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THE EFFICACY OF POLYVINYLPYRROLIDONE SODIUM HYALURONATE GEL ON PAIN AND PALATAL EPITHELIAL WOUND HEALING

PhD Thesis

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

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ABBREVATIONS

FGG	Free Gingival Graft
HA	Hyaluronic Acid
PVP	Polyvinylpyrrolidone
TGF	Transforming Growth Factor
PDGF	Platelet-derived Growth Factor
FGF	Fibroblast Growth Factor
VEGF	Vascular Endothelial Growth Factor
LLLT	Low-level Laser Therapy
PRF	Platelet-rich Fibrin
PBM	Photobiomodulation
ORC	Oxidized Regenerated Cellulose
OGS	Oxidized Gelatin Sponge
WBS	Wong and Baker Faces Scale
HMW-HA	High-molecular-weight HA
HAS	Hyaluronan Synthase
GCF	Gingival Crevicular Fluid
PI	Plaque Index
GI	Gingival Index
PBI	Papilla Bleeding Index
SRP	Scaling and Root Planning
CFU	Colony-forming Units
BOP	Bleeding on Probing
CAL	Clinical attachment Level
PD	Probing Depth
CAF	Coronally Advanced Flap
MWF	Modified Widman Flap
GR	Gingival Recession
LDF	Laser Doppler Flowmetry
CE	Complete Epithelization
CM	Color Match
FMPS	Full-mouth Plaque Score
FMBS	Full-mouth Bleeding Score

VAS	Visual Analog Scale
SD	Standart Deviation
H_2O_2	Hydrogen Peroxide
A-PRF	Advanced Platelet-rich Fibrin

ABSTRACT

DANACI, F. (2022) The Efficacy of Polyvinylpyrrolidone Sodium Hyaluronate Gel on Pain and Palatal Epithelial Wound Healing. Yeditepe University, Institute of Health Science, Department of Periodontology, Ph.D Thesis, İstanbul.

Palatal region is commonly preferred as a donor site in FGG procedures. Purpose of the study was to assess the effect of the topical polyvinylpyrrolidone sodium hyaluronate (HA) gel on postoperative morbidity and wound healing following the FGG operation. Eighteen patients with ≤1 mm width of keratinized gingiva were randomly assigned into test (FGG+HA) and control (FGG) groups. Full-mouth plaque score, full-mouth bleeding score, and probing depth were recorded on baseline and 6 months postoperatively. Postoperative pain and burning sensation were evaluated with visual analog score (VAS) by patients on days 3, 7, 14, and 21. Color match (CM), complete epithelization (CE), and wound surface area were evaluated on days 3, 7, 14, 21, and 42. There were not statistically significant differences by postoperative pain and burning sensation. CM was statistically significant between test (1.66 ± 1.4) and control (0.100 ± 0.3) groups on day 7 ($p<0.05$). None of the control patients were showed CE on day 14; 11% of the test patients showed CE. Wound surface area measurements were found statistically significant between test and control groups on days 3., 7., 14., and 21. In conclusion, use of topical HA gel was not showed an additional effect on postoperative pain and burning sensation following FGG procedure, but contributed positively on wound healing regarding CM, CE, and wound surface area measurements.

Key words: Free gingival graft, palatal donor region, hyaluronic acid, wound healing.

ABSTRACT (Turkish)

DANACI, F. (2022). Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Periodontoloji Bölümü, Doktora Tezi. İstanbul.

Serbest dişeti grefti operasyonunda verici saha olarak sıklıkla tercih edilen bölgelerden biri damak bölgesidir. Bu randomize kontrollü klinik çalışmada, SDG operasyonu sonrası topikal olarak uygulanan polivinilpirolidon sodyum hyaluronat (HA) jelin damak bölgesi yara iyileşmesine katkısı ve postoperatif hasta morbiditesine etkisinin incelenmesi amaçlandı. Yetersiz keratinize dişeti dokusuna sahip (≤1 mm) 18 yaşından büyük, sistemik olarak sağlıklı 18 hasta randomize edilerek; test (SDG+HA) ve kontrol (HA) gruplarına ayrıldı. Çalışmanın başlangıcında ve 6. ayda tüm ağız plak indeksi, tüm ağız kanama indeksi ve cep derinliği kaydedildi. Postoperatif ağrı ve yanma hissi parametreleri 3., 7., 14., 21. günlerde hastalar tarafından görsel analog ölçek (VAS) kullanılarak değerlendirildi. Renk uyumu, epitelizasyonun tamamlanması (ET) ve ortalama yara yüzey alan ölçümü parametreleri ise postoperatif 3., 7., 14., 21. ve 42. günlerde kaydedildi. Postoperatif ağrı ve yanma hissi anlamlı bir fark bulunamamıştır ($p>0.05$). Gruplar arası karşılaştırmada renk uyumunda, 7. günde test (1,66 ± 1,4) ve kontrol (0,100 ± 0,3) gruplarında anlamlı fark tespit edildi ($p<0,05$). 14. günde, test grubundaki hastalarda %11 oranında ET gözlemlenirken; kontrol grubu hastalarında ET gözlenmemiştir. Gruplar arası karşılaştırmada, ortalama yara yüzey alan ölçümü açısından 3., 7., 14. ve 21. günlerde test ve kontrol grubu arasında istatistiksel olarak anlamlı fark saptandı. Özetle, SDG operasyonu sonrası verici bölgeye uygulanan topikal polivinilpirolidon sodyum hyaluronat jelin ağrı ve yanma hissi açısından ilave bir etkisi bulunmadığı ancak renk uyumu, ET ve ortalama yara yüzey alan hesaplaması açısından verici bölge yara iyileşmesine olumlu katkı sağladığı saptanmıştır.

Anahtar kelimeler: Serbest dişeti grefti, palatinal verici bölge, hyaluronik asit, yara iyileşmesi.

1. INTRODUCTION and PURPOSE

Keratinized gingiva is a crucial factor to protect mucogingival complex (1). The creation of the sufficient width of keratinized gingiva is one of the important aims of periodontal plastic procedures and several techniques historically have been introduced to widen the zone of keratinized gingiva and obtain the periodontal health (2, 3). Among these, free gingival graft (FGG) procedure is considered as the gold standard for the gingival augmentation procedures among several other techniques with varying success rates (4).

FGG has been accepted as the most predictable procedure for increasing the width of keratinized tissue around a tooth and implant (3,5,6). Although this procedure has high predictability, it has some disadvantages such as requirement of an additional donor surgical area, involving a wound area that heals with secondary intention, postoperative pain and patient discomfort (7, 8). Various substances have been suggested in the literature to avoid postoperative surgical complications and discomfort (9). Among them hyaluronic acid (HA) is a non-sulfated glycosaminoglycan macromolecule that functions as a protective coating layer on the oral mucosa (9–12). HA containing agents have been used in both dentistry and medicine for plenty of reasons and advantages (13).

Currently, a new topical HA gel has been introduced, mainly indicated for oral ulcers, consisted of additional ingredients such as polyvinylpyrrolidone (PVP), glycyrrhetinic acid, and aloe barbedensis (10). There is no research in the literature evaluating the effects of 0.3% HA gel on palatal donor area following the FGG surgical procedure. The purpose of the current thesis is to assess the effects of topical HA agent on postoperative patient morbidity and palatal area healing following the FGG surgery.

2. GENERAL INFORMATION

The periodontium including gingiva, periodontal ligament, cementum, and alveolar bone that provides the support for maintaining the teeth in function throughout the entire life. The gingiva is classified as marginal, interdental, and attached gingiva (14). Marginal gingiva of approximately 1 mm wide, named also as free gingiva, is the border of the gingiva that surrounds the teeth and forms the soft tissue wall of the gingival sulcus (14). The interdental gingiva on the other hand, is the part filling the interproximal space under the teeth contact points. Various factors affect the shape of interdental gingiva including, presence or absence of the contact points between teeth, distance between the alveolar crest and the contact point, presence or absence of gingival recession (14). Attached gingiva is a collagenous tissue tightly bounded to the underlying alveolar bone periosteum. The width of attached gingiva, described as the distance between the free gingival groove (coinciding with the bottom of the gingival sulcus/periodontal pocket) and the mucogingival junction, is of critical functional importance (15). The term is different from the width of keratinized gingiva which involves the attached and free marginal gingiva. Keratinized gingiva has also a crucial role in maintaining function and gingival health as a protective barrier against any physical, thermal and chemical trauma around natural teeth and implants (5). Its presence promotes the achievement of an optimal level of oral hygiene (16). Moreover, it has an effective role as a barrier for inflammation passage into the tissues. It has also crucial role in buffering the tensional stress between the marginal gingiva and the alveolar mucosa (17). It has been showed that insufficient keratinized gingiva width increases the possibility for higher soft tissue inflammatory response and gingival recession against traumatic orthodontic forces, abrasive toothbrushing habits and subgingival restorations etc. In the literature, although there is no confirmed absolute amount of keratinized gingiva required, surgical tissue widening approaches to maintain gingival health may be needed in some clinical situations presenting thin gingival phenotype and inflammation due to inadequate oral hygiene instructions (18–21). Lack of keratinized gingiva is regarded as a crucial predisposing factor for the gingival recession development (22). Some studies indicate that 1 mm of attached gingiva and 2 mm of keratinized gingiva zone are needed to maintain a healthier periodontium (1,23,24). FGG operation is the most predictable surgical procedure to provide and widen the keratinized tissue zone.

2.1. Microscopic Features of the Gingiva

Microscopically, the gingiva consists of a stratified squamous epithelium, epithelium-connective tissue interface and connective tissue. Classification of gingival epithelium includes oral epithelium, sulcular epithelium, and junctional epithelium. Oral epithelium as the outer cover for the gingival surface, is a keratinized stratified squamous epithelium whose thickness and degree of keratinization vary according to the location, function and mechanical requirements. Sulcular epithelium is a nonkeratinized stratified squamous epithelium covering the gingival sulcular region. Junctional epithelium is a nonkeratinized stratified squamous epithelium providing attachment to the tooth acting as a barrier against microbial invasion (25).

The gingival connective tissue, also named as lamina propria, composed of gingival fibers, cells and ground substance. The gingival fibers which consist of type I collagen, have some important functions, such as providing stabilization of the attached gingiva to the alveolar process and to the tooth. Fibroblasts are found as a predominant cell type in the gingival connective tissue. These cells have a crucial role in the gingival connective tissue development, maintenance and also repairment. The ground substance which composed of proteoglycans (mainly hyaluronic acid) and glycoproteins, fills the space between cells and the fibers (26).

2.2. Keratinized Tissue Augmentation

Mucogingival deformities have an effect on patients in terms of esthetics and function (18). Mucogingival therapy as the term is generally used to identify the periodontal treatments involving surgical procedures for the correction of morphological defects, soft tissue positions, quality/quantity of gingiva and underlying bone support around teeth and implants (18). Sufficient keratinized tissue width has a protective function in the health of periodontal and peri-implant tissues (27, 28). Monje et al. reported that <2mm of keratinized tissue width was related with higher peri-implant disease incidence (28). Health might be affected by a number of oral conditions associated with insufficient keratinized gingival tissue (29). The main objectives of widening keratinized gingiva consist of enhancing microbial dental plaque removal, improving aesthetic concerns, reducing inflammation, and allowing soft tissue margin to bind better around teeth and implants (19). However, Wennström et al. were reported that there was only limited evidence between the sufficient keratinized mucosa (over 2 mm) and peri-implant health (30).

2.2.1. Free Gingival Graft Procedure

The FGG operation is a procedure to increase the zone of keratinized tissue. This operation is the gold standard technique in the gingival augmentation procedures for widening keratinized gingiva (16,29,31). FGG, which was first performed by Harlan, is a periodontal surgical procedure for the treatment of insufficient keratinized tissue (32). It is the most widely used technique to produce an extensive area of keratinized gingiva (33).

In the classic technique; the steps of procedure FGG as follows:

The first step is the preparation of the recipient connective tissue bed. A split thickness incision is performed along the mucogingival line extending to a desired horizontal additional zone. Alveolar mucosa is reflected leaving a thin connective tissue and periosteum on the bed. Following the dissection of muscle attachments, the marginal alveolar mucosa is stabilized at the base of the recipient bed with periosteal sutures. The second step includes the graft harvesting from the palatal donor site preferably of the second premolar and first molar area. Graft should involve epithelium and underlying connective tissue coinciding with the shape and dimensions of the recipient bed. Following the incision in a 45 degree of angle to the outer edge of the planned donor area, the scalpel, precisely splitting the connective tissue, should be moved parallel to the bone surface. During the graft harvesting, it can be hold with tissue forceps gently. Following the separation of the graft, it is immediately sutured to the recipient bed. Bleeding should be controlled by applying pressure with wet gauze both on the donor and recipient bed site. In the palatal donor region, primary closure of the wound is not possible and healing occurs inevitably by secondary intention.

Protection of the palatal donor wound area has a crucial role for the postoperative patient comfort especially for this procedure requiring to use adjunctive measures to relieve the patients at the postoperative period (34).

2.3. Wound Healing

Wound healing process have some biological phases; hemostasis, inflammation, proliferation, and tissue remodeling (35).

Following the disruption of the tissue integrity, body immediately responses to promote hemostasis by constriction of the damaged vessels. Platelets have a significant role in healing period. Activated platelets form a platelet plug which result in blood

coagulation formation to limit further blood loss. By producing growth factors and cytokines, platelets also involve in the cascades of wound healing process (35).

The most crucial aim in the inflammation phase is to prevent wound area from infection. Within an hour, neutrophils immediately infiltrate into the wound site to destroy bacteria and debris directly or by its toxic substances. Macrophages as larger phagocytic cells are found at peak level in about 48-72 hours following the tissue injury (35). Bacteria and necrotic cells are also eliminated by macrophages and the other inflammatory cells. These inflammatory cells also play an important role in the secretion of factors that stimulate division and migration of epithelial cells and fibroblasts (36).

After the inflammatory phase, proliferation phase begins including several steps, such as angiogenesis, granulation tissue formation, new collagen matrix formation, collagen deposition, epithelization, and contraction of the wound area. With the help of cytokines angiogenesis process begins and capillaries are stimulated throughout the wound site. During the third day of the healing, fibroblasts start to produce collagen, a key component of tissue strength (35). Fibroblasts, keratinocytes, and endothelial cells which are proliferated in the wound border, provide the formation of neoepithelium and granulation tissue (36). By the seventh day of the healing, wound contraction process occurs mediated by myofibroblast cells (35).

Remodeling phase is the final stage and might be a very long period up to two years. It includes several steps as synthesis and degradation process, collagen network remodeling, apoptosis of the cells which are no longer needed, and eventually regaining the tissue strength (35, 36).

Systemic factors, such as age, stress, diabetes mellitus, some medications, obesity, smoking, alcohol consumption, nutritional deficiencies etc. have an important negative impact on oral wound healing demonstrated in many studies that the closure and healing of the wound area are problematic (37, 38).

2.3.1. Wound Healing of the Recipient Site

A successful FGG treatment depends on keratinization process of the grafted tissue in the new location that is previously non-keratinized, mucosal area. Keratinization

is determined by underlying connective tissue which carries the genetic property for this process. FGG survival depends on vascular supply (19).

The healing of the FGG recipient site may be observed in three phases:

-The initial phase,

-The revascularization phase,

-The tissue maturation phase.

2.3.1.1. The Initial Phase (0-3 days)

Due to the lack of blood supply, FGG can be seen as a blanched, white appearance (19). Following the FGG surgery, a thin blood clot, which is the only attachment between surfaces, determined between the graft and the recipient bed site. Exudate accumulation between the graft collagen fibers and blood cells presents in some of the pre-existing vessels. Epithelial degeneration is evident with shedding of the outer layers. Leukocytes are present within the degenerating epithelium (39). Graft survival depends on the plasmic circulation, which can be defined as diffusion from the recipient bed area, since there is no vascularization yet. In the clinical point, pressure should be applied to the harvested graft with wet gauze for several minutes. This will help the graft to be immobilized in the recipient bed site. Any movement of the graft can be resulted in necrosis.

2.3.1.2. The Revascularization Phase (4-11 days)

During 2-5 days of the healing, acute inflammatory cells, especially polymorphonuclear leukocytes reach the wound area. Graft adjustment to the recipient area is well maintained. Inflammatory cells are found at this interface area. Vasodilation can be seen in both graft and recipient bed site. In superficial layers of the graft epithelium reveals degenerative changes like pyknotic degeneration of cells and desquamation of the epitelium (40).

By the 4th day, the periosteum under the graft is intact and fibroblasts proliferate into the area between the periosteum and graft (39). During 4-5 days of healing phase, circulation re-establishes joining of the blood vessels in the recipient bed site to the FGG.

Reddish graft tissue turns into pink as the blood supply is provided. Blood clot between the graft and recipient bed site is resorbed and replaced by connective tissue (19).

Fibrous attachment occurs between graft and the underlying periosteum at the 11th day. Five days following the operation, desquamation of the graft epithelium nearly completes (39). Between the graft and the root surface, a long junctional epithelium formation can be determined with new connective tissue formation potential (41). Seven days following the FGG operation, it is almost not possible to detect the interface between the recipient area and harvested graft. The grafted area is covered by migrated epithelium. In the connective tissue, fibroblasts are mainly dominated. While there is no reaction on the bone, all the other tissues display inflammation with vasodilation. There is a relationship between epithelium and connective tissue at the peripheral regions. A thin epithelium covers the central area of the graft (40). Additionally, minimal alveolar crest resorption occurs. By the 11-day, epithelium covers the graft continual with the marginal epithelium (39).

2.3.1.3. Tissue Maturation Phase (12-42 days)

Fourteen days after the operation, while keratinization process cannot be determined, the epithelium shows morphologic characteristics of the attached gingiva. Epithelization process is completed entirely (40). Fibers in the connective tissue increase at the graft-bed interface (39).

Twenty-eight days following the FGG operation, healing of the connective tissue can be presented. In the deeper connective tissue, elastic fibers take place. In addition, the graft epithelium is differentiated completely (40).

During 42 to 72 days, the connective tissue maturation is completed. Epithelium can be shown in the same arrangement with twenty-eight days following the operation (40).

2.3.2. Wound Healing of the Donor Site

Palatal donor site heals by secondary intention within two to four weeks (7). In contrast to buccal mucosa, palatal mucosa, which is a mucoperiosteum containing epithelium and submucosal connective tissue, is more keratinized and thicker than the buccal mucosa. It contains less elastin fibers (42). Beside the differences, intraoral mucosal healing process is similar to skin healing.

When tissue injury occurs, coagulation cascade starts in a few seconds. Blood clot acts like a matrix for migration of some inflammatory cells. It also contains many platelets

that are reservoirs of cytokines and growth factors. Growth factors such as TGFs and PDGF stimulates neutrophils and macrophages. These inflammatory cells have a crucial role in cleaning the bacteria and debris from wound bed. This phase called inflammatory phase because of the vasodilation-related redness and swelling (42).

In the tissue formation phase; migration of keratinocytes, fibroblasts, and endothelial cells into the wound bed result in neoepithelium and granulation tissue formation. Large amounts of collagen, especially collagen type III, are produced by fibroblasts. Endothelial cells start to form new capillaries. Growth factors such as FGFs and vascular endothelial growth factor (VEGF) have also role in neo-angiogenesis process. Collagen accumulation also results in decreased amount of collagen synthesis. In this stage, the most important difference of the palatal wound healing might be observed. The number of cells and the amount of collagen is higher. Type I collagen fibers are arranged transversely. The number of vessels is reduced and scar tissue formation can clearly be determined (42).

In the remodeling phase, while collagen type III is degraded by matrix metalloproteinases, collagen type I is deposited by fibroblasts. Some of the fibroblasts differentiates into myofibroblasts, so contraction takes place during 1-2 weeks. Contractile process results in the differentiation of neo-epidermis to stratified epithelium (42).

2.4. Agents Accelerating the Wound Healing of the Donor Site

FGG technique has satisfactory outcomes in terms of increasing the keratinized tissue width. However, this method might create some discomfort in both recipient and donor sites. In the recipient site; undesirable outcomes due to color and texture discrepancies and bulky appearance of the graft might be observed (16). In the donor region, some postoperative complications such as pain, bleeding, infection, extended period of healing, burning sensation, delayed wound healing, paresthesia, herpetic lesions, mucocele might be observed (9,11,43). Palatal region has mostly been considered as a source of soft tissue grafts in the periodontal plastic surgeries. In many years, in order to accelerate palatal donor site healing and diminish the postoperative patient morbidity, some therapeutic options including low-level laser therapy (LLLT), ozone therapy, platelet-rich fibrin (PRF), topical hemostatic agents, periodontal dressings, some simple formulations of hyaluronic acid (HA) etc. have been used to relieve the donor area following FGG operations (9,11,44–51)

2.4.1. Low-Level-Laser Therapy

Photobiomodulation (PBM), which also named LLLT, has been defined as laser treatment with significant roles in wound healing acceleration by contributing many biological processes like extracellular matrix remodeling, collagen production, angiogenesis, growth factor stimulation etc. (52). In medical fields, LLLT has been used for the treatment of chronic wound ulcers. In dentistry, it has been stated that LLLT enhances orthodontic movement, periodontal regeneration and wound healing in animal studies. However, to the best of our knowledge, there is not enough randomized clinical trials on this topic, Miguel et al. studied the effect of laser therapy on palatal wound healing in FGG operation. They randomized the patient into test and control groups. In the study group, patients received LLLT (<1 mAmp) while in patients in the control group were treated with sham laser application on palatal donor region following the FGG harvesting. They reported that the test group patients had more rapid wound healing and epithelization on days 7 and 14. Additionally, laser therapy revealed less postoperative pain on day 3 following the surgery (53).

2.4.2. Ozone Therapy

Ozone therapy is a medical method administering ozone gas to treat diseases. Therapeutic usage of ozone was reported in some studies in terms of its adjunctive tissue repair and regeneration features (52, 54, 55). In a randomized controlled clinical trial, Isler et al. showed the adjunctive effect of ozone therapy on palatal donor site wound healing and enhancement of postoperative comfort of the patients following the FGG operation (52). They evaluated the palatal wound area measurements and postoperative morbidity of the patients. In the ozone group, they performed ozone irradiation immediately after harvesting, and at days 1, 3, 7 following the surgery. Wound area epithelization was evaluated by using a digital image system and 3% hydrogen peroxide clinically on follow-up periods. It was also reported that patients were asked to score their pain, burning sensation and dietary habits by using VAS in terms of postoperative morbidity. There were statistically significant differences between ozone (36.04 ± 9.66 mm^2) and control (48.21 ± 13.2 mm^2) groups for palatal wound remaining area on day 14 ($p=0.034$). For postoperative comfort, on day 7, the ozone group revealed statistically lower scores than the control group ($p<0.001$) (52).

2.4.3. Topical Hemostatic Agents

As well as in medical fields, topical hemostatic agents have been widely used in dentistry. Following the FGG surgery, bleeding is one of the postoperative complications due to an open wound on the palatal region. Local hemostatic agents may be considered as a choice to minimize these complications (56). Topical hemostatic agents have a significant role in hemostasis during surgery and/or postoperatively. In periodontal surgeries, adjunctive wound healing properties of the topical hemostatic agents were also reported due to their bacteriostatic features (57).

They might be classified as passive and active agents. Passive hemostatic agents have the capability of adhering to the wound site and activate the coagulation pathway by their physical matrix forms (58, 59).

Some passive hemostatic agents are:

-Collagen-based agents. The mechanism of microfibrillary collagen agents is based on stimulation of intrinsic pathway of the coagulation cascade. In a few seconds when contacted with blood, adhesion, thrombus formation and platelet activation are activated (58, 46).

-Cellulose-based products, support matrix for the clot initiation and formation. Application and manipulation are very easy since they resemble a cotton swab (46, 60).

-Gelatin-based products are hemostatic agents made from purified animal collagen, and have a crucial role as a physical matrix for clot initiation. They induce hemostasis with its physical properties and absorb blood more than forty times its weight (58, 61).

Active hemostatic agents affect the pathways of coagulation through their biological activities. They might be used in the patients under the treatment with antiplatelet or anticoagulation medications (58).

Rossmann et al. examined the differences between two types of hemostatic agent groups as gelatin sponge and oxidized generated cellulose with a control group in terms of achieving hemostasis and palatal wound healing (57). The test groups were included two types of agents; oxidized regenerated cellulose (ORC) and resorbable gelatin sponge. The control group was comprised pressure with steril gause. In terms of clinical benefits in achieving hemostasis, they concluded that hemostatic agents were superior compared with the control group. Palatal wound healing, as a secondary parameter, were evaluated by measuring the percentage of epithelium formation on palatal wound area. Eventually,

they were reported that complete wound healing was recorded only in the ORC group on day 21 following the FGG procedure (57).

In 2020, Uner et al. studied the effect of oxidized gelatin sponge (OGS) on palatal donor site in terms of postoperative pain. They included 34 patients with Miller class I and II gingival recessions treated with FGG procedure. In experimental group, palatal area covered with OGS whereas the control group donor site was left to spontaneous healing. On days 2 and 7 following the operation, pain assessment was done with VAS forms administered to the patients. Eventually, they concluded that there was not statistically significant VAS score differences between the groups on 2^{nd} and 7^{th} days (control group; 5.71 ± 0.88 and 2.82 ± 0.62 and experimental group 3.88 ± 0.95 and 1.67 ± 0.80 ($p>0.05$) (62).

2.4.4. Periodontal Dressings

In 1923, periodontal dressings were first introduced by Dr. A.W Ward (56). After the first usage, several periodontal dressing materials have been introduced over the years to be used to cover and protect the wound site (56). Since postoperative morbidity associated with secondary healing of the wound site, it can be covered with a variety of periodontal dressing materials in order to be protected from the external conditions following the periodontal surgery. (50, 8). There are many advantages of the periodontal dressings as follows:

-Protection of the wound area from mechanical trauma,

-Providing stability of the surgical area,

-Providing patient comfort,

-Prevention of hemorrhage or infection of the wound site

-Protecting the blood clot stability,

-Providing extra support in FGG area (56, 63, 64).

Conventional periodontal dressings have ability to protect the wound area acting like a mechanical barrier. With these mechanical barrier properties, wound site can be protected from external influences, results in improvement of the healing process (8, 50).

Biological dressings, such as collagen dressings, have the ability to provide hemostasis by accelerating the cascade events. They are also chemotactic to platelets and fibroblasts, and inductive to mesenchymal cell proliferation and differentiation (48–50). Biological dressings have an important role in supporting wound healing (50).

Composition of conventional periodontal dressings for mechanical purposes can be divided into three categories; containing eugenol and zinc oxide, zinc oxide without eugenol, and neither eugenol nor zinc oxide (56). Coe-Pak™ which contains zinc oxide without eugenol, is one of the most widely used periodontal dressings. It is supplied in two pastes to be mixed; one of them contains zinc oxide with added oil, gums, and lorothidol. The other paste contains coconut fatty acids, chlorothymol as an anti-bacterial agent etc. (56, 45). To reduce the risk of toxic effects of liquid eugenol, eugenol-free periodontal dressings were developed. However, in some studies, pain perception of the patients measured with VAS score after the periodontal surgery, was found less with eugenol containing dressings compared with non-eugenol ones (45,65).

2.4.5. Platelet-rich Fibrin

Platelets have a significant role in regulating the process in wound healing phases. Some biomolecules, such as platelet-specific proteins, PDGF, coagulation factors, adhesion molecules, angiogenic factors, and cytokines might be stimulated by platelets. They also function in the activation of some cells like fibroblasts, neutrophils, macrophages, and mesenchymal cells involved in wound healing (66,67). Platelet-rich fibrin (PRF) has been used in various medical fields such as orthopedics, skin wound ulcers therapy and sports medicine as well as in dentistry including periodontology, oral and maxillofacial surgery (47). In several studies it was reported that the use of PRF was associated with enhanced palatal wound healing and diminished postoperative discomfort due to its supportive role in the soft tissue healing. Cell migration and proliferation are increased by its physiologic three-dimensional fibrin network. It induces angiogenesis, immunity and epithelization (47,68,69). The study conducted by Kulkarni et al. included systemically healthy 18 patients to observe the effects of PRF on palatal wound healing following the FGG surgery. On days 7, 14 and 21, palatal wound healing was assessed via direct clinical examination. Additionally, patients were asked to rate their postoperative pain according to Wong and Baker Faces Scale (WBS). Researchers reported wound closure with less inflammation and less postoperative morbidity in the PRF groups compared to the control groups (68).

2.4.6. Hyaluronic Acid

Hyaluronic acid (HA), a member of glycosaminoglycan, has been used medically such as ophthalmology, dermatology, and rheumatology fields (70). HA has been found in body fluids including serum, synovial fluid, saliva, and gingival crevicular fluid (11).

Besides the body fluids, HA can be determined in all periodontium compartments. Some of the major features of HA are hygroscopicity, viscoelasticity, biocompatibility and non-immunogenic nature which allows anti-inflammatory, bacteriostatic, fungistatic, anti-edematous, osteoinductive, and proangiogenic characteristics (11). HA, also named as hyaluronan, is a high-molecular-weight, negatively charged, non-sulfated glycosaminoglycan component of the extracellular matrix that is found in many tissues such as cartilage, connective tissue of the dermis, vitreum, muscle, brain and dental pulp matrix (71–77) HA is consists of repeating disaccharides of glucuronic acid and *N*-acetylglucosamine (Figure 4.1.).

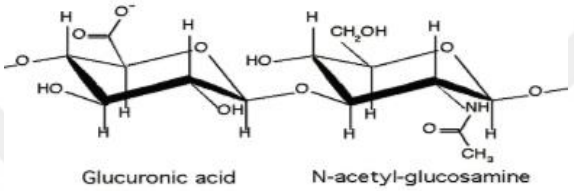

Figure 2.1. Molecular Structure of HA

HA plays very crucial role in some significant biological procedures, such as cell signaling, adhesion, proliferation, and differentiation (77). As a natural component of many body fluids and tissues, HA is considered as an option to be used in improving wound healing by early granulation tissue formation, diminishing inflammation phase, promoting angiogenesis and re-epithelization through the cells and some components in the connective tissue (73). It was shown that some proinflammatory cytokines such as TNF-α, and lL-8 are increased by HA, promoting early inflammatory phase of wound healing (66). HA also acts in granulation phase in terms of cell migration, proliferation and angiogenesis. Because of its hydrated matrix structure, HA-rich extracellular matrix is an excellent environment for cell migration (78).

Due to its surface receptors (CD44, ICAM-1, RHAMM), HA can mediate directly of the migration process. However, the exact mechanisms of the HA in wound healing and repair process are not clear entirely (73).

HA has many features including:

-Hygroscopicity that provides conformational stiffness to retain water,

-Viscoelasticity that provides tissue elasticity and obstructs the penetration of viruses and bacteria,

- Anti-inflammatory, bacteriostatic, fungistatic, anti-edematous, osteoinductive and proangiogenic features lead to promotion of wound healing due to its high biocompatible and non-immunogenetic nature (10,11,13,79–83)

2.5. Hyaluronic Acid in Medical Field and Dentistry

2.5.1. Hyaluronic Acid in Medical Field

In 1934, HA was founded by Karl Meyer and John Palmers in the bovine vitreous (84). In 1940s, it was first used in medical field to control cartilage and bone healing. As a viscous material, HA was also used for vitreous of the eye and in 1980s, the first commercial HA named Healon® emerged as an ophthalmic device (85). Since then, HA has been investigated in many medical fields such as rheumatology, ophthalmology, and dermatology for many years (86).

In 2005, Johnson et al. stated that HA eyedrops had been found more effective than saline in the treatment of dry eyes. Thirteen patients with moderate dry eye disease had been treated with eyedrops with different concentrations (0.1% and 0.3%) of sodium hyaluronate. It was concluded that there was significant improvement in the HA group when compared to saline. Additionally, it was said that 0.3% concentration of HA resulted in better clinical outcomes in terms of the relieved symptoms (87). Beside its anti-inflammatory features, the lubricant structure and characteristics of HA have been used for osteoarthritis treatment. In a study, Hermans et al. reported that high-molecular-weight HA (HMW-HA) could be a treatment option for patients suffering from knee osteoarthritis. They included 156 patients divided into the intervention (intraarticular injections of HMW-HA added on regular care) and control groups (only regular care). 52 weeks following the treatments, they concluded that the addition of intraarticular HMW-HA to routine care revealed effective outcomes. As secondary parameters, pain and knee related function were also improved (86).

Moreover, HA has been studied in the fields of dermatology and cosmetics. Thanks to its low immunogenic and long-lived effect, HA-based fillers recommended as a dermal filler and anti-wrinkle device. This HA-based fillers are most widely used agents against age-related facial defects (88). It was reported that modified (cross-linked) HA-based fillers were related with the prolonged intradermal resistance time (88–90).

2.5.2. Hyaluronic Acid in Dentistry

In dentistry, HA has been used regarding bone repair in post-extraction sockets and periodontal bony defects, temporomandibular joint disorders, recurrent aphthous ulceration management and wound healing (11,91–95)

In periodontology, HA has been specifically used:

-As monotherapy or as an adjunctive agent to nonsurgical periodontal therapy or surgical periodontal therapy (70,96–99)

-As a topically applied agent to enhance oral wound healing and bone regeneration (11,13,100,101)

HA is a very important element in soft and hard periodontal tissues; gingiva, periodontal ligament, alveolar bone and cementum (101). Fibroblasts and keratinocytes in gingival tissues and periodontal ligament, cementoblasts in cementum, and osteoblasts in alveolar bone are responsible for the synthesis of HMW- HA via hyaluronan synthase (HAS) enzymes (13,102). HA has a crucial role in cell adhesion, migration, and differentiation. It has been investigated as an inflammatory diagnostic marker of the gingival crevicular fluid (GCF). HA has also an important role in development, growth, and tissue repair processes (13). HA may play a regulatory role in inflammatory response. During the chronic inflammation of the periodontal tissues, such as gingival tissue inflammation or postoperative period following a periodontal surgery, HMW- HA in the soft and hard periodontal tissues undergoes low molecular weight HA. HMW- HA prevents excessive exacerbation of inflammation. However, low-molecular-weight HA can be found in the gingival tissues during the initial stages of periodontitis (101).

Beside the supra and subgingival mechanical debridement, local adjunctive application of topical HA may provide better clinical outcomes in periodontal therapy (13). Due to its non-toxic, biocompatible and physiochemical features, it has been referred as a topical agent used in periodontal diseases.

HA can be classified into spray, gel, and mouthwash forms. Historically, HA was firstly used for the treatment of periodontal diseases, such as gingivitis. Sahayata et al. studied the effects of 0.2% HA concentration on 105 patients with gingivitis and evaluated the clinical parameters such as Plaque Index (PI), Gingival Index (GI) and Papilla Bleeding Index (PBI). Patients were classified into three groups; placebo control, negative control, and test. In the negative control group, only scaling was performed. In placebo control group, a placebo gel was applied in addition to scaling.

In the test group, application of 0.2% HA gel and scaling were performed. It was reported that GI and PBI parameters in the test group showed a statistically significant reduction compared to the other groups between baseline and 1, 2 and 3 weeks (103).

In the literature, there are studies about HA used as an adjunctive to non-surgical treatment in the patients with chronic periodontitis (13,98,99,101). In a split-mouth study, Polepalle et al. evaluated the clinical and microbiological effects of subgingival application of 0.8% HA gel on 72 teeth in 18 patients with chronic periodontitis. In the test sites, 0.8% HA gel was applied following scaling and root planning (SRP). In the control sites, only SRP was performed without any placebo gel. A significant improvement in microbiological changes with an important Colony-forming units (CFU) reduction in the test group was obtained. All clinical parameters in the test sites showed statistically significant improvements than the control sites (104). Similarly, Rajan et al. showed statistically significant improvements in Bleeding on probing (BOP), clinical attachment level (CAL), and probing depth (PD) parameters when the two groups, mechanical debridement only and HA combination were compared (105).

HA usage has been considered in periodontal mucogingival surgeries to get better healing, thus better clinical outcomes. One of the studies conducted by Pilloni et al., investigated the adjunctive effects of HA (mixture of 16 mg/ml cross-linked and 2 mg/ml natural HA) application during the treatment of gingival recession. In this randomized controlled clinical trial, 30 patients with Miller class I single gingival recessions were randomly assigned into two groups of coronally advanced flap (CAF) + HA application and CAF alone. 18 months after the operation, they found statistically significant differences on recession reduction, complete root coverage, mean root coverage parameters in favor of the HA group. In addition, they were also reported less swelling and discomfort on postoperative day 7 (106).

As well as soft tissue effects by means of mesenchymal cell chemotaxis, proliferation and differentiation, bone regeneration process is also accelerated by HA via the effects on osteoblastic bone formation (13). Aslan et al. conducted an animal study examining the bone formation effects of HA on rabbits. They created bone cavities on rabbits' tibia, then they filled them with bone graft with or without HA. Bone segments from sacrificed rabbits were evaluated under microscope and eventually, HA was declared to be responsible for increased bone healing scores (107).

Regarding the periodontal defects, adjunctive effect of HA gel application to bone regeneration was also studied. El-Sayed et al. conducted a randomized controlled study including 14 chronic periodontitis patients having interproximal bony defects (3 mm intrabony component) with probing depth (>5 mm). Patients were randomized in two groups; modified Widman flap (MWF) operation with a placebo gel and MWF operation with 0.8% HA gel. Following the nonsurgical periodontal treatment and re-evaluation, defects were treated. Clinical measurements were recorded at baseline, 3 and 6 months. Results of this study revealed a significant gain in CAL and reduction in gingival recession (GR) in favor of the test group at 3 and 6 months. There were no statistically significant differences in PD, BOP, and PI parameters between the test and control groups at baseline, 3 and 6 months (108).

Later on, Sculean and co-workers started their clinical investigations based on the in vitro and animal studies in intrabony defects, recessions, Class III furcation defects that resulted in encouraging improvements (96,97). Regarding the clinical human study comparing healing of intrabony defects treated by HA or enamel matrix derivative, the authors concluded that the use of HA with single flap approach showed significant PD reduction and CAL gain, stating the positive impact of HA in regenerative periodontal surgery (109).

HA formulations have been reported to reveal a promotive role in wound healing and re-epithelization processes which consists of inflammation, granulation tissue formation, epithelium formation, and tissue remodeling phases in both mineralized and non-mineralized tissues. Thanks to its high higroscopic features, HA may stick to the wound area easily and lead to the accelerating coagulation cascades (110). It can stimulate fibroblast proliferation, migration, adhesion, and also collagen production in the wound site (106,111). In an in vitro study, Asparuhova et al. showed the effects of HA on human oral fibroblasts obtained from palatal and gingival donor regions. They pointed out the increased proliferative and migratory effects of HA on fibroblasts as well as the inductive effect on wound healing related-genes encoding growth factors and cytokines (96).

In the inflammatory phase of wound healing, interaction between HA and fibrin clot modulates the host inflammatory response and infiltration of extracellular matrix cell into the inflamed region. In addition, HA can also prevent microbial proliferation directly which prevents periodontal pathogen colonization. It may also stimulate the proinflammatory cytokine production.

In the granulation phase, cell proliferation, matrix cell migration, and granulation tissue organization processes are promoted by HA. With the formation of low molecular weight of HA, angiogenesis mechanism is promoted by new blood vessels (13). Cankaya et al. observed the effects of HA (20 mg/ml Na- hyaluronate) on vascularization of palatal and recipient regions following FGG surgery. Forty systemically healthy patients were randomly assigned into the groups of FGG + HA and FGG without HA application. They used Laser Doppler Flowmetry (LDF) device to determine the microcirculation of the donor and recipient areas pre- and post-operatively. They reported that the application of HA between recipient and the graft sites resulted in better vascularization one week following the surgery and eventually less shrinkage of the graft. Hence, they also stated that there was no significant difference between the groups in terms of LDF findings on palatal donor region (100).

Yıldırım et al. examined the effect of two different formulations of HA (0.2% and 0.8%) compared to a control group (spontaneous healing) on postoperative patient morbidity and wound healing on palatal donor area following the FGG surgery (11). The evaluated parameters were postoperative pain, burning sensation, complete epithelization (CE), and color match (CM). Postoperative pain and burning sensation were evaluated by patients with VAS scores on days 3, 7, 14, and 21. As secondary outcome parameters, CE and CM were evaluated on days 3, 7, 14, 21 and 42. CE and CM were assessed visually; CE was recorded by dichotomous scoring as ‘‘yes’’ or ‘‘no’’ following the clinical assessment and CM was scored by VAS scoring system from 0 to 10 following the clinical examination of palatal wound area in comparison with the adjacent mucosal tissues. As a result of this study, test groups were reported with less VAS scores in terms of mean postoperative pain than the control group on days 3 and 7. They also stated that burning sensation mean VAS scores were statistically lower in the test gorups than the control group on day 3.

On day 21, there were statistically significant differences in terms of CM related VAS scores in favor of the test groups with HA gels.

Additionally, they reported that patients in the test group who applied 0.2% HA gel were showed statistically significant faster CE (11). Currently, HA-based viscous oral gel was introduced in a different formulation. It was basically indicated for the treatment of oral aphthous lesions to obtain pain relief and enhance healing. In addition to sodium hyaluronate (0.3%), it also contains polyvinylpyrrolidone (PVP), aloe barbadensis,

maltodextrin, propylene glycol, sodium benzoate, PEG-40 hydrogenated castor oil, ksantam extract, potassium sorbate, aroma, benzalkonium chloride, disodium EDTA, sodium saccharin, and dipotassium glycyrrhizate. Each of the significant ingredients are listed as the following:

- PVP; enhances tissue hydration by its film-forming and muco-adherent features,
- Aloe barbadensis; supports the wound healing,
- HA; covers the oral mucosa, provides the tissue hydration, and accelerates the wound healing,
- Glycyrrhetinic acid; has anti-inflammatory feature and is a flavoring agent (10).

In a pilot study, the pain management effects of Aloclair® plus HA gel (0.3%) was studied in children with oral apthous lesions. In this study, 20 patients were included. The parents were educated to apply the HA gel on aphthous lesions for every 5-8 hours during one week. Pain perception was recorded using a 4-point scale model; none, moderate, slight, severe. In all subjects except one, pain perception was found as 'none' following the treatment.

However, there is no investigation regarding the effects of this new formulation HA gel (0.3%) applied on palatal wound after FGG operation. In the light of the current knowledge through literature review, the purpose of this thesis is to evaluate the potential effects of the topical HA (0.3%) gel on postoperative discomfort and palatal donor site healing following the FGG surgery.

3. MATERIALS AND METHODS

3.1. Study Population

The individuals involved in this study were selected among the patients who applied Yeditepe University, Faculty of Dentistry, Department of Periodontology, Istanbul, Turkey.

The selection of individuals was made by considering the following criteria;

1- Patients over 18 years of age,

2- Patients who need FGG surgery with ≤ 1 width of keratinized gingiva in the mandibular anterior and premolar region,

3- Patients who are systemically healthy,

4- Non-smoking patients,

5- Patients whose non-surgical periodontal treatment is completed.

Patients with the following characteristics were excluded from the study;

1- Having a systemic disease,

2- Patients with history of periodontal surgical treatment,

3- Patients with loss of maxillary premolars and molars,

4- Medication or antibiotics used in the previous six months,

5- Pregnancy and lactation.

Study plan was explained to the patients by giving detailed information about the periodontal diseases, microbial dental plaque, oral hygiene instructions, etiology of insufficient keratinized tissue and periodontal treatments. The study protocol was confirmed by the Ethics Committee, Yeditepe University, Istanbul, Turkey (dated 29.01.2020; number 1161) and Turkish Ministry of Health (dated 04.03.2020; number 68869993-511.06-E.63694) (Appendix 2 and 3). The informed consent forms (Appendix 1) were signed by the volunteering patients.

3.2. Study Groups

Group I (Test): Palatal donor site of FGG surgery with adjunctive HA application.

Group II (Control): Palatal donor site of FGG surgery left to spontaneous healing

3.3. Sample Size and Randomization

The power analysis was performed with a software program*. Postoperative pain was chosen as the primary parameter. The effect size was 1.67, standard deviation 1.90, 95% confidence level and 5% type I error. Therefore, it was determined that at least 9 patients were needed in both groups. In each group, 10 patients were included considering 10% dropouts.

20 patients who need FGG were assigned into two groups. Randomization was carried out (BK) according to a computer-based randomization table (Table 3.1.). Patients were included in test or control groups according to this grouping system.

Table 3.1. Randomization Table

Patient no	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Group no	1	2	1	2	2	2	2	2	1	1
Patient no	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Group no	1	1	2	1	1	1	2	1	2	2

3.4. Study Design and Flow Chart

The flow-chart of the research is shown in Figure 3.1. The study was designed as an examiner-blind, randomized and controlled parallel design clinical trial. Patients who met the initial inclusion criteria was required to demonstrate a full-mouth plaque score (FMPS) of ≤ 20% and full-mouth bleeding score (FMBS) of ≤ 20% (112,113). FGG surgery was applied in both groups in the same manner. In the test group following the FGG surgery, 0.3% topical polivnylpyrolidone sodium HA gel was applied on the palatal donor site. In the control group following the FGG surgery, palatal wound area was left to spontaneous healing. In both groups, palatal donor sites were covered with periodontal dressing. On day 3, topical HA gel was reapplied on the palatal donor site followed by a new periodontal dressing application.

*G Power 3.1.9.2.

No medication was prescribed postoperatively. One week after the operation, sutures were removed. Postoperative pain and burning sensation were evaluated by the patients on days 3, 7, 14, and 21.

Complete epithelization (CE) and color match (CM) were evaluated following the surgery on days 3, 7, 14, 21, and 42. Additionally, palatal wound area measurements were recorded on days 0, 3, 7, 14, 21, and 42. Patients were taken into maintenance phase after the completion of experimental period.

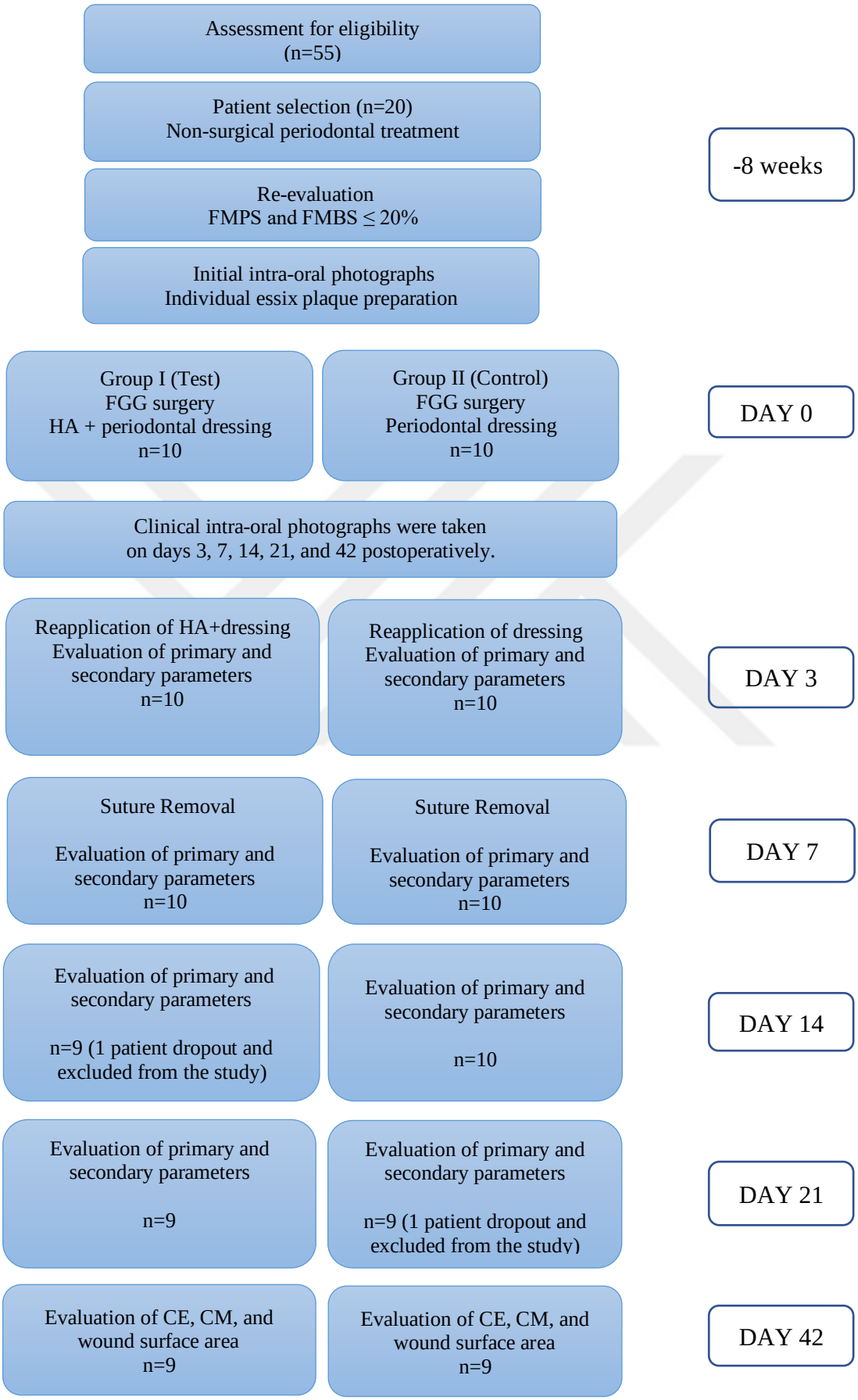

Figure 3.1. Flow Chart

3.5. Periodontal Measurements

Periodontal parameters were recorded by the same blinded examiner (EÖK) with a periodontal probe*.

3.5.1. Full Mouth Plaque Score

FMPS was recorded with a periodontal probe*. It was scored dichotomously (+/-) according to the presence or absence of plaque. A percentage value was calculated in terms of positive plaque regions on four periodontal sites (mesio-buccal, mid-buccal, disto-buccal, and mid-lingual/palatal) of each tooth. Patients were expected to meet the criteria of FMPS value with equal or less than 20% (22,112–114)

3.5.2. Full Mouth Bleeding Score

FMBS was also scored dichotomously (+/-) according to the presence or absence of bleeding on probing. A percentage value was determined relative to positive bleeding on probing areas. It was measured on four periodontal sites (mesio-buccal, mid-buccal, disto-buccal, and mid-lingual/palatal) of each tooth with a periodontal probe. Patients were expected to meet the criteria of FMBS $\leq$ 20% (22,112,114)

3.5.3. Probing Depth

Probing depths were measured from gingival margin to the deepest side of the gingival sulcus by using periodontal probe* from four periodontal sites (mesio-buccal, mid-buccal, disto-buccal, and mid-lingual/palatal) for each tooth throughout the dentition.

3.6. Clinical Procedures

3.6.1. Initial Periodontal Treatment

Since the selected patients were undergone initial periodontal treatment to meet the inclusion criteria of the study, they were only given oral hygiene instructions to keep the oral hygiene levels throughout the experimental period. Modified Stillman brushing technique was given at the insufficient keratinized gingival regions, whereas for the rest of the mouth, the Bass technique was recommended. They were also instructed to perform interdental cleaning with dental floss once a day. Initial periodontal treatment was performed before the inclusion of the patients (FD) consisted of mechanical

*University of North Carolina PCPUNC15, Hu-Friedy Ins. Co., ABD

debridement sessions using ultrasonic devices[*] and hand instruments[**]. After mechanical debridement, polishing was done with polishing paste and bristle brushes. 4 weeks following the initial periodontal treatment, FMPS, FMBS and PD were measured before the surgery.

3.6.2. Surgical Treatment

In both test and control groups, FGG surgery was performed (FD) according to the method described by Sullivan and Atkins (115).

3.6.2.1 Preparation of Recipient Site

After the local anesthesia[***], a horizontal incision was made at the mucogingival line, by using #15 blade[****]. Blade was inserted parallel to the periosteal bed and partial thickness flap consisting epithelium and underlying connective tissue was separated without disturbing the periosteum. A supra-periosteal recipient area was prepared to receive the palatal graft in pre-planned dimension of ~13x8 mm. Partial thickness flap was fixated using periosteal propylene sutures[*****] at the base of the vestibular sulcus which finalized the recipient bed preparation. Bleeding control was properly done applying one-minute compression with a wet gauze.

3.6.2.2. Palatal Donor Site

The region between maxillary first premolar and first molar was determined as the palatal donor site (Figure 3.2.1, Figure 3.3.1). Following the local anesthesia administration, a 13 mm long horizontal incision was made at least 2 mm apical from

---

[*] *Cavitron Woodpecker®, Guilin Medical Instrument Co. Ltd., Guangxi, China.*

[**] *Gracey, SG 5/6, 7/8, 11/12, 13/14, Hu-Friedy Ins. Co., ABD.*

[***] *Ultracaine® D-S Forte, Sanofi-Aventis, Frankfurt, Germany.*

[****] *Beybi®, Istanbul, Turkey.*

[*****] *Doğsan®, Istanbul, Turkey.*

the gingival margin using the individual essix plaque prepared with the insertion of a 13 mm orthodontic wire as the guide. Following the horizontal incision, 8 mm of distance perpendicular to the mid-point of the horizontal incision was measured with a periodontal probe to standardize the vertical dimensions of the graft. Graft thickness was standardized to approximately 1-1.5 mm (116). The thickness of the harvested graft was measured using an endodontic reamer, silicon stopper, and a caliper during the surgery (Figure 3.2.4, Figure 3.3.4). Following harvesting the graft from palatal donor site, bleeding control was properly done applying one minute compression with wet gauze.

3.6.2.3. Transfer of the Graft

FGG was sutured to the recipient site by 5-0 propylene sutures[*]. Following the suturing, graft was kept under compression with a wet gauze to prevent the dead space and excessive blood clot formation. In the test group, topical HA gel[**] was applied on the donor area, whereas the controls were left to spontaneous healing. In both test and control groups, palatal donor wound was covered with periodontal dressing[***] to avoid any possible trauma jeopardizing the healing.

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[*] *Doğsan®, Istanbul, Turkey.*

[**] *Aftadur® Plus Gel, Milano, Italy.*

[***] *Coe-Pak™, Gc America Inc.*

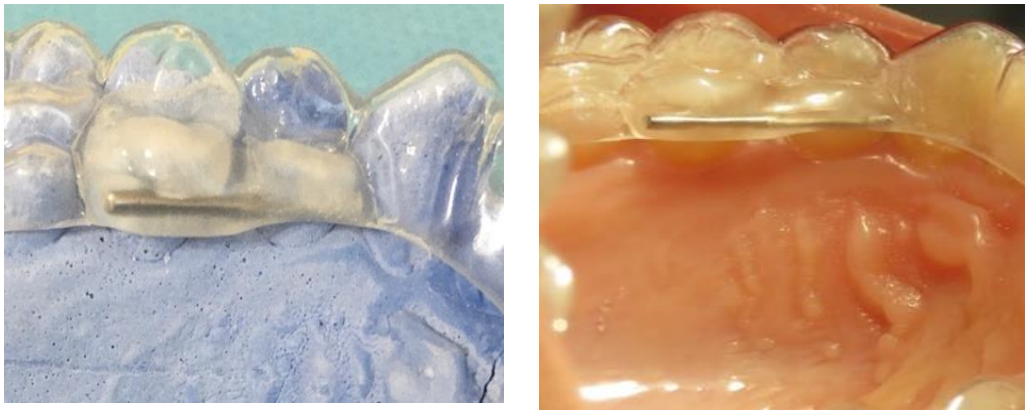

Figure 3.2.1. Pre-operative Palatal View of a Patient with Essix Plaque in the Group I (Test)

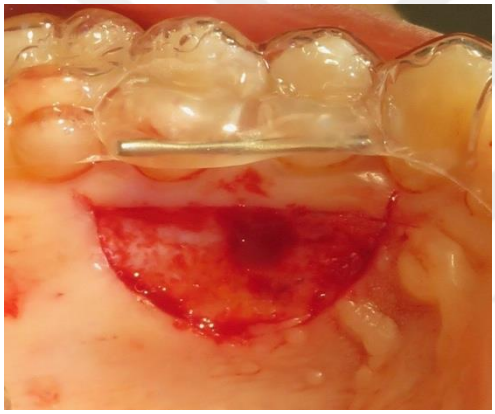

Figure 3.2.2. Immediate Postoperative View

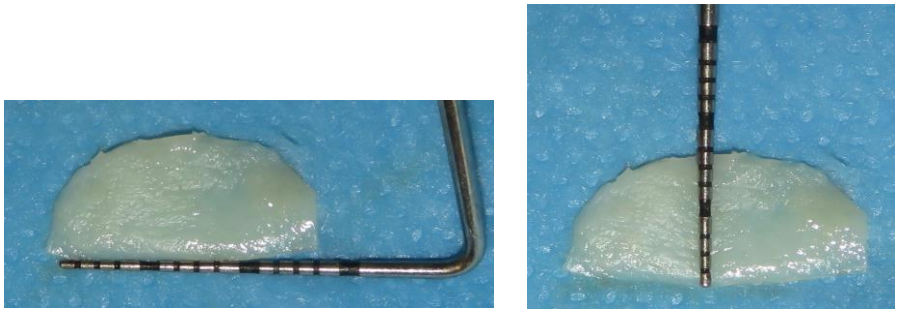

Figure 3.2.3. Horizontal and Vertical Dimensions of the Graft

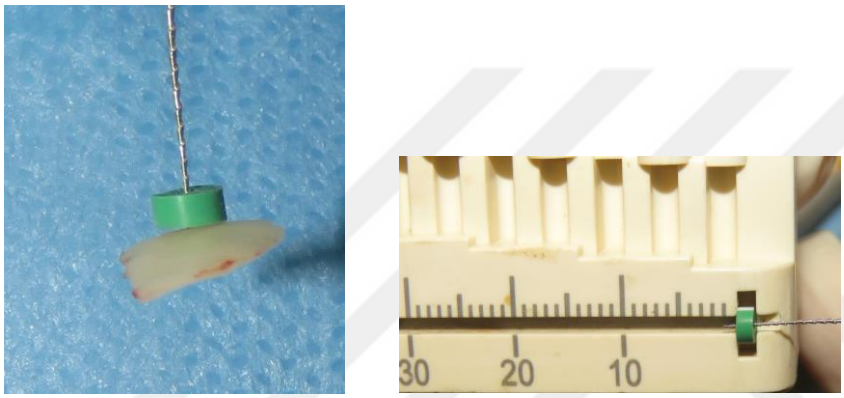

Figure 3.2.4. Graft Thickness Measurement

Figure 3.2.5. Endodontic Reamer

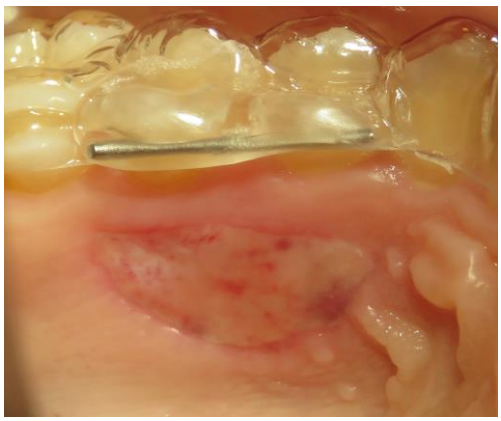

Figure 3.2.6. Day 3

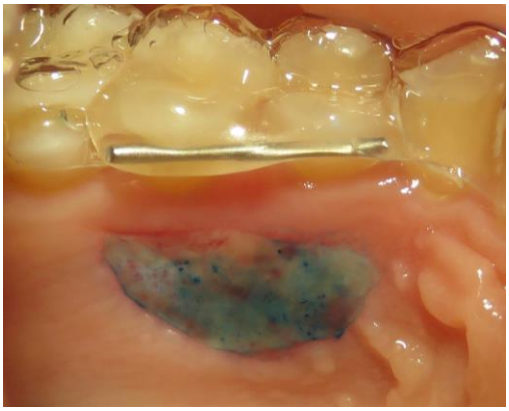

Figure 3.2.7. Day 3 (Methylene-blue stain)

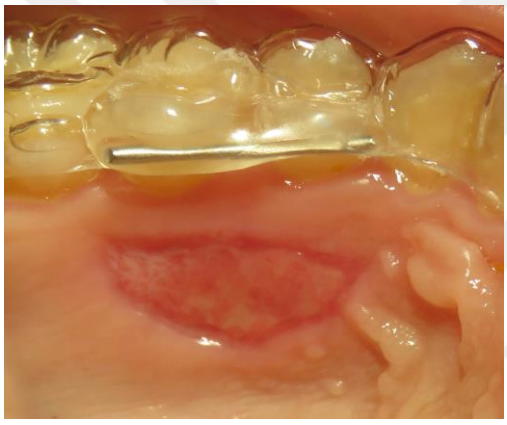

Figure 3.2.8. Day 7

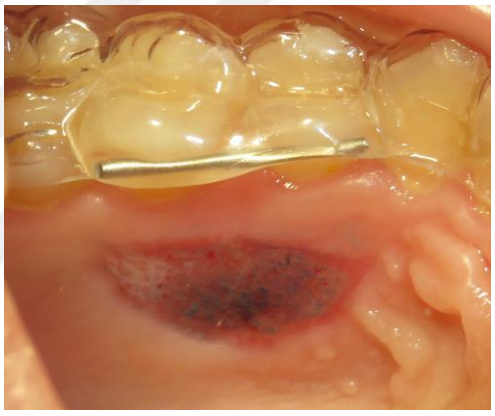

Figure 3.2.9. Day 7 (Methylene-blue stain)

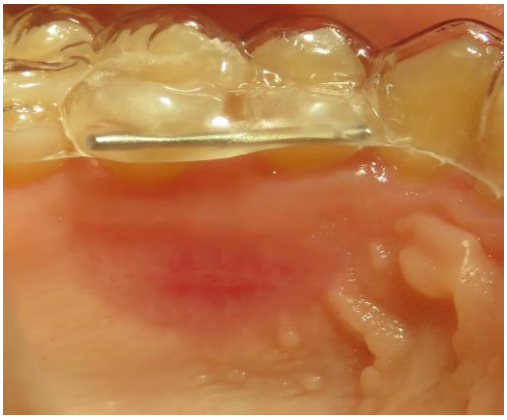

Figure 3.2.10. Day 14

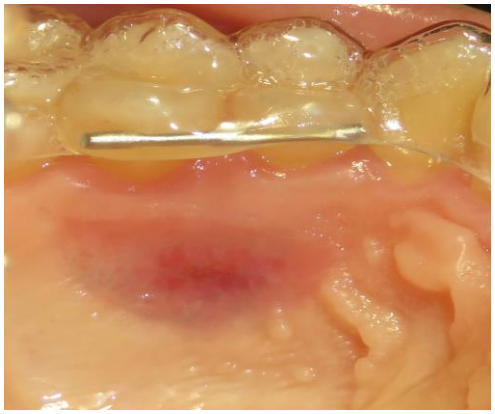

Figure 3.2.11. Day 14 (Methylene-blue stain)

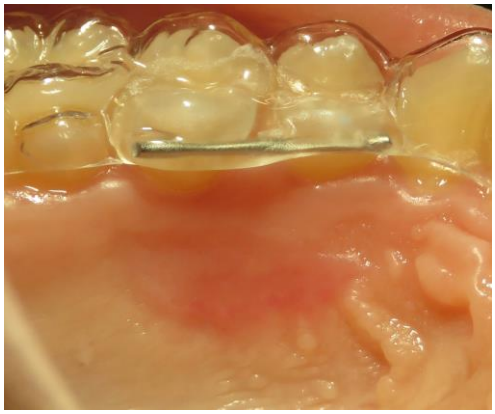

Figure 3.2.12. Day 21

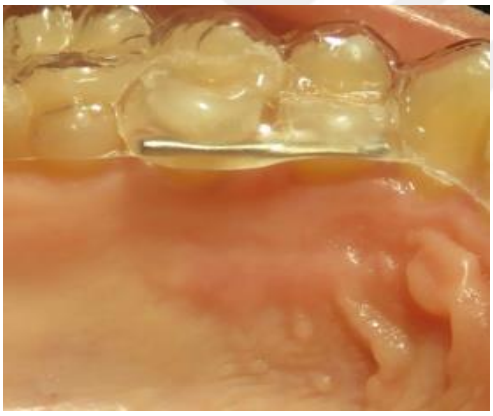

Figure 3.2.13. Day 42

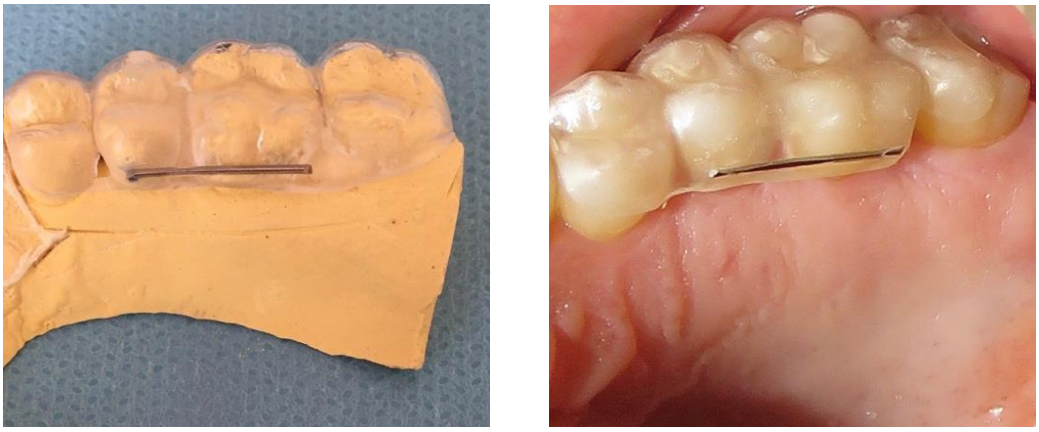

Figure 3.3.1. Pre-operative Palatal View of a Patient and Essix Plaque in the Group II (Control)

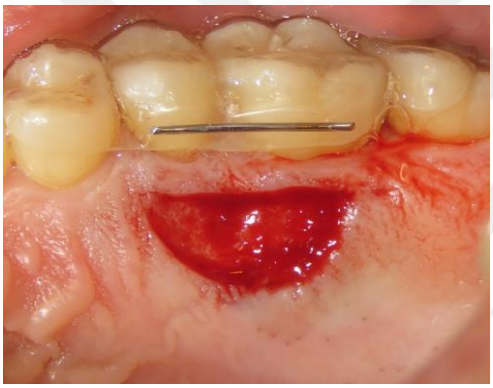

Figure 3.3.2. Immediate Postoperative View

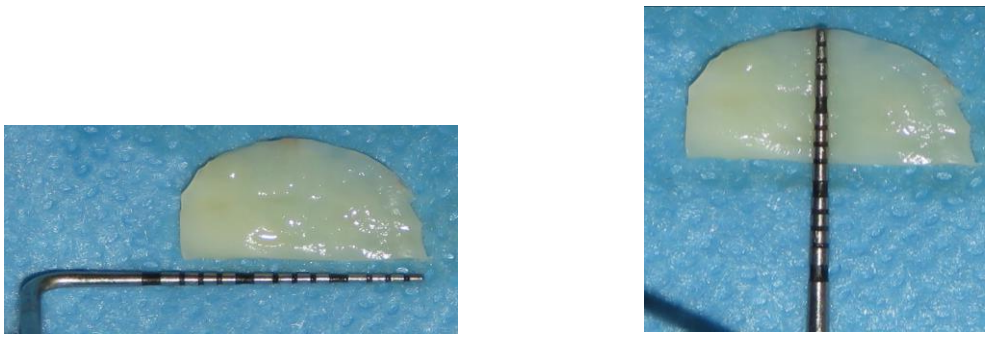

Figure 3.3.3. Horizontal and Vertical Dimensions of the Graft

Figure 3.3.4. Graft Thickness Measurement

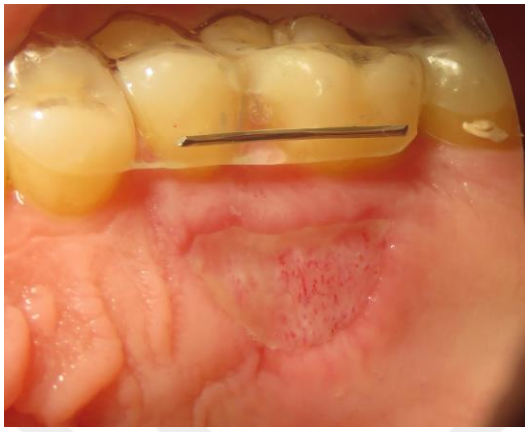

Figure 3.3.5. Day 3

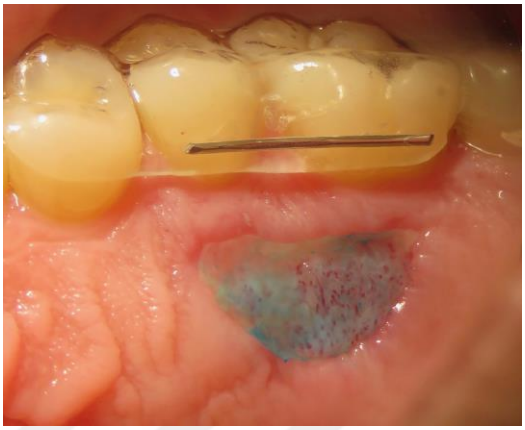

Figure 3.3.6. Day 3 (Methylene-blue stain)

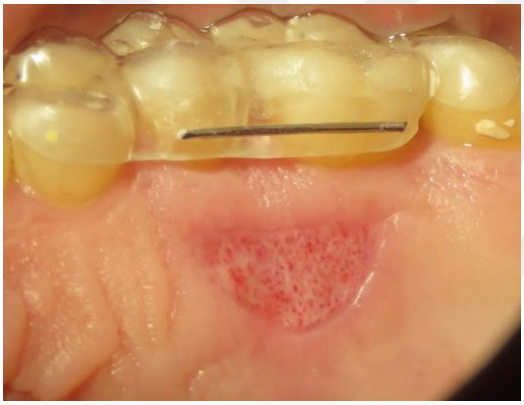

Figure 3.3.7. Day 7

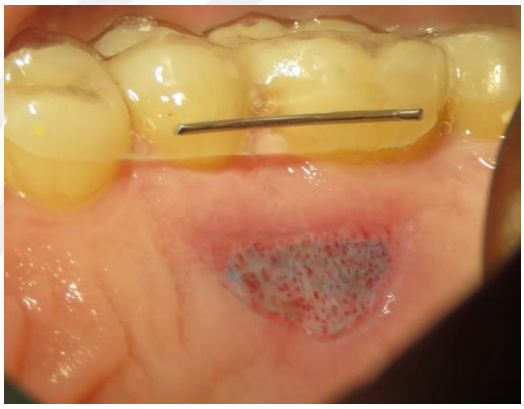

Figure 3.3.8. Day 7 (Methylene-blue stain)

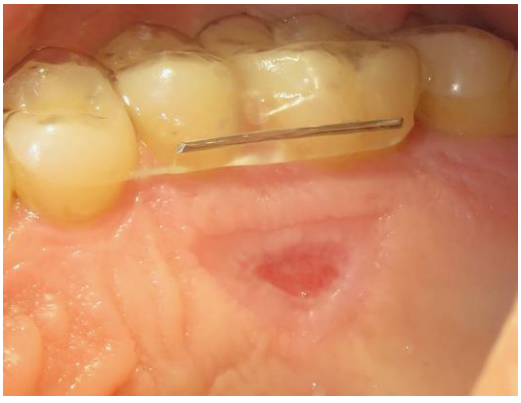

Figure 3.3.9. Day 14

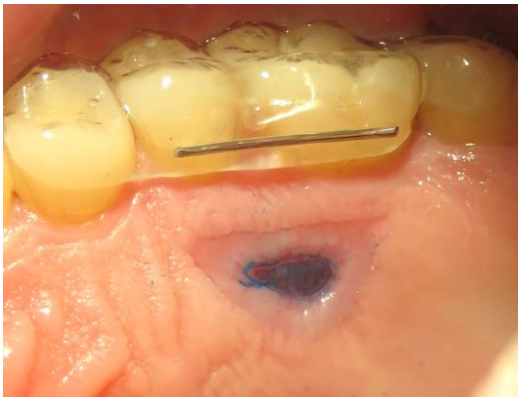

Figure 3.3.10. Day 14 (Methylene-blue stain)

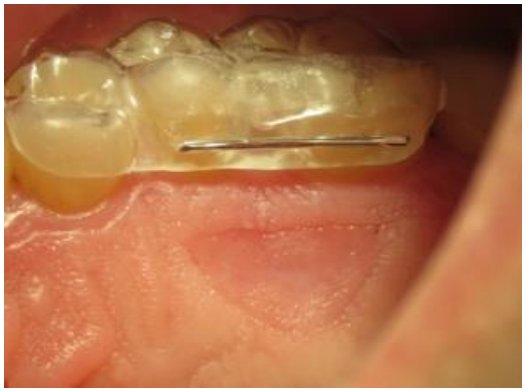

Figure 3.3.11. Day 21

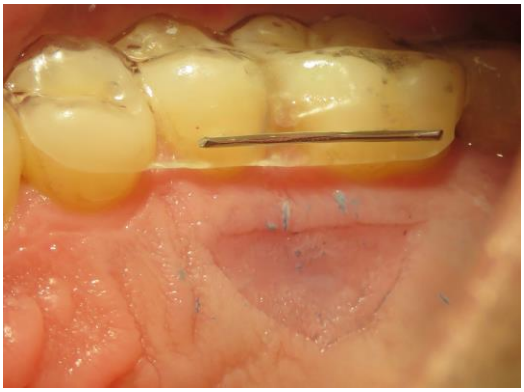

Figure 3.3.12. Day 21 (Methylene-blue stain)

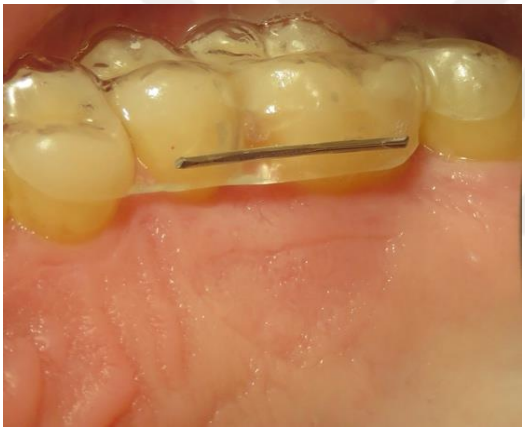

Figure 3.3.13. Day 42

3.6.3. Postoperative Instructions and Protocol

After the completion of the surgery, oral and written postoperative instructions were given to patients. Medication was deliberately not prescribed.

Postoperative instructions included; consumption of soft foods to avoid any mechanical trauma to the surgical sites, avoiding hot foods and liquids as well as spicy foods, fruit juices, and alcoholic drinks, keeping away from spit out not to trigger bleeding, discontinuing toothbrushing and flossing until the periodontal dressing removal. Applying ice during twenty-four hours to avoid inflammation and swelling, and avoiding excessive physical activities for a few days were recommended.

Patients were cared and followed professionally and appointments were scheduled on days 3, 7, 14, 21, and 42. In all of the postoperative appointments, clinical photographs were taken by the same periodontist using the same digital camera* with standardized parameters (dark chamber, ISO 125, aperture f/7.1, shutter speed 1/60 s, distance 31.4 cm) (Figure 3.2- Figure 3.3). Nikon's R1C1 wireless close-up speedlight system with twin flash was used. The camera was held with a vertical angle to intra-oral mirror. Each photograph was taken following individual essix plaque placement on palatal donor area. On day 3, periodontal dressing was removed to evaluate the donor site in both groups. Topical HA gel was again applied only in the test group before the reapplication of the periodontal dressing in both groups. On day 7, periodontal dressing was removed to re-evaluate the palatal wound area. For further evaluation, patients were followed up on days 14, 21, and 42.

3.6.4. Postoperative Procedures

On days 3, 7, 14, and 21, pain and burning sensation were assessed by the patients using visual analog scale (VAS) scale (117). Scoring was made between values 0 (no pain/burning sensation) and 10 (extreme pain/burning sensation) (Figure 3.4).

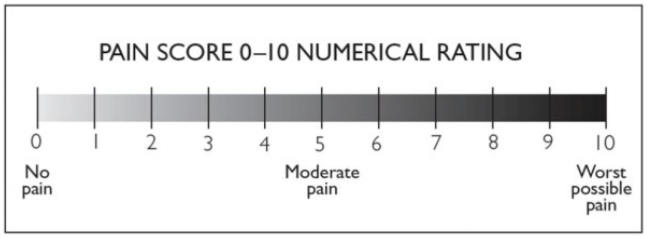

Figure 3.4. Visual Analog Scale

At each appointment, clinical photographs were taken from the palatal donor site with the guidance of individual essix plaque in place and evaluated by EÖK (intra-class correlation (ICC) close to 1; 0.98).

CE parameter was recorded on days 3, 7, 14, 21, and 42 by using dichotomous scoring system (yes/no). For CE assessment, clinical evaluations were performed according to wound surface characteristics and wound outline by using vision and staining (disclosing

*Nikon D5300 camera, Tokyo, Japan.

agent; methylene blue). Scoring system was performed as ‘yes’ or ‘no’, if the wound edges was unclear or clear, respectively (11). Palatal wound surface area measurements were also evaluated on days 0, 3, 7, 14, 21, and 42 by using methylene blue to determine the areas lacking epithelium. It was applied to the palatal region by using disposable cotton pellets for 2 min. Following the application, the patients were asked to rinse with water (118). Intra-oral photographs, which were taken from the stained area, were calculated with an image processing software program named ImageJ (119). CM was evaluated professionally on days 3, 7, 14, 21, and 42. CM was recorded using VAS score ranged between 0 (no match) and 10 (excellent match) by comparing the adjacent and contra-lateral palatal site (9,11).

3.7. Statistical Analyses

Statistical analyses were performed using SPSS software version 25. Descriptive analyses were presented using means, standard deviations, median, minimum, and maximum values for continuous data. Frequencies and percentages were used for categorical data. The variables investigated using Shapiro-Wilks test for normal distribution to determine if the variables were normally distributed, two sample independent t test was used to compare two groups. If the variables are not normally distributed, Mann-Whitney U test was used for comparison. For normally distributed data, change in the measurements by time was investigated using repeated measure ANOVA. Greenhouse-Geisser correction was used when the sphericity assumption was violated. Bonferroni test was performed to test the significance of pairwise differences for multiple comparisons. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. For variables that were normally distributed, change in the measurements between baseline and 6 month investigated using paired samples t test. For the variables that were not normally distributed, Wilcoxon’s test was used. Intra-observer agreements were determined by ICC. A 5% type-I error level was used to infer a statistical significance.

4. RESULTS

4.1. Descriptive Data

20 patients participated in the study. 2 patients dropped out during the follow-up period. They were excluded from the study. Therefore, 9 patients were randomized into test and control groups for the final analysis. Mean age and standard deviations (SD) and gender distribution of the patients are shown in Table 4.1. There were no statistically significant differences between the groups regarding mean age ($p>0.05$) and distribution of gender ($p>0.05$).

Table 4.1. Age and gender distribution in the test and control groups

	Test Group (n=9)	**Control Group (n=9)**	**p**
Age (Mean ± SD) (Range)	39.8 ± 7.5 (26-50)	42.2 ± 16.3 (18-64)	0.701[a]
Male n (%)	2 (22.2)	2 (22.2)	1.000[b]
Female n (%)	7 (77.8)	7 (77.8)	

a: Two sample independent t test, b: Fisher's exact test, $p<0.05$.

4.2. Clinical Data

4.2.1. Full-mouth Plaque and Full- mouth Bleeding Scores

The mean and SD of FMPS and FMBS at baseline and 6th months are shown in Table 4.2. and Table 4.3. There were no significant differences between the groups at baseline and 6th months. In test and control groups, intra-group comparisons showed statistically significant reductions for both FMPS and FMBS ($p<0.05$).

Table 4.2. Intra- and inter-group comparisons of FMPS at baseline and 6th months

		Test Group n=9 Mean ± SD	**Control Group** n=9 Mean ± SD	**p**
FMPS (%)	**Baseline**	14.62 ± 0.84	14.81 ± 1.03	0.675[a]
	6th Months	13.79 ± 0.82	13.85 ± 0.59	0.869[a]
	p	**0.011**[c]	**0.006**[c]	

a: Two sample independent t test, c: Paired samples t test, p<0.05.

Table 4.3. Intra- and inter-group comparisons of FMBS at baseline and 6th months

		Test Group n=9 Mean ± SD	**Control Group** n=9 Mean ± SD	**p**
FMBS (%)	**Baseline**	8.3 ± 1.67	7.7 ± 2.2	0.531[a]
	6th Months	6.8 ± 1.67	6.6 ± 2.2	0.835[a]
	p	**0.008**[c]	**0.047**[c]	

a: Two sample independent t test, c: Paired samples t test, p<0.05.

4.2.2. Full-Mouth Probing Depths

The mean and SD of FMPD at baseline and 6th months are shown in Table 4.4. Intra-group comparisons showed statistically significant reductions for PD in both test and control groups (p<0,05). Inter-group comparisons at baseline showed statistically significant difference. In the test group, PD baseline measurements were higher than the control group, (3.01 ± 0.4) vs (2.4 ± 0.5), respectively (p<0.05). However, 6th month measurements were not found significantly different between the groups.

Table 4.4. Intra- and inter-group comparisons of PD at baseline and 6th months

	Test Group n=9 Mean ± SD	**Control Group** n=9 Mean ± SD	**p**
PD (mm) Baseline	3.01 ± 0.4	2.4 ± 0.5	**0.030[a]**
PD (mm) 6th Months	2.8 ± 0.5	2.3 ± 0.5	0.080[a]
p	**0.008[c]**	**0.004[c]**	

a: Two sample independent t test, c: Paired samples t test, p<0.05.

4.2.3. Graft Thickness

Comparison of the mean FGG thickness between the groups is presented in Table 4.5. There was no statistically significant difference between the groups in terms of thickness.

Table 4.5. Comparison of the graft thickness in the test and control groups

	Test Group (n=9)	**Control Group (n=9)**	**p**
Graft Thickness (mm) (Mean ± SD)	1.24 ± 0.07	1.23 ± 0.09	0.953

Two sample independent t test, p<0.05.

4.2.4. Postoperative Pain

Postoperative pain scores in terms of VAS evaluation by the patients are presented in Table 4.6. and Figure 4.1. Intra-group measurements at 4 time points followed a pattern confirming that postoperative pain decreased during the healing period in both test and control groups (p<0.05). The Wilcoxon test was used to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons and pair-wise comparison after Bonferroni correction revealed no

statistically significant differences (p>0.05) between the evaluation days in the test and control groups. Inter-group comparison of mean values also showed no statistically significant postoperative pain differences between test and control groups at any observation periods. Although the differences were not statistically significant, the mean VAS values in the control group were found higher than the test group on days 3 and 7 (Fig 4.1)

Table 4.6. VAS scores of postoperative pain on days 3, 7, 14 and 21

	Test group (n=9)	**Control group (n=9)**	**p** [a]
Day 3			
Median (min to max)	1 (0 to 5)	2 (0 to 7)	
Mean ± SD	1.33 ± 1.58	2.88 ± 3.01	0.367[a]
+/- (0) pain (n)	6/3	6/3	
Day 7			
Median (min to max)	0 (0 to 1)	1 (0 to 9)	
Mean ± SD	0.22 ± 0.44	1.88 ± 2.97	0.161[a]
+/- (0) pain (n)	2/7	5/4	
Day 14			
Median (min to max)	0 (0 to 0)	0 (0 to 1)	
Mean ± SD	0.00 ± 0.00	0.11 ± 0.33	0.730 [a]
+/- (0) pain (n)	0/9	1/8	
Day 21			
Median (min to max)	0 (0 to 0)	0 (0 to 0)	
Mean ± SD	0.00 ± 0.00	0.00 ± 0.00	1.000 [a]
+/- (0) pain (n)	0/9	0/9	
p [b]	**0.002**[b]	**0.004**[b]	

a: Mann Whitney U test, b: Friedman test, p<0.05

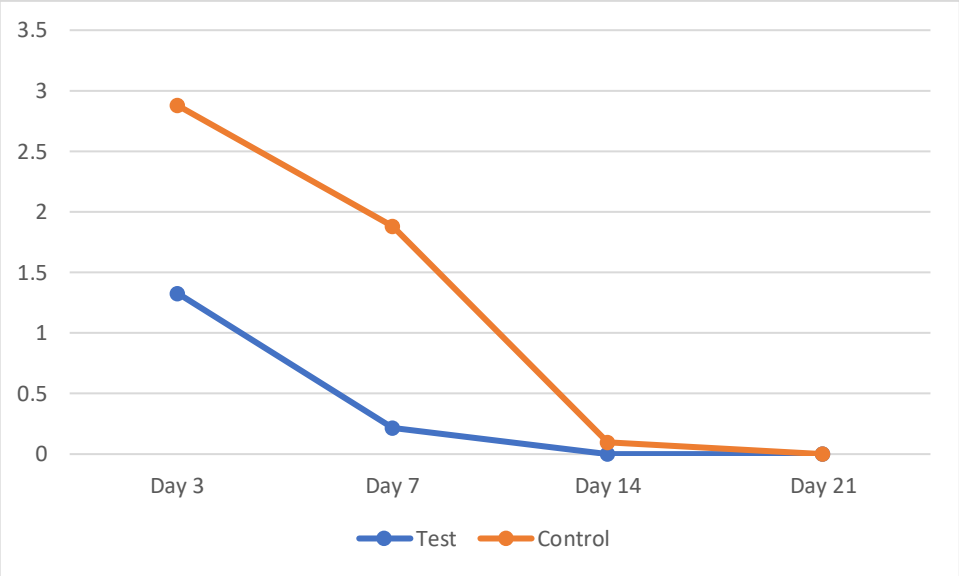

Figure 4.1. VAS scores of postoperative pain in the test and control groups

4.2.5. Burning Sensation

The VAS scores for burning sensation evaluated by the patients are shown in Table 4.7. and Figure 4.2. Intra-group comparisons of multiple time points confirmed that burning sensation gradually decreased during the healing period in both test and control groups. The Wilcoxon test was applied to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons and pair-wise comparison after Bonferroni correction showed no statistically significant differences between days in the test and control groups. Inter-group comparisons for burning sensation also revealed no statistically significant differences on days 3, 7, 14, and 21 between the groups. Although the differences were not statistically significant, the mean VAS scores in the control group were found higher than the test group on days 3 and 7.

Table 4.7. VAS scores of burning sensation on days 3, 7, 14, and 21

	Test group (n=9)	**Control group (n=9)**	**p** [a]
Day 3			
Median (min to max)	0 (0 to 3)	2 (0 to 5)	
Mean ± SD	0.66 ± 1.11	2.11 ± 1.96	0.136 [a]
+/- burning (n)	3/6	6/3	
Day 7			
Median (min to max)	0 (0 to 0)	0 (0 to 5)	
Mean ± SD	0.00 ± 0.00	1.11 ± 1.83	0.258 [a]
+/- burning (n)	0/9	3/6	
Day 14			
Median (min to max)	0 (0 to 0)	0 (0 to 1)	
Mean ± SD	0.00 ± 0.00	0.22 ± 0.44	0.436 [a]
+/- burning (n)	0/9	2/7	
Day 21			
Median (min to max)	0 (0 to 0)	0 (0 to 0)	
Mean ± SD	0.00 ± 0.00	0.00 ± 0.00	1.000 [a]
+/- burning (n)	0/9	0/9	
p [b]	**0.029**	**0.003**	

a: Mann Whitney U test, b: Friedman test, significant: $p<0.05$.

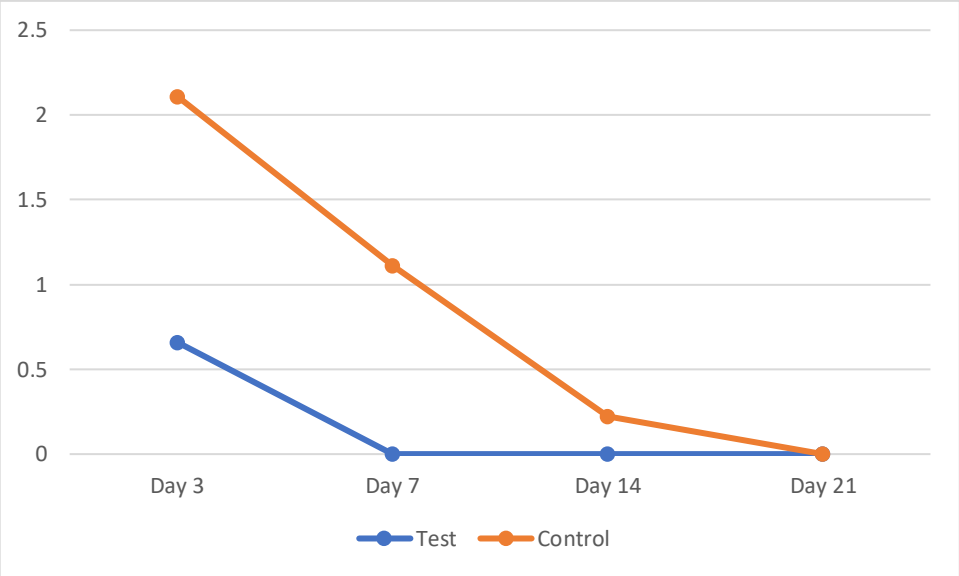

Figure 4.2. VAS scores of burning sensation in the test and control groups

4.2.6. Color Match

VAS scores for CM, evaluated professionally, are shown in Table 4.8. and Figure 4.3. Intra-group comparisons showed increasing CM scores during the healing period up to day 42, at which the matching scores reached the maximum mean value of (9.11 ± 0.92) and (8.88 ± 0.92) in both test and control groups, respectively. Pair-wise comparison revealed statistically significant differences ($p<0.05$) between days (3-21), (3-42), (7-21), (7-42) both in the test and control groups. Inter-group comparison for mean CM scores was found statistically significant between test and control groups on day 7. The test group with the application of HA revealed better mean CM values (1.66 ± 1.4) than the control (0.1 ± 0.3) ($p<0.05$).

Table 4.8. VAS scores of CM on days 3, 7, 14, 21, and 42

	Test group (n=9)	**Control group (n=9)**	p[a]
Day 3			
Median (min to max)	0 (0 to 2)	0 (0 to 0)	
Mean ± SD	0.40 ± 0.80	0 ± 0	n.c
Day 7			
Median (min to max)	2 (0 to 4)	0 (0 to 1)	
Mean ± SD	1.66 ± 1.4	0.100 ± 0.3	**0.024** [a]
Day 14			
Median (min to max)	4 (2 to 9)	2 (1 to 6)	
Mean ± SD	4.55 ± 2.24	3.00 ± 1.65	0.136 [a]
Day 21			
Median (min to max)	7 (6 to 10)	7 (3 to 9)	
Mean ± SD	7.55 ± 1.33	6.22 ± 1.7	0.113 [a]
Day 42			
Median (min to max)	9 (8 to 10)	9 (7 to 10)	
Mean ± SD	9.11 ± 0.92	8.88 ± 0.92	0.666 [a]
p [b]	**0.000**[b]	**0.000**[b]	

a: Mann Whitney U test, b: Friedman test, n.c (not computed), significant: $p<0.05$.

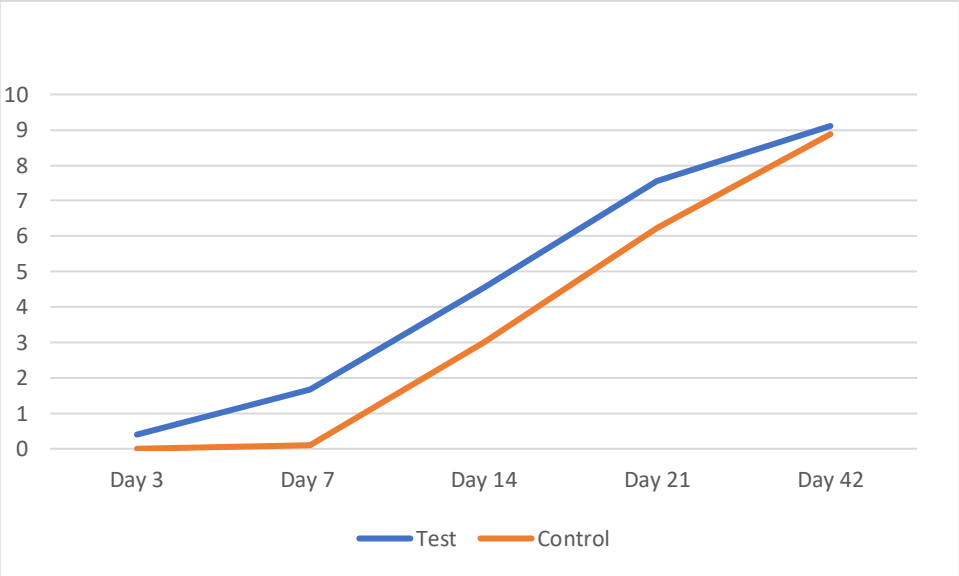

Figure 4.3. VAS scores of color match in the test and control groups

4.2.7. Wound Surface Area

Wound surface area measurements are shown in Table 4.9. and Figure 4.4. There were statistically significant differences in intra-group multiple comparisons for both test and control groups ($p<0,05$). Pair-wise comparison revealed significant differences ($p<0.05$) in the test and control groups between days (0-14), (0-21), (0-42), (3-21), (3-42), (7-42). Intra-group comparisons showed decreasing wound surface area measurements during the healing period up to the day 42 in both groups. Inter-group comparisons showed that there were statistically significant differences in mean values on days 3, 7, 14, and 21 between test and control groups ($p<0.05$). Wound surface area of the control group was greater than the test group.

Table 4.9. Wound surface area measurements (mm^2) on days 3, 7, 14, 21, and 42

	Test group (n=9)	**Control group (n=9)**	**p**
Day 0			
Median (min to max)	107.02 (98.58 to 115.96)	108.97 (101.76 to 110.27)	
Mean ± SD	108.37 ± 6.8	107.37 ± 3.3	0.863[d]
Day 3			
Median (min to max)	83.67 (72.23 to 89.9)	100.39 (90.18 to 106.08)	**0.000[a*]**
Mean ± SD	81.11 ± 6.2	99.7 ± 4.6	
Day 7			
Median (min to max)	46.43 (35.44 to 52.99)	54.28 (45.39 to 57.74)	**0.024[d*]**
Mean ± SD	44.74 ± 6.8	52.44 ± 5.1	
Day 14			
Median (min to max)	12.45 (0.23 to 18.89)	17.7 (11.35 to 32.6)	**0.049[d*]**
Mean ± SD	10.3 ± 6.9	17.88 ± 6.2	
Day 21			
Median (min to max)	1.26 (0 to 8.45)	10,2 (0 to 12.71)	**0.008[d*]**
Mean ± SD	2,37 ± 2,7	8,54 ± 4,2	
Day 42			
Median (min to max)	0 (0 to 1.34)	0 (0 to 4.55)	0.666[d]
Mean ± SD	0.14 ± 0.4	0.94 ± 1.8	
p[b]	**0.000[b]**	**0.000[b]**	

a: Two sample independent t test, b: Friedman test, d: Mann Whitney U test, *p<0.05.

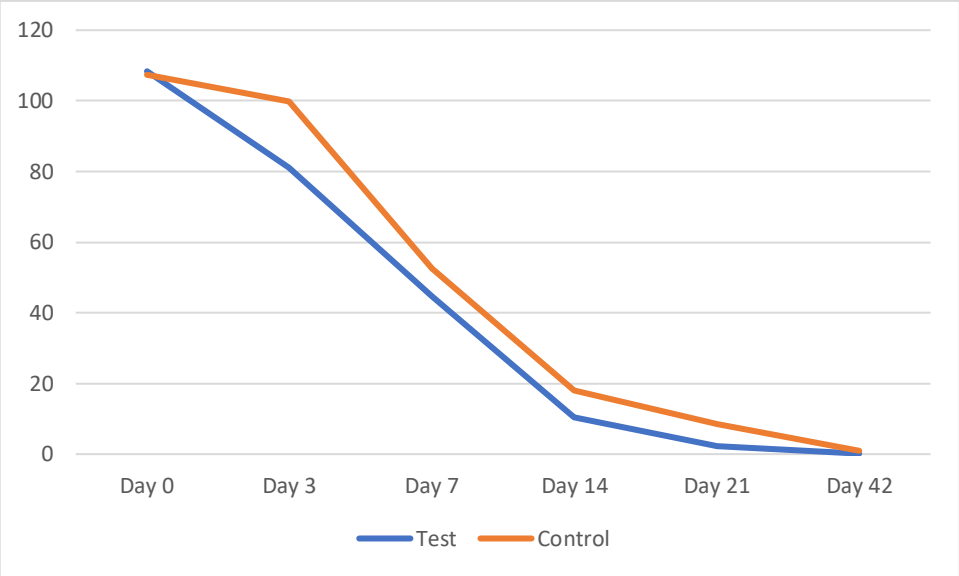

Figure 4.4. Wound Surface Area Measurements (mm^2) in the test and control groups

4.2.8. Complete Epithelization

Table 4.10. and Figure 4.5. show the CE data. On days 3 and 7, no CE was observed in any of the patients. On day 14, 11% of the patients in the test group showed CE, whereas none of the patients exhibited CE in the control group. On day 21, CE was observed 33% and 11% of patients in the test and control groups, respectively. On day 42, CE was detected in 89% of the patients in the test group while this value was 78% in the control group.

Table 4.10. Complete Epithelization (n) (%) on days 3, 7, 14, 21, and 42 in the test and control groups

CE n (%)	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 42**
Test Group	0 (0)	0 (0)	1 (11)	3 (33)	8 (89)
Control Group	0 (0)	0 (0)	0 (0)	1 (11)	7 (78)

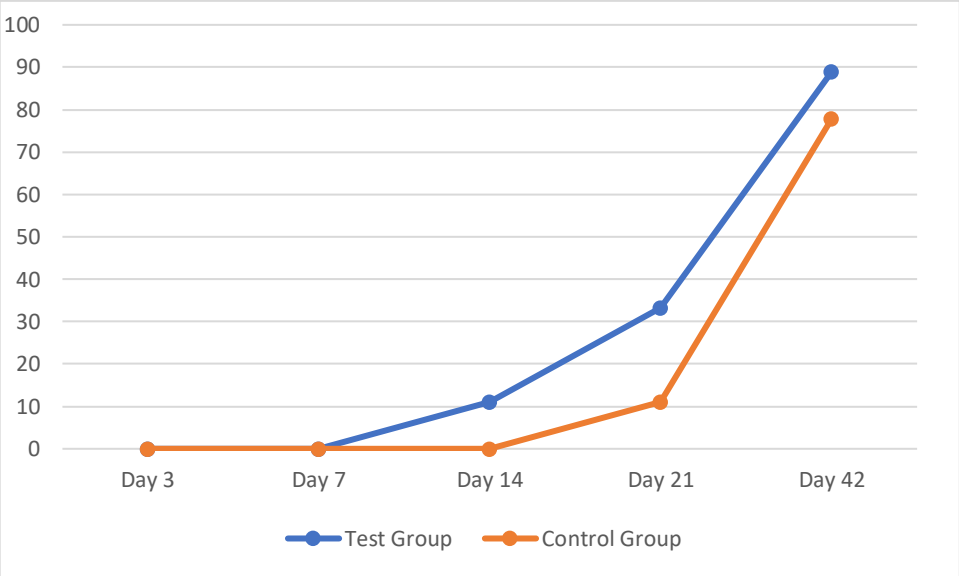

Figure 4.5. Complete epithelization (%) in the test and control groups

5. DISCUSSION and CONCLUSION

Among the soft tissue augmentation techniques, FGG is one of the most performed surgical methods to increase the thickness and the keratinized gingiva (120–122). In the literature, it has been shown that an adequate size of keratinized gingiva acts like a barrier against periodontal inflammation, provides a vestibular depth to ease oral hygiene measures, prevents physical trauma such as subgingival restoration margins and masticatory stress (16).

The hard palate has been mostly preferred region as a donor site in the FGG operations. However, secondary healing of this region might be related with some postoperative discomfort and complications. Postoperative pain and burning sensation, mostly reported as the postoperative complications, reach the peak level during the initial phase of wound healing, and eventually eliminated with the epithelization of the wound area (11,39,123–128).

Several materials have been suggested to reduce postoperative morbidity, such as herbal products, antibacterial agents, low-dose laser, dressing materials, platelet-rich fibrin, or topical hemostatic agents (121–123,129,130). In a systematic review, it was revealed that HA might be used adjunctively in the non-surgical and surgical periodontal therapies (131). In a few studies, the effect of HA with different concentrations on palatal wound site following the FGG operation have been evaluated (11,100,130,132,133). Currently, a new HA concentration is available different from the ones used in other studies. HA (0.3%) gel has mainly been indicated for the treatment of oral aphthous lesions to obtain pain relief and enhance healing. In the present study, topical HA (0.3%) gel was adjunctively used to reduce postoperative pain and enhance palatal wound healing.

In this randomized controlled clinical study, clinical measurements which are FMPS, FMBS, and FMPD were recorded at baseline and 6 months following the surgery. In the intra-group comparisons, statistically significant reductions for test and control groups were observed in FMPS and FMBS at 6 months postoperatively ($p<0,05$) without significant differences between the groups (Table 4.2., Table 4.3.). There were also no significant differences between the test and control groups at baseline. The initial inclusion criteria were 20% for both parameters and the reduction in plaque and bleeding

values were expected during the keen observation experimental period. In terms of inter-group comparisons of FMPD, statistically significant difference was found at baseline.

The mean FMPD of the test group was 3.01 ± 0.4 mm whereas it was 2.4 ± 0.5 mm in the control. Since the probing depths were measured only to give the overall periodontal health of the patients, the initial difference of the 2 groups is not expected to interfere with the aims of the study. Patient population in both groups were non-periodontitis patients.

Postoperative pain was the primary parameter. Patients were asked to score their level of pain and burning sensation using VAS scores on days 3, 7, 14, and 21. VAS has been used to assess subjective characteristics (50,133). Patients evaluated their discomfort scored between 0 (no pain) to 10 (extreme pain). No pain killer medication was used in this study. Hence, palatal region was covered with periodontal dressings (Coe-Pak^{TM}) in both groups. In the test group, HA (0.3%) gel was applied on the donor area with a single use dental micro-brush prior to the placement of periodontal dressing while in the control group, wound region was left to spontaneous healing with the conventional use of periodontal dressing. Inter-group comparisons revealed insignificant VAS score differences for postoperative pain and burning sensation at any observation periods (Table 4.6., Table 4.7.) ($p>0.05$).

This study was constructed to show the effects of the topical HA (0.3%) gel on postoperative morbidity and palatal wound healing following the FGG surgery. Although, the postoperative pain (3rd day: test, 1.33 ± 1.58, 7th day 0.22 ± 0.44 versus control, 2.88 ± 3.01 and 1.88 ± 2.97, respectively) and burning sensation scores (3rd day: test; 0.66 ± 1.11, 7th day 0 ± 0.00 versus control, 2.11 ± 1.96 and 1.11 ± 1.83, respectively) were lower in the test group, inter-group comparisons did not reveal statistically significant differences at any observation period. However, it was observed that the mean VAS scores for CM were significantly higher in the test group than in the control group on day 7 ($p<0.05$). CE started on day 14 in the test group whereas on day 21 in the control.

Additionally, on days 3, 7, 14, and 21, wound surface area of the test group was found significantly lesser than the control group ($p<0.05$).

López-Jornet et al. were studied the use of topical HA gel with the same concentration of 0.3% following the incisional oral biopsies three times a day for one week and reported improvement in biopsy wound healing, although no direct comparison is possible due to different study designs (134). At 2 hours following the biopsy, it was

reported that there were statistically significant differences in terms of median ranges for VAS pain scores between the groups favoring the test group. It was found that the maximum pain value was obtained in the control group compared to HA and chlorhexidine gel groups with median ranges of 2.2, 0.3, and 1.5, respectively. However, no statistically significant differences were reported during the rest of the 7 days of observational period (134).

There are only few studies assessed the effects of HA gel with different concentrations on palatal donor site healing following the FGG operation. Yıldırım et al. revealed the effects of the topical HA (0.2% and 0.8%) gels on pain perception and palatal wound healing following the FGG procedure. In terms of postoperative pain, they observed that patients in the test group I (0.2% HA) and test group II (0.8% HA) had lower VAS scores than the control group on days 3 and 7. On day 3, the mean VAS pain scores were reported as (1.67 ± 1.55), (1.92 ± 1.83) and (6.42 ± 1.83) in the test groups I, II and the control, respectively. On day 7, pain scores were reported as (1.25 ± 1.54), (0.83 ± 1.52) and (4.50 ± 2.27) in the test groups I, II and the control, respectively (11). The difference of the pain perception scores obtained in the control group and the involved patient numbers between the 2 studies may explain the statistically insignificant outcomes.

Recently, Hassan et al. conducted a study investigating the effects of HA (0.2%) and an herbal extract (MEBO) on pain and palatal wound healing during one-week period of time. They aimed to report postoperative pain as primary parameter following the FGG procedure. On day 3, the MEBO group presented the lowest pain followed by HA gel and the control. Moreover, they evaluated the consumption of painkillers at the postoperative period to support the VAS pain scores which makes the biggest difference versus our study design reflected in the selected parameter outcomes. The highest mean and range values for total painkiller consumption were recorded in control group patients. The median scores for postoperative pain in the test group I (herbal extract), test group II (0.2% HA) and the control group were 0, 0.5, and 4.5, respectively ($p=0.008$) (132).

The latest report by Khalil et al. investigated the local effects of HA (0.2%) for both recipient and donor sites regarding postoperative pain and wound healing following the FGG operation. They recorded VAS pain scores for two weeks. In the first week following the operation, test group with HA (0.2%) showed statistically significant lower median pain values than the control group (saline application). In the test group median

pain scores were reported as 5, 5, 3, 3, 2, 1, 1 whereas they were 8, 8, 6, 4, 4, 2, 2 in the control group between day 1 and 7, respectively (130). The differences of patient numbers and the formulation of HA gel between the groups may have affected the significance in statistics.

In brief, HA gels are found effective in postoperative pain in the literature (11,130). In the present study, inter-group comparisons of postoperative pain parameter did not show significant differences between test and control groups at any observation period. However, some of the above mentioned studies, postoperative pain evaluated indirectly on the basis of mean consumption of analgesics (130,132). On the other hand, in the present study, postoperative discomfort was treated by means of periodontal dressing. This discrepancy in terms of postoperative pain VAS outcomes may be due to the differences in the percentage, methodology of postoperative pain evaluation and the contents of topical HA gel formulation which was used in the present randomized controlled study. In addition, the difference in sample sizes of the three-armed randomized controlled studies by Yıldırım et al., and Hassan et al., may also lead to different study outcomes. This is the first study evaluating 0.3% concentration of HA gel in palatal wound healing after FGG surgery.

Re-epithelization process, defined as the coverage of epithelial surface which is previously denuded, has a significant role in wound healing phases (135). In this study, approximately 13x8 mm palatal grafts were obtained in a standardized model in order to make proper assessment of palatal wounds which has been used as a healing assessment method previously (70,127,136). In the literature, there are several studies evaluating the palatal donor site wound healing by using different techniques, such as various staining agents, clinical examination via direct visualization, hydrogen peroxide (H_2O_2) etc. (9,18,124). In our study, CE was scored dichotomously (+/-) following the methylene blue dye application. In the test group, CE was observed %11 of the patients on day 14. However, none of the patients showed CE on day 14 in the control group. It might be considered as a sign of a positive effect of HA on wound healing. On day 21, CE was 33% in the test group patients while 11% in the controls. On day 42, it was higher in the test group (89%) than the control (78%) (Table 4.10.). Yıldırım et al. also assessed CE of palatal wound area after FGG procedure by clinical examination, and then by dichotomous scoring in accordance to epithelization level. On day 14, they reported that CE was statistically significant in favor of the patients in the test group I (0.2% HA gel)

compared to test group II (0.8% HA gel) and the control. CE was observed 50% of the test group I while 8.3% of the test group II and 8.3% of the control group. On day 21, it was found that the control group showed significantly poor outcomes than the test groups. They reported that CE was obtained 100% of the test I and test II group patients. However, control group patients revealed 66.7% CE. In the present study, as a contributory difference, CE was evaluated following methylene blue dye application to ease the visional evaluation. In this way, it was thought that epithelization may be scored more objectively. However, a statistical analysis of CE cannot be performed due to the smaller sample size in this study.

As a wound healing parameter, tissue CM scores was assessed in many studies. It is recorded by using VAS (ranged between '0-10' or '0-100') scores to evaluate palatal wound healing following FGG or connective tissue graft (CTG) operations (9,11,137). Additionally, there are some studies using 'colorimetric analysis' software programs to analyze the CM (138). In our study, CM was recorded between 0 (no CM) to 10 (perfect CM) with using VAS. It was scored by a blinded investigator according to the opposite site and neighboring tissue of the palatal wound area. In the present study, inter-group comparison for CM showed statistically significant difference between the test (1.66 ± 1.4) and the control (0.1 ± 0.3) groups on day 7 in favor of the test group with 0.3% HA ($p<0.05$). However, no statistically significant differences were found in terms of CM scores between test and control groups on days 3, 14, 21 and 42. Similar to our study, Alpan et al. showed the effect of PRF on palatal wound healing following CTG operation by using VAS scores. On day 7, patients in the PRF group (70.50 ± 11.45) showed statistically significant higher VAS CM scores than the control group (59.47 ± 15.08). On day 14, PRF group (93.50 ± 6.70) revealed higher VAS CM scores than the control group (87.37 ± 4.52) ($p=0.002$) (137). Besides, Yıldırım et al. demonstrated a statistically significant higher CM scores in the test group I (0.2% HA gel) and test group II (0.8% HA gel) than in the control group on days 7, 14, 21, and 42. It was also shown that the test groups revealed similar outcomes regarding VAS CM scores. By all means, the difference in the sample sizes and the usage of different HA gel formulation matter in terms of the study outcomes.

As another secondary parameter in our study, in addition to visual evaluation, wound surface area was calculated digitally with a software program named ImageJ. In the literature, there are different scales and indices used to evaluate the wound healing

(117,138–143). Many advantages of the ImageJ program were reported; easy to use, open access, a practical way for manipulation of the images without requiring any complex operating systems (144–145). In the present study, regarding wound surface area, statistically significant differences in multiple intra-group comparisons for both test and the control groups ($p<0,05$). Inter-group comparisons showed statistically significant differences between the groups on days 3, 7, 14, and 21, with lower wound surface area calculations in the test group than the control group (3^{rd} day 81.11 ± 6.2 versus 99.7 ± 4.6; 7^{th} day 44.74 ± 6.8 versus 52.44 ± 5.1; 14^{th} day 10.3 ± 6.9 versus 17.88 ± 6.2 ;21^{st} day 2.37 ± 2.7 versus 8.54 ± 4.2, respectively) ($p<0,05$). Regarding wound surface area, the control group was greater than test group.

Hassan et al. assessed the wound surface size using planimetric method with a metric grid system. Eventually, they reported that there were no statistically significant differences in terms of palatal wound surface size between test group I (MEBO), test group II (0.2% HA) and the control group. In another study Sousa et al. studied the effect of advanced platelet-rich fibrin (A-PRF) on palatal wound healing following the FGG surgery. On the follow-up period, they used a probe to measure the percentage of reduction of the palatal wound area (mm^2) to evaluate the epithelization rate. On days 7, 14, and 30, they reported that the reduction in palatal wound area were significantly higher in the A-PRF group than the control (43). In the present study, from a clinical point of view, it might be concluded that the HA (0.3%) gel had an effect on the enhanced wound healing outcomes. This may be taken as a marker of better healing effects of HA gel leading to tissue maturation.

In this randomized controlled study, as a contributory difference, wound surface area was evaluated following methylene blue dye application to obtain more objective results. Methylene blue dye is a safe, inexpensive and easy staining method used to assess wound healing progression (147). It was reported that clinical epithelization rate was evaluated with methylene blue and also stated that chronic, unhealed, unviable and non-epithelialized wounds might easily labelled with the methylene blue dye (118,148).

To be concluded, within the limitations of this thesis study, HA (0.3%) gel applied together with periodontal dressing is useful and might be a promising agent for reducing postoperative pain and accelerating palatal wound area after the FGG operation. However, further randomized controlled clinical trials in wider populations are needed to

confirm the effects of this HA gel on postoperative discomfort and wound healing in the future.

6. REFERENCES

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7. APPENDICES

7.1. Informed Consent Form

KLİNİK ARAŞTIRMALAR ETİK KURULU
BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Hastanın veya yerine onam verecek kişinin okuma, anlama, konuşma, dil sorunu mevcut mu? Evet ☐ Hayır ☐ Cevabınız EVET ise Hasta İlişkileri Sorumlusu ile iletişim kurunuz.	**Tercüman gerektiyse;** Tercümanın adı _____ İmza _____ Tarih _____

Sayın Hastamız,

- Bu belge bilgilendirilme ve aydınlatılmış onam haklarınızdan yararlanabilmenizi amaçlamaktadır.
- Size gerçekleştirilebilecek klinik araştırmalar amaçlı girişimler konusunda, tüm seçenekler ile bu girişimlerin yarar ve muhtemel zararları konusunda anlayabileceğiniz şekilde **bilgi alma hakkınız ve bir kopyasını isteme hakkınız** vardır.
- Yasal ve tıbbi zorunluluk taşıyan durumlar dışında **bilgilendirmeyi reddedebilirsiniz**. Yazılı bildirmek koşulu ile bilgi almama veya yerinize güvendiğiniz bir kimsenin bilgilendirilmesini talep etme hakkına sahipsiniz.
- Klinik araştırmalara katılım konusunda bilgilendirildikten sonra bunu kabul edebilirsiniz. Ya da **karar verebilmek için uygun zaman talep edebilirsiniz.**
- Hayatınız veya hayati organlarınız tehlikede olmadığı sürece onamınızı (yazılı talep etme koşulu ile) **dilediğiniz zaman geri alabilir** ya da önceden kabul etmediğiniz herhangi bir tanı/tedavi amaçlı girişimi **tekrar talep edebilirsiniz**.
- Hastanemizde verilen hizmetleri **Hastane Tanıtım Broşürü**nden edinebilirsiniz. Ayrıca Hastanemiz personeli hakkında http://www.yeditepehastanesi.com.tr/ web sayfamızdan daha detaylı bilgilere ulaşabilirsiniz.
- Burada belirtilenlerden başka sorularınız varsa bunları yanıtlamak görevimizdir.

KLİNİK ARAŞTIRMALAR ETİK KURULU
BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

TANIMLAMA
Araştırmanın Adı / Protokol numarası

Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi/ 282

Sorumlu Araştırmacının Adı: *Prof. Dr. Bahar Eren Kuru*

Araştırma Konusu

Serbest dişeti grefti operasyonu, keratinize dişeti genişliğinin arttırılmasını sağlayan operasyonlardan biridir. Bu amaçla damak bölgesinden dişeti dokusu alınır ve sorunlu bölgeye dikişlerle sabitlenir. Dişeti dokusu alındıktan sonra damak bölgesinde açık bir yara yüzey alanı bırakıldığı için ağrı, yanma hissi gibi birtakım sorunlar oluşabilmektedir. Araştırmamızda damak bölgesine uygulanacak olan jelin, ameliyat sonrası ağrı hissi üzerine ilave etkisi değerlendirilecektir. Ayrıca ameliyat sonrası damak bölgesi bir yara örtücü pat ile kapatılacaktır.

Araştırma konusu ile ilgili başka çalışmalar olup olmadığı:

Araştırmada kullanılacak olan jel ile benzer içeriğe sahip, farklı konsantrasyonlarda olan hyaluronik asit jelin kullanıldığı, operasyon sonrası damak bölgesindeki yara iyileşmesine etkisinin değerlendirildiği benzer çalışmalar bulunmaktadır.

Araştırmaya Katılımcı Sayısı

Çalışmaya tek merkezde (Yeditepe Üniversitesi Diş Hekimliği Fakültesi Periodontoloji Anabilim Dalı) 18-65 yaş arasındaki 18 bireyin dahil edilmesi planlanmıştır. Çalışmamızda, kliniğimize başvuran hastalardan çalışmaya dahil edilme kriterine uyanlar basit randomizasyon yöntemi ile rastgele seçilecektir.

Bu çalışmaya katılmalı mıyım? (Bu bölüm aynen korunacaktır)

Bu çalışmada yer alıp almamak tamamen size bağlıdır. Eğer katılmaya karar verirseniz bu yazılı bilgilendirilmiş olur formu imzalanmak için size verilecektir. Şu anda bu formu

imzalasanız bile istediğiniz herhangi bir zamanda bir neden göstermeksizin çalışmayı bırakmakta özgürsünüz. Eğer katılmak istemez iseniz veya çalışmadan ayrılırsanız, doktorunuz tarafından sizin için en uygun tedavi planı uygulanacaktır. Aynı şekilde çalışmayı yürüten doktor çalışmaya devam etmenizin sizin için yararlı olmayacağına karar verebilir ve sizi çalışma dışı bırakabilir; bu durumda da sizin için en uygun tedavi seçilecektir.

Bu araştırmanın

Amacı
Serbest dişeti grefti operasyonu sonrası damak bölgesine topikal olarak uygulanan polivinilpirolidon sodyum hyaluronat içeren bir jelin yara iyileşmesine katkısını ve post-operatif hasta konforuna (damak bölgesindeki ağrı, yanma hissi ve yara iyileşmesi) ilave etkisi incelenecektir.

Süresi
Ameliyat sonrası her bireyin damak bölgesi yara iyileşmesi takibi 42 gün boyunca devam edecektir. Çalışmanın toplam süresinin ise 6 ay olması beklenmektedir.

İzlenecek Yöntem / Yöntemler
Hastalara başlangıç periodontal tedavi kapsamında diştaşı temizlikleri yapılacak ve bireye uygun diş fırçalama yöntemi, diş ipi ve/veya arayüz fırçası kullanımı anlatılacaktır. Ağız içi fotoğraflar çekilecektir. Tüm ağızdan klinik ölçümler alınacaktır. Hastalar kontrole çağırılacak ve ağız hijyenini yeterli düzeyde sağlayabilen hastalar çalışmaya dahil edilecektir. Ameliyat öncesi üst çeneden ölçü alınacak ve 0.7 cm çapında ve 13mm uzunluğunda ortodontik tel içeren bireye özgü SX dişli plak yapılacaktır. Başlangıç periodontal tedavisi tamamlanmış hastalara keratinize dişeti genişliğinin arttırılmasını sağlayan yöntemlerden biri olan serbest dişeti grefti operasyonu yapılacaktır. İşlem esnasında, damak bölgesinden dişeti dokusu alınarak keratinize dişeti yetersizliği olan bölgeye dişeti dokusu sabitlenecektir. Ameliyat sonrası damak bölgesi bir yara örtücü olan periodontal pat ile kapatılacaktır. 3., 7., 14., 21. ve 42. günlerde hastaların kontrol seansları yapılacaktır.

Hastalarımızı 2 gruba ayıracağız. Bu gruplardan hangisinde yer alacağınız rastgele belirlenecektir. Eğer test grubuna dahilseniz operasyon sonrası geldiğiniz randevularda damak bölgesine jel uygulaması yapılacak; kontrol grubunda iseniz herhangi bir jel uygulaması yapılmadan yara iyileşmesi takip edilecektir. Kontrol randevuları sırasında her seferinde damak bölgenizden fotoğraf çekilecektir.

Ne yapmam gerekiyor, sorumluluklarım nelerdir?

Yapılacak işlem sonrası hekiminizin önerilerine uymanız ve kontrol randevularınıza aksatmadan gelmeniz gerekmektedir.

Araştırma Sonunda Beklenen Fayda
Kullanılan jelin hastanın yaşadığı ameliyat sonrası hissedilen ağrı ve yara iyileşmesi üzerine olumlu katkı sağlaması.

Alternatif Tedavi Veya Girişimler
Damak bölgesinin açıkta bırakılması ya da damak bölgesine farklı konsantrasyonda bir jelin uygulanması.

Araştırma Sırasında Karşılaşılabilecek Riskler ve Rahatsızlıklar

Yapılan bu operasyon sonrası oluşabilecek ağrı, yanma hissi, kanama gibi yan etkilerin görülmemesi açısından verilen önerilere uyulması ve ağız hijyeninin optimal seviyede tutulması gönüllünün sorumluluğundadır.
Çalışmamızdan dolayı herhangi bir zarar veya yan etki görmeniz durumunda her türlü tıbbi müdahale yapılacaktır ve konu ile ilgili harcamalar tarafımızdan karşılanacaktır

Riskleri	***Rahatsızlıklar***
a) Kanama	a) Operasyon sonrası ağrı
b)	b) Yanma hissi
c)	c)
d)	d)
e)	e)
f)	f)
g)	

Risk / rahatsızlık durumlarında yapılması gerekenler
Aşağıda iletişim bilgileri verilen araştırmacıya ulaşmak.

Aşağıdaki özel durumlara ait katılımcı var mı?

	EVET*	**HAYIR**

Çocuk		**X**
Mahkum		**X**
Gebe		**X**
Mental yetersizlik		**X**
Sosyoekonomik eğitim olarak yetersiz	**X**	

*Ancak çocuklarda, hamilelik, lohusalık ve emzirme dönemlerinde ve kısıtlılık durumunda; gönüllüler yönünden araştırmadan doğrudan fayda sağlanacağı umuluyor ve araştırma gönüllü sağlığı açısından öngörülebilir ciddi bir risk taşımıyor ise, usulüne uygun bir şekilde alınmış bilgilendirilmiş gönüllü olur formu ile birlikte ilgili etik kurulun onayı ve Bakanlık izni alınmak suretiyle araştırmaya izin verilebilir.

Çalışma hakkında yeni bilgiler elde edilirse ne olacak? (Bu bölüm aynen korunacaktır)

Araştırmaya katılmaya devam etme isteğinizi etkileyebilecek, araştırma konusuyla ilgili yeni bilgiler elde edildiğinde siz veya yasal temsilciniz zamanında bilgilendirilecektir.

Araştırmadan kendi isteğim dışında çıkmam gerekebilir mi?

Seanslara düzenli geldiğiniz sürece ve kendi isteğiniz dışında araştırmadan çıkmanız gerekmemektedir.

Bu çalışmaya katılmamın maliyeti nedir? (Bu bölüm aynen korunacaktır)

Çalışmaya katılmakla parasal yük altına girmeyeceksiniz ve size de herhangi bir ödeme yapılmayacaktır.

Varsa, gönüllülere yapılacak ulaşım, yemek gibi masraflara ilişkin ödemeler hakkındaki bilgiler burada verilmelidir.

Kişisel bilgilerim nasıl kullanılacak? (Bu bölüm aynen korunacaktır)

Çalışma doktorunuz kişisel bilgilerinizi, araştırmayı ve istatiksel analizleri yürütmek için kullanacaktır. Çalışmanın sonunda, bu bilgiler hakkında bilgi istemeye hakkınız vardır. Çalışma sonuçları çalışma bitiminde tıbbi literatürde yayınlanabilecektir ancak kimliğiniz açıklanmayacaktır.

İzleyiciler, yoklama yapan kişiler, Etik Kurul, Sağlık Bakanlığı ve diğer ilgili sağlık otoriteleri orijinal tıbbi kayıtlarınıza doğrudan erişebilir. Bu yazılı bilgilendirilmiş gönüllü olur formunu imzalayarak yalnızca adı geçen kişi ve kurumlara erişim izni vermiş olacaksınız. Ancak kimlik bilgileriniz gizli tutulacak, kamuoyuna açıklanamayacak; araştırma sonuçlarının yayımlanması halinde dahi kimliğiniz gizli kalacaktır.

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Daha fazla bilgi, yardım ve iletişim için kime başvurabilirim?

Çalışma yöntemi/ilacı ile ilgili bir sorununuz olduğunda ya da çalışma ile ilgili ek bilgiye gereksiniminiz olduğunuzda aşağıdaki kişi ile lütfen iletişime geçiniz.

ONAM (RIZA)

Bilgilendirilmiş Gönüllü Olur Formundaki tüm açıklamaları okudum. Bana, yukarıda konusu ve amacı belirtilen araştırma ile ilgili yazılı ve sözlü açıklama aşağıda adı belirtilen hekim tarafından yapıldı. Araştırmaya gönüllü olarak katıldığımı, istediğim zaman gerekçeli veya gerekçesiz olarak araştırmadan ayrılabileceğimi ve kendi isteğime bakılmaksızın araştırmacı tarafından araştırma dışı bırakılabileceğimi biliyorum. Bu durumda hastanenin çalışma düzeni ve hastalara verilen bakımda aksaklık olmayacağı konusunda bilgilendirildim. Bu araştırmaya katılırken zorlama, maddi çıkar ve ast üst ilişkisine dayalı herhangi bir baskı olmaksızın bu çalışmaya katıldığımı beyan ederim. Bu bilimsel çalışmanın devamı esnasındaki süreçle ilgili olarak ayrıca eklenen çalışma protokolü ile bilgilendirildim.

KLİNİK ARAŞTIRMALAR ETİK KURULU
BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Söz konusu araştırmaya, hiçbir baskı ve zorlama olmaksızın kendi rızamla katılmayı kabul ediyorum. İmzalı bu form kağıdının bir kopyası bana verilecektir.

Gönüllünün Adı / Soyadı / İmzası / Tarih

Açıklamaları Yapan Kişinin Adı / Soyadı / İmzası / Tarih

Gerekiyorsa Olur İşlemine Tanık Olan Kişinin Adı / Soyadı / İmzası / Tarih

Gerekiyorsa Yasal Temsilcinin Adı / Soyadı / İmzası / Tarih

24 saat ulaşılabilir iletişim bilgileri

7.2. Ethical Approval

Araştırmanın Açık Adı	**"Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi "**
VARSA ARAŞTIRMANIN PROTOKOL KODU	

KLİNİK ARAŞTIRMALAR ETİK KURULU	
ETİK KURULUN ÇALIŞMA ESASI	İlaç ve Biyolojik Ürünlerin Klinik Araştırmaları Hakkında Yönetmelik, İyi Klinik Uygulamaları Kılavuzu
BAŞKANIN UNVANI / ADI / SOYADI:	Prof. Dr. Turgay Çelik

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Cinsiyet		Araştırma ile ilişki		Katılım *		İmza
Prof. Dr. Turgay Çelik (Etik Kurul Başkanı)	Tıbbi Farmakoloji	Y.Ü. Eczacılık Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Ferda Özkan	Patoloji	Y.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Pelin Yazgan	Fiziksel Tıp ve Rehabilitasyon	Okan Üniversitesi Hastanesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Esra Can	Diş Hekimi	Y.Ü. Diş Hekimliği Fakültesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Hasan Aydın	Endokrinoloji	Y.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Hasan Erdem	Hukuk (Av.)	Serbest Meslek	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Dr. Öğr. Üyesi Gökhan Ertaş	Biyo Medikal	Y.Ü. Mühendislik Fakültesi	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Doç. Dr. Baki Ekçi	Genel Cerrahi	Y.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Buket Dirgen	Sivil Üye	Acıbadem Hastanesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Recep Erol Sezer	Halk Sağlığı	Y.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Arzu Tatlıpınar	KBB	Y.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	
Doç. Dr. Muhammed Hamitoğlu	Eczacı	Y.Ü. Eczacılık Fakültesi	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Dr. Öğr. Üyesi F. Ferda Kartufan	Anesteziyoloji ve Reanimasyon	Y.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	

*:Toplantıda Bulunma

ASLI GİBİDİR

Prof. Dr. Turgay ÇELİK
Yeditepe Üniversitesi KAEK Başkanı

Araştırmanın Açık Adı	**"Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi "**
VARSA ARAŞTIRMANIN PROTOKOL KODU	

	Belge Adı	**Tarihi**	**Versiyon Numarası**	**Dili**
DEĞERLENDİRİLEN BELGELER	ARAŞTIRMA PROTOKOLÜ	29.01.2020	2	Türkçe ☒ İngilizce ☐ Diğer ☐
	BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU	29.01.2020	2	Türkçe ☒ İngilizce ☐ Diğer ☐
	OLGU RAPOR FORMU	29.01.2020	2	Türkçe ☒ İngilizce ☐ Diğer ☐
	ARAŞTIRMA BROŞÜRÜ	29.01.2020	2	Türkçe ☒ İngilizce ☐ Diğer ☐

	Belge Adı		**Açıklama**
DEĞERLENDİRİLEN DİĞER BELGELER	KLİNİK ARAŞTIRMA BAŞVURU FORMU GÖZLEMSEL RETROSPEKTİF	☒ ☐ ☐	
	TIBBİ CİHAZ TC KLİNİK ARAŞTIRMA (AKADEMİK) TC GÖZLEMSEL KLİNİK ARAŞTIRMA TC İN VİTRO KLİNİK ARAŞTIRMA	☐ ☐ ☐ ☐	
	SİGORTA	☐	
	ARAŞTIRMA BÜTÇESİ	☒	
	BİYOLOJİK MATERYEL TRANSFER FORMU	☐	
	ÖZGEÇMİŞLER	☒	
	HELSİNKİ BİLDİRGESİ	☒	
	ÇIKAR İLİŞKİSİ BELGESİ	☐	
	KURUM İZNİ	☒	
	ARŞİV FORMU	☐	
	CİDDİ ADVERS OLAY (CAO) BİLDİRİMİ	☒	
	KURUM DIŞI ARAŞTIRMACI BAŞVURU FORMU	☐	
	İTHALAT FORMU	☐	
	DEPO BAŞVURU FORMU	☐	
	CD	☒	
	SONLANIM BİLDİRİMİ BAŞVURU FORMU	☒	

14.02.2020
ASLI GİBİDİR

KARAR BİLGİLERİ	**Karar No:1161** **Tarih: 29.01.2020**

Yukarıda bilgileri verilen **"Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi"** klinik araştırmanın başvuru dosyası ile ilgili belgeler araştırmanın /çalışmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş ve uygun bulunmuş olup araştırmanın/çalışmanın başvuru dosyasında belirtilen merkezlerde gerçekleştirilmesinde etik ve bilimsel yönden yeterli bulunduğuna toplantıya katılan etik kurul üye tam sayısının salt çoğunluğu ile karar verilmiştir.
İlaç ve Biyolojik Ürünlerin Klinik Araştırmaları Hakkında Yönetmelik kapsamında yer alan araştırmalar/çalışmalar için Türkiye İlaç ve Tıbbi Cihaz Kurumu'ndan izin alınması gerekmektedir

Prof. Dr. Turgay ÇELİK
Yeditepe Üniversitesi KAEK Başkanı

Araştırmanın Açık Adı	**"Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi "**
VARSA ARAŞTIRMANIN PROTOKOL KODU	

ETİK KURUL BİLGİLERİ	ETİK KURULUN ADI	**Yeditepe Üniversitesi KAEK (2012-KAEK-70)**
	AÇIK ADRESİ:	Yeditepe Üniversitesi Hastanesi İçerenköy Mahallesi, Hastane Yolu Sokak no:102-104 34755 Ataşehir İstanbul
	TELEFON	
	FAKS	
	E-POSTA	

BAŞVURU BİLGİLERİ	KOORDİNATÖR/SORUMLU ARAŞTIRMACI UNVANI/ADI/SOYADI	Prof. Dr. Bahar Eren Kuru			
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ UZMANLIK ALANI	Diş Hekimliği Fakültesi			
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ BULUNDUĞU MERKEZ	Yeditepe Üniversitesi			
	VARSA İDARİ SORUMLU UNVANI/ADI/SOYADI				
	DESTEKLEYİCİ				
	PROJE YÜRÜTÜCÜSÜ UNVANI/ADI/SOYADI (TÜBİTAK vb. gibi kaynaklardan destek alanlar için)				
	DESTEKLEYİCİNİN YASAL TEMSİLCİSİ				
	ARAŞTIRMANIN FAZI VE TÜRÜ	FAZ 1	☐		
		FAZ 2	☐		
		FAZ 3	☐		
		FAZ 4	☐		
		Gözlemsel ilaç çalışması	☐		
		Tıbbi cihaz klinik araştırması	☒		
		İn vitro tıbbi tanı cihazları ile yapılan performans değerlendirme çalışmaları	☐		
		İlaç dışı klinik araştırma	☐		
		Diğer ise belirtiniz	☐		
	ARAŞTIRMAYA KATILAN MERKEZLER	TEK MERKEZ ☒	ÇOK MERKEZLİ ☐	ULUSAL ☒	ULUSLARARASI ☐

14.02.2020
ASLI GİBİDİR

Prof. Dr. Turgay ÇELİK
Yeditepe Üniversitesi KAEK Başkanı

7.3. Approval of Turkish Ministry of Health

T.C.
SAĞLIK BAKANLIĞI
Türkiye İlaç ve Tıbbi Cihaz Kurumu

NORMAL

Sayı : 68869993-511.06-E.63694 11.03.2020
Konu : 2019-216

Sayın Prof. Dr. Bahar EREN KURU
Yeditepe Üniversitesi Diş Hekimliği Fakültesi
Diş Hastanesi Periodontoloji Anabilim Dalı
Caddebostan Mah. Bağdat Cad. No:238
Göztepe / İSTANBUL

İlgi : 04.03.2020 tarihli ve E.119496 sayılı başvurunuz.

Sorumlu araştırmacısı olduğunuz, aşağıdaki tabloda bilgileri verilen ilgi klinik araştırma başvuru dosyası ve belgeler; araştırmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak 06.09.2014 tarihli ve 29111 sayılı Resmî Gazete 'de yayımlanan Tıbbi Cihaz Klinik Araştırmaları Yönetmeliği gereğince incelenmiş olup **Uzmanlık Tezleri ve/veya Akademik Amaçlı Yapılacak Tıbbi Cihaz Klinik Araştırmaları Başvuru Formunda** belirtilen merkezde araştırmanın başlaması uygun bulunmuştur.

Araştırmanın Adı	Topikal Olarak Uygulanan Polivinilpirolidon Sodyum Hyaluronat Jelin Ağrı ve Damak Yüzeyi Epitelyal Yara İyileşmesine Etkisi
Koordinatör Merkez	Yeditepe Üniversitesi Diş Hekimliği Fakültesi Diş Hastanesi Periodontoloji Anabilim Dalı
Koordinatör / Sorumlu Araştırmacı	Prof. Dr. Bahar EREN KURU
Protokol tarihi / versiyon no	29.01.2020 V:2
BGOF tarihi / versiyon no	29.01.2020 V:2
ORF tarihi / versiyon no	29.01.2020 V:2
Araştırma Broşürü tarihi / versiyon no	-

Bu kapsamda yukarıda ayrıntıları verilen çalışma ile ilgili olarak;

- İthal edilecek araştırma cihazının ithalat izni için Kurumumuza müracaat edilmesi,
- CE işareti taşımayan klinik araştırma amaçlı cihazın araştırma haricinde kullanılmaması,
- Gönüllülerden alınan ve ülke dışına çıkarılacak olan numuneler için biyolojik materyal transfer formunda belirtilen şartların yerine getirilmesi,

Sögütözü Mahallesi, 2176.Sokak No:5 06520 Çankaya/ANKARA
Tel: (0 312) 218 30 00– Fax : (0 312) 218 34 60 www.titck.gov.tr

T.C.
SAĞLIK BAKANLIĞI
Türkiye İlaç ve Tıbbi Cihaz Kurumu

- Araştırmanın başlamaması, iptali veya sonlandırılması halinde tarafımıza bilgi verilmesi,
- Araştırma süresince ortaya çıkan advers olayların/etkilerin tarafımıza bildirilmesi,
- Araştırmanın Helsinki Bildirgesi'nin son metni, İyi Klinik Uygulamalar İlkeleri ve ilgili mevzuata uygun olarak yürütülmesi,
- Araştırmada kullanılan her türlü araştırma ürününün ve ürünlerin kullanılmasına mahsus her türlü malzeme ile muayene, tetkik, tahlil ve tedavilerin bedeli için gönüllüden herhangi bir ücret talep edilmemesi,
- Araştırmaya ait yıllık bildirim formunun düzenli olarak Kurumumuza gönderilmesi,
- Sorumlu araştırmacı olarak yazımızın bir örneğinin ilgili etik kurula iletilmesi hususlarında, bilgilerinizi ve gereğini rica ederim.

Dr. Asım HOCAOĞLU
Kurum Başkanı a.
Daire Başkanı

7.4. Clinical Form

YEDİTEPE Üniversitesi

PERİODONTOLOJİ ANABİLİM DALI HASTA KARTI

Hastanın Adı Soyadı: ..... Cinsiyeti: ..... Doğum Tarihi: ...../...../.....

Meslek: ..... Tel: ..... Kayıt Tarihi: ...../...../.....

☐ Başlangıç ölçümü ☐Yeniden değerlendirme ☐ Recall Hekim: .....

DENTAL ANAMNEZ	
Hastanın geliş nedeni/ Hastanın asıl şikayeti	
Ağrı	☐Var, Bölgesi:..... ☐Yok
Acil tedavi ihtiyacı	☐Apse ☐Perikoronitis ☐ANUG ☐Akut streptokok gingivitis ☐Akut herpetik gingivitis ☐Primer oklüzal travma
Dişeti kanaması	☐Var, ☐Fırçalama sırasında ☐Hemen yerken ☐Kendiliğinden ☐Yok
Dentin Hassasiyeti	☐Var ☐ Soğuk ☐ Ekşi ☐ Tatlı ☐ Sıcak ☐ Dokunurunca ya da fırçalamada (Değeri VAS skalasına göre 1-10) :..... ☐Yok
Dişetinde iltihabi pekil benekliliği	☐Ödemli ☐Fibrotik ☐Ödemli + Fibrotik
Mukogingival problem	☐Var ☐Sığ vestibül ☐Yetersiz yapışık diş eti ☐Keratinize diş eti ☐Diş eti çekilmesi ☐Yok
Diş eti çekilmesi	☐Generalize ☐Lokalize Diş no:..... Nedeni: ☐Travmatik ☐Periodontitis ☐Yaşlanma
Ağız kokusu/ Kötü tat hissi	☐Var ☐Yok
Dişlerde yer değiştirme	☐Var, Diş no:.... ☐Yok
Dişlerde sallanma	☐Var, Diş no:.... Derecesi: 1/ 2/ 3 ☐Yok
Diş sıkma	☐Var ☐Yok
Diş gıcırdatma	☐Var ☐Yok
Tek taraflı çiğneme	☐Sağ ☐Sol Nedeni: ..... ☐Yok
Ağızdan solunum	☐Var ☐Yok
Tırnak yeme	☐Var ☐Yok
Sigara kullanımı	☐***Never Smoker:*** Tüm hayatı boyunca hiç sigara kullanmamış ya da 100 sigaradan az kullanmış ☐***Former Smoker:*** Tüm hayatı boyunca en az 100 sigara kullanmış, fakat şuan kullanmayan ☐***Non-smoker:*** Şuan sigara kullanmayan (Never Smokers + Former Smokers.) ☐***Current Smoker:*** Her gün ya da aralıklarla sigara kullanan (adet/gün, hafta, ay) ☐≤ 5 Sadet/..... ☐≤ 10 adet/..... ☐≥1 paket/.....
Daha önce yapılan periodontal tedaviler	☐Var Zamanı/Uygulanan tedavi/Yeri:..... ☐Yok
Diş fırçalama sıklığı/zamanı	
Diş fırçalama şekli	☐ ☐ ☐ ☐ ☐
Ara yüz temizleyicisi	☐Kullanmıyor ☐Diş ipi ☐Ara yüz fırçası ☐Diğer .....
Diğer ağız hijyeni ajanları ve araçları	☐Şarj edilebilir fırça ☐Ağız duşu ☐Gargara
Hastanın kullandığı diş macunu	
Hastanın kullandığı diş fırçası tipi	☐Sert ☐Orta sert ☐Yumuşak

SİSTEMİK ANAMNEZ	
Şuan tedavi altında olunan sistemik bir hastalık var mı?	
Geçirilmiş önemli bir hastalık ve ameliyatlar	
Ateşli romatizma	
Alerjik problem	
Hormonal hastalıklar	
Kan hastalıkları	
Kardiyovasküler sistem hastalıkları	
Diğerleri	
Süreklı Kullanılan İlaçlar ve süresi	
Ailede genel hastalıklar	
Ailede dişeti hastalıkları	

İNTRA-ORAL MUAYENE	
RENK (Damak, Dil, Ağız Tabanı, Alveolar Mukoza, Tonsil)	
ŞİŞME (Damak, Dil, Ağız Tabanı, Alveolar Mukoza, Tonsil)	☐ Var Lokalizasyonu: ☐ Yok
FİSTÜL (Damak, Dil, Ağız Tabanı, Alveolar Mukoza ve Dişeti)	☐ Var Lokalizasyonu: ☐ Yok
ÜLSER (Damak, Dil, Ağız Tabanı, Alveolar Mukoza ve Dişeti)	☐ Var Lokalizasyonu: ☐ Yok
NEKROZ (Damak, Dil, Ağız Tabanı, Alveolar Mukoza)	☐ Var Lokalizasyonu: ☐ Yok
DİĞER	☐ Var Lokalizasyonu: ☐ Yok
OPERCULUM	☐ Var Lokalizasyonu: ☐ Yok
APSE	☐ Var Lokalizasyonu ve tipi: ☐ Yok
PÜ VARLIĞI	☐ Var Lokalizasyonu: ☐ Yok

TEŞHİS:

TEDAVİ PLANI:

PERT.F.08.-F.01Rev.0,27-9-2016

PERİODONTOLOJİ ANABİLİM DALI ÖLÇÜM KARTI

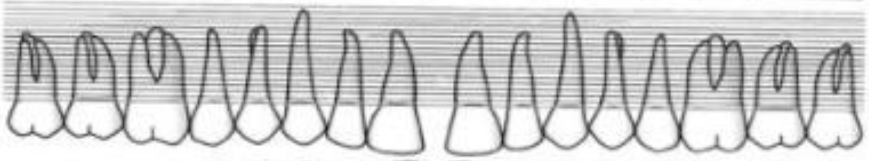
Hastanın Adı Soyadı: ..... Cinsiyeti: ..... Doğum Tarihi: ../../..

Meslek: ..... Tel: ..... Kayıt Tarihi: ../../..

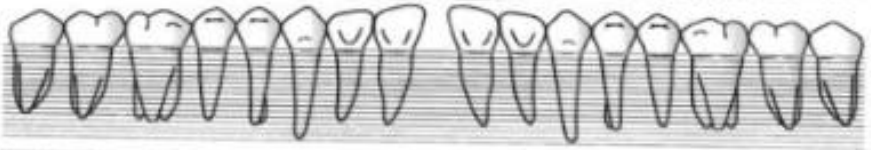
☐ Başlangıç ölçümü ☐ Yeniden değerlendirme ☐ Recall Hekim: .....

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Furkasyon																
Fremitus																
Mobilite																
ndalamada kanama (SK)																
Cep Derinliği																
Gingival marjin																
Gingival indeks (GI)																
Plak indeksi (PI)																

BUKKAL



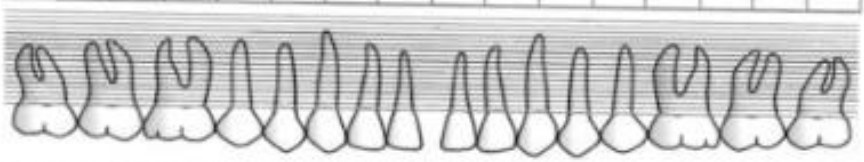
PALATİNAL



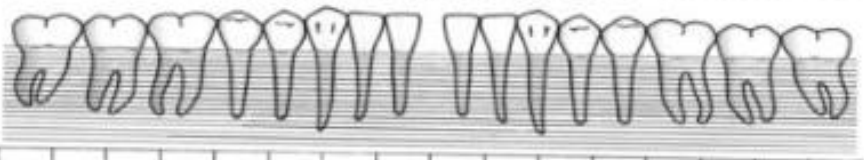
	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Plak indeksi (PI)																
Gingival indeks (GI)																
Gingival marjin																
Cep Derinliği																
ndalamada kanama (SK)																
Furkasyon																

	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Plak indeksi (PI)																
Gingival indeks (GI)																
Gingival marjin																
Cep Derinliği																
ndalamada kanama (SK)																
Mobilite																
Fremitus																
Furkasyon																

BUKKAL



LİNGUAL



	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Furkasyon																
ndalamada kanama (SK)																
Cep Derinliği																
Gingival marjin																
Gingival indeks (GI)																
Plak indeksi (PI)																

ORTALAMA KONDALAMA DERİNLİĞİ: ..... mm. ORTALAMA KLİNİK ATAŞMAN SEVİYESİ: ..... mm. ORTALAMA PI: ..... ORTALAMA GI: ..... % KONDALAMADA KANAMA

PERT.P.08-F.01/Rev.0,17.6.2016

8. CURRICULUM VITAE

Personal Informations

Name	Fulya	**Surname**	DANACI

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Doctorate	Periodontology	Yeditepe University	2022
License	Dentistry	Yeditepe University	2016
High school	-	Çorum Fen Lisesi	2010

Language	Grades
English	60 (YDS)