wet gauze compress on early wound healing results at the free gingival graft (FGG) harvested palatal donor region.

Principal findings: According to the present findings indicating the slight contribution of MPE to the early wound healing, the use of the mentioned agent may be preferred in routine FGG clinical practice with the incrementation of the supporting evidence.

Practical implications: A new haemostatic, MPE, can be a promising agent in reducing the donor site disturbances after FGG surgery.