T.C.

YEDİTEPE UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES
THE DEPARTMENT OF PERIODONTOLOGY

DIMENSIONAL CHANGES OF FREE GINGIVAL GRAFT FOLLOWING CYANOACRYLATE STABILIZATION

PhD THESIS

KÜBRA BURCU YILDIRIM

İstanbul-2022

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APPROVAL
This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..... and numbered .....

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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.

15.04.2022

Kübra BURCU YILDIRIM

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ABBREVIATIONS

ADM	Acellular Dermal Matrix
BoP	Bleeding on Probing
CAF	Coronally Advanced Flap
CAL	Clinical Attachment Level
CT	Connective Tissue
CTG	Connective Tissue Graft
FGG	Free Gingival Graft
GI	Gingival Index
KTW	Keratinized Tissue Width
MGJ	Mucogingival Junction
Mm	Milimeter
PD	Probing depth
PI	Plaque index
®	Registered Trademark

ABSTRACT

Yıldırım, K.B. (2022). Dimensional changes of free gingival graft following cyanoacrylate stabilization. Yeditepe University, Institute of Health Sciences, Department of Periodontology, Ph.D Thesis, Istanbul.

The aim of this controlled clinical study was to evaluate and compare the vertical graft height (VGH) within two different stabilization techniques on clinical parameters in the treatment of insufficient keratinized tissue amount. Twenty-four patients with insufficient keratinized tissue (KT≤ 1 mm) were enrolled to this study. Patients were operated with FGG and grafts were stabilized with either butyl-cyanoacrylate (test group) or non-resorbable sutures (control group). Clinical parameters including probing depth (PD), full mouth plaque score (FMPS), full mouth bleeding score (FMBS), KT, and vertical recession (VR) were measured at baseline and 6 months after surgery. The total graft surface area (TGSA) and VGH were measured digitally with clinical photographs at baseline, 1, 3 and 6 months after surgery. Visual analogue score (VAS) parameter was evaluated for post-operative pain and comfort by patients between day 0 and day 6. KT increase was statistically significant for both groups, yet inter-group comparison showed no statistically difference. VR was also decreased significantly in both groups with higher decrease in the control group. Mean VGH and mean TGSA for the test and control groups at 6 months were 6.15±1.20, 6.51±0.60, and 73.36±21.37 mm^2 and 82.67±7.92 mm^2 respectively. There was no statistically significant difference observed in inter-group comparisons on graft area parameters ($p>0.05$). VAS parameter showed no statistically difference between groups ($p>0.05$). In conclusion, FGG is the gold standard for increasing KT, however shrinkage is inevitable for this procedure and use of butyl-cyanoacrylate showed no difference in terms of graft shrinkage. The use of material showed shorter operation time which may be consiredered as an advantage.

Key Words: Free gingival graft, shrinkage, keratinized tissue width, cyanoacryalte, adhesives.

ABSTRACT (Turkish)

Yıldırım, K.B. (2022). Serbest dişeti grefti stabilizasyonunda siyanoakrilat kullaniminin greftin boyutsal değişimi üzerine etkisi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Periodontoloji Bölümü, Doktora Tezi. İstanbul.

Kontrollü klinik çalışamızın amacı yetersiz keratinize doku(KT) varlığında uygulanan SDG operasyonunda vertikal greft boyutunun iki farklı stabilizasyon tekniğini değerlendirmek ve karşılaştırmaktı. Çalışmamıza yetersiz KT tespit edilen 24 hasta dahil edildi. Hastalar test (butil-siyanoakrilat ile SDG) ve kontrol (dikiş ile SDG) gruplarına rastgele dağıtıldı. Sondalanan derinlik(SD), bütün ağız plak skoru (BAPS), bütün ağız kanama skoru(BPKS), (KT) ve vertikal çekilme (VÇ) miktarı gibi klinik parametrelerin ölçümleri başlangıçta ve operasyon sonrası 6. ayda yapıldı. Alınan greftlerin vertikal boyutları (VGY) ve total alanlarının (TGA) ölçümleri klinik fotoğraflar üzerinden dijital olark başlangıçta ve operasyon sonrası 1., 3. Ve 6. ayda yapıldı. Görsel analog ölçek (VAS) parametresi hastalar tarafından operasyon sonrası 0. Ve 6. Günler arası değerlendirilerek kaydedildi. Operasyon süresi ise ameliyat sırasında kaydedildi. VGY ortalaması test ve kontrol gruplarında sırasıyla 6,15 ± 1,20 , 6,51 ± 0,60 mm olarak ölçüldü. Ortalama TGA test grubunda 73,36±21,37 mm^2 olarak ölçülürken kontrol grubunda 82,67±7,92 mm^2 olarak ölçüldü. Gruplar arası kıyaslamada greft alanı parametrelerinde anlamlı bir farklılık saptanmadı ($p>0.05$). Test ve kontrol grupları arasında VAS parametresi incelendiğinde de herhangi bir anlamlı farklılık görülmedi. Ek olarak, gruplar arasındaki klinik periodontal parametrelerde de anlamlı bir farklılığa rastlanmadı. Yalnızca VÇ değişiminin kontrol grubunda, test grubuna kıyasla daha fazla olduğu bulunmuştur. Operasyon sürelerine bakıldığında test ve kontrol gruplarında sırasıyla 20:23±02:08, 26:15±05:21 dakika sürdüğü tespit edildi. Buna göre kontrol grubunun operasyon süresi, anlamlı olarak daha uzun sürmüştür ($p<0.01$). Sonuç olarak SDG operasyonlarında bütil-siyanoakrilat kullanımının greft büzülmesi üzerinde herhangi bir etkisine rastlanmamış olup, tek farklılığın operasyonun daha hızlı bitmesi gibi bir avantaj sağladığı söylenebilir.

Anahtar Kelimeler: Serbest dişeti grefti, büzülme, keratinize doku yüksekliği, siyanoakrilat, adeziv

1. INTRODUCTION and AIM

Periodontium is a unique structure that contains soft and hard tissues which are; gingiva, cementum, periodontal ligament and alveolar bone (1, 2). Periodontium keeps each tooth in place by surrounding and supporting it (3). The gingiva between the gingival margin and mucogingival junction (MGJ) is termed as keratinized gingiva. The gingival tissue located in the coronal part of the mucogingival junction contains two parts, the attached and free gingiva. The gingiva consists of a keratinized stratified squamous epithelium. The keratinized feature of the gingiva protects the periodontium against the rubbing forces that occur during mastication and ensures that the gingival tissues would resist towards the pulling forces of the mucosal muscle connections. The appropriate width of the keratinized gingival tissue allows the patient to use tools and methods for the optimal plaque control, thereby maintain the periodontal health (1).

Mucogingival problems arise with disruption of the healthy relationship between the gingiva and alveolar mucosa. The factors that may damage this relationship can be listed as anatomical factors such as dehiscence and fenestrations of alveolar bone, tooth malposition and thin gingival biotype, physiological factors such as orthodontic movement and pathological factors like toothbrushing, improper flossing, intraoral piercing, excessive occlusal forces and maladjusted restorations. Insufficient width of keratinized gingival tissue is one of the major mucogingival problems. It may occur as a result of decrease in the dimension of the attached gingiva in the apical direction. Insufficient amount of keratinized gingival tissue width may result in subgingival plaque accumulation, favor the attachment loss and gingival recession.

Many studies have investigated the appropriate milimetrical value of the keratinized gingival tissue width to maintain periodontal health. According to clinical and histological data, rather than a certain millimeter value, the maintenance of optimal oral hygiene provided by the patient and not having a pathological condition in the future prognosis are prominent (4, 5, 28, 106).

The free gingival graft (FGG) procedure is considered as the gold standard in increasing the keratinized gingival tissue width due to the ease of the technique and its application in large operation areas involving many teeth, in addition to the predictability of the surgical results (6, 101). The graft tissue harvested from the gingiva and palate has been shown to maintain its own characteristics in the area that it is placed (1).

After the gingival graft is sutured to the recipient site, it is very crucial to protect it without any movement in the recipient bed until the vascular proliferation occurs. Since the existing vessels in the graft anastomose with the vessels of the recipient bed, vascular structures should not be damaged during the graft stabilization process.

Cyanoacrylates have been used as tissue adhesive in medical fields such as opthalmology, pediatric surgery, general surgery and dentistry for decades. Butyl cyanoacrylate is a bacteriostatic, biodegradable and hemostatic agent that has a long half-life, a good tissue compatibility and it preserves strong adhesive characteristics in humid environments (7-9, 102).

In the light of the current knowledge based on literature review, different studies showed controversial results depending on many factors. The aim of this randomized, controlled clinical study was to evaluate the effects of fixation with cyanoacrylate application versus 5/0 propylene sutures on FGG shrinkage, patient perception and operation time excluding all known contributing factors as much as possible.

2. LITERATUR REVIEW

2.1. Periodontium

Periodontium is a unique structural unit which surrounds and supports teeth and maintains its function. It consists of the following four principal components:

1. Gingiva
2. Periodontal ligament
3. Cementum
4. Alveolar bone

Each of these elements is different in composition, location and microscopic structure but they function as a single unit (9, 10).

2.2. Gingiva

2.2.1. Macroscopic anatomy

The oral mucosa consists of masticatory mucosa which includes the gingiva and the covering of the hard palate, the specialized mucosa covering the dorsum of the tongue and the remaining part called the lining mucosa.

Anatomically, the gingiva has three components: marginal gingiva, attached gingiva and interdental gingiva (9-11).

2.2.1.1. Marginal gingiva

The marginal gingiva, also called as unattached gingiva, which is the ending border of the gingiva, surrounds the teeth like a collar (9). In about 50% of cases, it is separated from the attached gingiva with the free gingival groove. Marginal gingiva is usually about 0.5-2 mm wide.

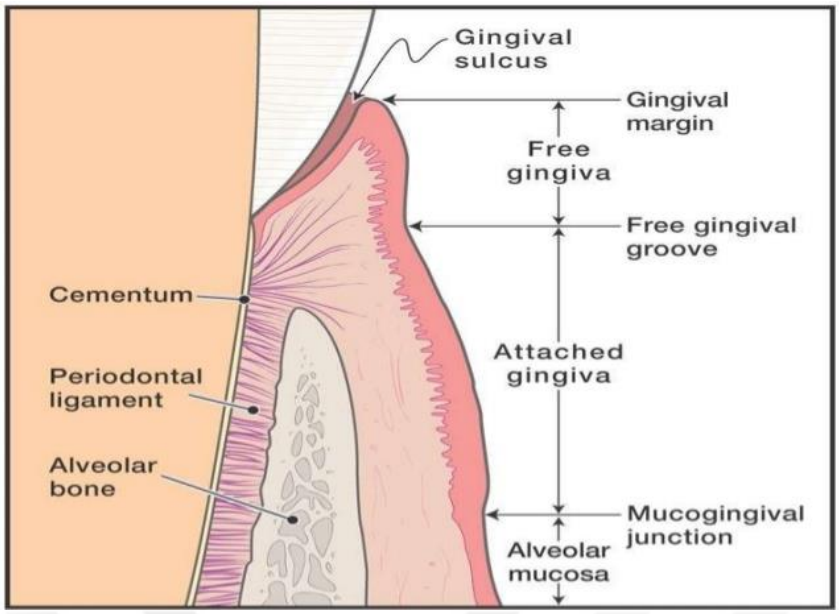

Figure 2.1. Schematic display of gingiva

2.2.1.2. Attached gingiva

The attached gingiva is the portion that tightly bounds to the underlying periosteum of the alveolar bone. It has a firm texture and often shows small depressions which is called “stippling” that gives the appearance of orange peel. The mucogingival junction divides the attached gingiva from the oral mucosa which is relatively mobile and loosely bound to underlying periosteum. The width of the attached gingiva differs in different areas of the mouth. It is generally wider in the incisor areas (3.5-4.5 mm in upper jaw, 3.3-3.9 in lower jaw) and narrower in the posterior areas (1.9 in the maxillary premolars and 1.8 in the mandibular premolars) (6-12)

The location of the mucogingival junction remains stable lifelong. Therefore, the changes in the width of the attached gingiva is because of the modifications of its coronal portion. For example, to compensate the occlusal abrasions, the continuous eruption of teeth occurs, which causes the widening of the attached gingiva (9, 10, 13, 14).

2.2.2. Microscopic anatomy

Microscopically, the free and attached gingiva are composed of the overlying stratified squamous epithelium and central core of connective tissue (CT) and locate under the squamous epithelium and are keratinized. There is a basal membrane between the

squamous epithelium and CT. From the basal membrane to the surface epithelium, the free and attached gingiva consist of the following four layers.

-Stratum basale

-Stratum corneum

-Stratum granulosum

-Stratum corneum (1, 2, 9, 15)

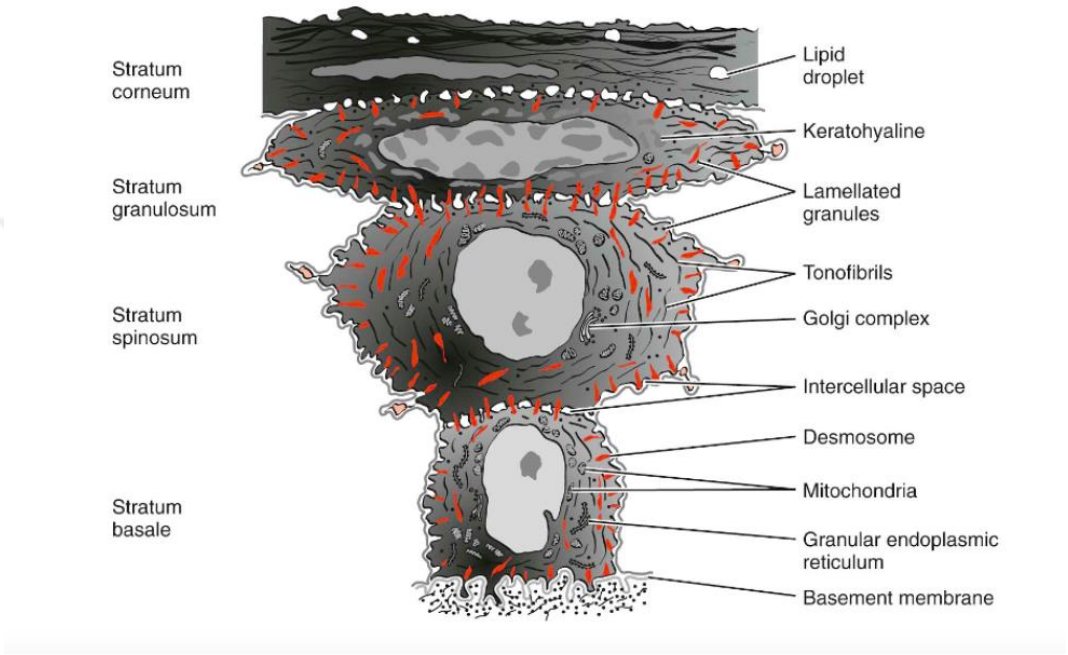

Figure 2.2. Microscopic anatomy of the gingiva

The major cell type of the gingival epithelium is keratinocytes, which consists approximately 90% of the total cell amount. The main function of these cells is protection. Keratinocytes also have a proliferation and differentiation system which allows for a selective interchange between underlying structures and oral cavity. Melanocytes, Langerhans cells and inflammation cells are other cell types of the epithelium. The gingiva has a defense system against infections; the gingival epithelium acts as a barrier to infections and also the cell content plays an active role in initial host defense (16).

The 'proliferation' of keratinocytes mostly occur in the stratum basale and less frequently in other layers. The majority of these cells begin to migrate to the surface while a small portion remain as proliferative component. 'Differentiation' involves the changing of these cells in terms of keratinization.

The journey of a keratinocyte begins at the basal layer. Throughout migration, keratinocytes lose their nuclei, and cytoplasma, which produce energy for cell and morphologic changes. The main morphologic change is the continuous flattening of the cylindrical and cubic cell with an increasing amount of tonofilaments. The keratinocyte migration from the basale to corneum layer takes approximately a month. Keratinization and desquamation continuously occur in cycles. The cell numbers peeled off during desquamation and produced during keratinization are approximately similar (1, 2, 17, 18).

The presence of keratinized epithelium on the masticatory mucosa has been considered to represent an adaptation to mechanical irritation released during mastication and prevents the forces by muscle attachments of the oral mucosa. The sufficient width of keratinized epithelium contributes the patients' oral hygiene efforts and prevents the possible periodontal attachment loss and gingival recessions (1).

2.2.2.1. Keratinization Process

It has been suggested that epithelial keratinization in oral mucosa can be influenced by environmental factors and this keratinization process originates from the adaptation to these factors. It has been proposed that the keratinization is eventuated against the rubbing effect of the mastication function (19).

Figure 2.3. An animal study showing that the gingiva (G) retained the characteristic of keratinization whereas alveolar mucosa (AM) remained non-keratinized
*NG: New keratinized gingiva

Numbers of clinical and histological studies in animals have revealed that keratinization is determined based on genetic factors (1, 8). In one study on monkeys, the alveolar mucosa and the gingival sites were replaced by suturing and the alveolar mucosa was placed adjacent to the tooth (1). According to the clinical findings, the gingiva has

been observed to retain its keratinized structure whereas the alveolar mucosa has remained non-keratinized. Histological findings have similarly showed that; there are dense elastic fibers in the connective tissue of the alveolar mucosa, while not observed in the connective tissue of the gingiva. Both connective tissue and epithelium have been found to be compatible with the original structures (1) (Figure 2.3).

In a similar study model, it was demonstrated both clinically and histologically that the gingival part sutured on alveolar connective tissue retains its keratinized features. As a result of these study models, it has been revealed that keratinization was determined genetically rather than functional adaptation (1).

2.2.3. The role of attached gingiva

The structure of the gingival tissues is the basis for healthy gingival function. The presence of a thick keratinized gingival covering serves as an effective preventive barrier that is resistant to damage from the physical trauma of mastication and the thermal and chemical stimuli from the dietary components that have direct contact with the gingiva (20).

Keratinized tissue (KT) consists of the marginal gingiva and the attached gingiva. The width of the keratinized gingiva is thought to play a critical role in maintaining periodontal health (21). This has led to a lot of research on this subject (22–26). Hall (27) suggested that narrow KTH alone is not a mucogingival surgery indication. In case of sufficient oral hygiene level, if there are still signs of inflammation and progression of recession then surgical intervention may be needed.

The results of the related studies vary in the literature. Most of the researchers performed to clarify the role of attached gingiva have shown that there is no absolute amount of attached gingiva required for periodontal health to exist. Miyasato et al. (28) stated that, with proper oral hygiene and absence of bacterial plaque, gingival health “in the form of no attachment loss and absence of inflammation” can exist in areas where minimal or no attached gingiva is present. Lang & Löe (29) on the other hand, suggested that a minimum width of 2 mm of gingiva is needed to exist for gingival health. According to that report, areas with attached gingiva of 1 mm or less often presented with clinical signs of inflammation. While the width of attached gingiva or its absence cannot solely determine a pathological diagnosis, it is of critical importance to be able to diagnose what constitutes a mucogingival problem. Even though it is possible for gingival health to exist

in sites of little or no attached gingiva, it is commonly agreed that sites with less than 2 mm of attached gingiva are at a higher risk for recession (20). These sites should be carefully evaluated longitudinally for the presence of inflammation, development of recession and therefore treatment needs.

Chambrone et al. reported in a systematic review and meta-analysis that the presence of KT and/or greater width of KT decrease the progression of recession or new gingival recession development (30).

In the last consensus report, it was declared that, in the presence of inadequate plaque control there is a minimum amount of KT. A minimum amount of 2 mm KT with 1 mm of attached gingiva has been recommended under these circumstances. There are other clinical scenarios of traumatic etiology, such as the presence of subgingival restorative margins or clasps from removable appliances, specific orthodontic tooth movement or anatomic situations in which the literature does not provide guidelines on the needed minimum amount of KT. There is insufficient evidence on the interplay between gingival inflammation and/or direct mechanical trauma (e.g., toothbrushing) in sites with minimum KT as the etiology of progressive recession (31).

2.3. Periodontal Plastic Surgery

Mucogingival therapy is a common title used to define periodontal therapies including approaches for the correction of defects in the morphology, position of soft tissue and/or volume of soft tissue and bone support around teeth and implants (32).

The term “Mucogingival surgery”, which was first introduced by Friedman (33) for the first time in 1957, includes surgical approaches involving mucosa and gingiva. These surgical approaches include:

- Preserving keratinized tissue,
- Root coverage procedures,
- Removing aberrant frenum or muscle attachments,
- Increasing the depth of the vestibule.

In 1993, the definition of “mucogingival surgery” was explained by Miller (34) as the surgical approaches for correcting or removing the anatomical, developmental or traumatic deformities of gingiva and/or alveolar bone and mucosa, including gingival augmentation correcting alveolar bone deformities, removing frenum attachments,

ectopic tooth eruption for orthodontic treatment and crown lengthening procedures. Afterwards, Allen (35) included various treatment approaches such as correcting the gingival pigmentations, deformities of gingival margin, soft tissue contours within the smile line.

Finally, in a consensus report in 1996, the AAP (10) accepted the term "Periodontal plastic surgery" that was suggested by Miller back in 1988 (34), which was described as the surgical approaches for the correction of anatomical, developmental, traumatic and plaque-induced deformities of gingiva, alveolar mucosa and alveolar bone. These approaches include:

- Soft tissue augmentations,
- Root coverage procedures,
- Correction of mucosal defects around implants,
- Crown lengthening,
- Removal of aberrant frenulum and muscle attachments,
- Prevention of alveolar ridge collapse associated with extraction,
- Preservation of gingival tissues during ectopic tooth eruption (34, 145).

The coverage of gingival recessions and the correction of insufficient KT have been the most common focal spots of "Periodontal plastic surgery". Free gingival graft (FGG)procedure is one of the surgical techniques to create sufficient KT zone.

2.3.1. Free Gingival Graft

FGG surgery has been used to increase KT in cases of insufficiency around natural teeth or dental implants or insufficient vestibular depth for decades. However, the decision regarding the insufficiency of KT is related to clinicians' judgement (27). The clinician should consider several parameters, including the width of the KT, attached gingiva, probing depths, age of the patient, recession history, oral hygiene habits, number of teeth involved, dental clinical parameters such as full mouth plaque (FMPS) and bleeding (FMBS) scores, etc. It has been stated that, FGG alone is a gold standard for widening the KT zone, but not a predictive technique to be used in sites where root coverage is indicated. More predictable techniques are available to achieve more aesthetic

and successful outcomes (27, 31, 36, 37).

FGGs were first used by Harlan (38) in the beginning of the 1900s to increase KT width . In 1966, Nabers (39) published the first case report about increasing the vestibule depth with FGG. Hattler(40) used interdental keratinized papilla tissue to cover an exposed root surface. Afterwards, Sullivan and Atkins (41) reported that using FGG obtained from palatal area may treat shallow-narrow and deep-narrow recessions. Back in that time, there was only one research and a few case reports published about using FGG for coverage of deep-wide recessions and root coverage procedures in such defects resulted in unsuccessful or partially successful outcomes(42-44). This conclusion is mostly about Mlinek's (43) research reporting a success rate of 20% after treatment. Later on only with applied modifications, various studies with decent methodology have been published and have shown that better outcomes could be achievable in root coverage with FGG (42–64).

The original technique to increase KT, proposed by Sullivan and Atkins, requires (6):

- an adequate size of supra-periosteal recipient bed preparation,
- palatal graft harvesting,
- stabilization of the graft.

2.3.1.1. Recipient bed preparation

The preparation of the recipient site is initiated with a horizontal split thickness incision made with a scalpel just above the mucogingival line. This is extended laterally to a distance which approximates the length of the desired additional zone of attached gingiva (65). With a blunt dissection, alveolar mucosa is reflected leaving the periosteum on the recipient area. This dissection is carried down to and below the superior attachment of muscle fibers. The prepared recipient site is then compressed with wet gauze sponge until hemorrhage is well controlled. This hemostasis is necessary for prevention of a hematoma beneath the graft, the most important cause of failure of any graft (9, 15, 66-69).

2.3.1.2. Graft harvesting

FGG is mostly harvested from the palate (70–72). The second premolar and first molar area is usually the site of choice. The palatal donor site should not include rugae areas because they may persist in the grafted tissue (73,74). Caution should be given to

the anatomy of the palate, avoiding the greater palatine foramen area due to potential of excessive bleeding and paresthesia possibility.

The dimensions and shape of the gingival graft to be removed from the palate should be exactly in the same dimensions and shape as the recipient site. Metal foil can be used as a template on the recipient site to guide tissue harvesting (75–77). An initial incision should be made with a 45-degree angle to the border of the graft. Then, in an atraumatic way, the scalpel should be placed parallel to the bone surface and moved precisely to split the connective tissue underneath the epithelium. After harvesting process, the graft should be immediately transferred to a moist gauze and thick adipose tissues if any should be removed and the graft should be placed on the recipient bed as soon as possible (9, 15, 67-69, 78, 79).

2.3.1.3. Graft Stabilization

In the original technique, which was proposed by Sullivan and Atkins (6), the harvested graft should be stabilized with a minimum number of sutures to preserve the vascularization of the graft. Following stabilization, 5 minutes of manual compression with a wet gauze should be applied to achieve hemostasis to avoid the accumulation of blood clot between the graft and recipient bed (80).

2.3.2. Healing process

The wound-healing of soft tissue grafts has been a subject of a limited number of studies (81–85). These studies generally divided the healing process into 3 phases (83, 86–88): initial (plasmic circulation) phase, (re)vascularization phase and tissue maturation (organic union) phase.

2.3.2.1. Initial phase (0–3 days)

At the initial phase, a thin blood clot forms between FGG and the periosteum. There is no attachment at this point except for fibrin organization. The vascularization does not form until the third post-operative day. The tissue survives and nourishes via diffusion from the adjacent gingiva and alveolar mucosa, which is termed “plasmatic circulation” (89). Excessive blood clot accumulation under graft tissue should be prevented to provide adequate nourishment. Movement or the presence of late bleeding may separate the transferred graft from its sustaining bed, resulting in necrosis. Digital pressure application after graft placement for several minutes will result in a thin blood

clot and improved immobility through fibrin bridging. During this early period, the epithelium of the graft desquamates, and once the vascularization is reestablished, the keratinized epithelium forms again. The initially placed graft presents a whitish appearance as a result of separation from its blood supply. By the third day, a gradual return of circulation begins, and a reddish color appears (9, 20, 90, 91).

2.3.2.2. (Re)vascularization phase (4–11 days)

At the revascularization phase, most of the blood vessels which remain in the graft are degenerated and replaced with newly formed vessels. After 4-5 days, capillaries of the recipient site proliferate into grafted tissue and create anastomoses (92). Blood clot resorption occurs and transforms into connective tissue. As a result, bridging is formed between the grafted tissue and the recipient site. Collagen attachment begins at day 4 and becomes firmer at day 10 (83, 89, 92). By the 8^{th} day, adequate blood supply is achieved while the fibrous attachment by the 10^{th}. Early in this stage, the color of the grafted tissue is still red and after the occurrence of gradual vascularization, the color changes into pink. Re-epithelialization of the graft eventuates by proliferation of the epithelium from epithelialized adjacent tissues and in its rete ridges. Newly formed epithelialized tissue takes place at day 4 while rete ridges take place at day 7 (89, 92). The keratinization potential of grafts is determined by the donor site connective tissue (93–96).

2.3.2.3. Tissue maturation (organic union) phase (12–42 days)

The renewed vascular plexus in maturated graft is gradually reduced to normality within approximately 14 days. Keratinization occurs on the graft epithelium at this stage. As an outcome, the graft color becomes lighter than adjacent gingival color (9, 20, 90, 91).

The wound at donor site heals with epithelization migrating from the wound margins to the center by means of secondary intention. The migration of the epithelial cells occurs at a predictable rate of 0.5 to 1 mm of lateral progress per day, moving under the surface of the blood clot (1, 97). As a result, healing time is related to the surface area of the wound.

2.3.3. The effect of graft thickness on healing

Sullivan and Atkins (6,41) reported that graft thickness has a direct effect on healing. Several authors have proposed that the optimal graft thickness is 1.5 to 2.0 mm (9, 98). However, preparing thick transplants of palatal mucosa with deep wounds may

enhance the possibility of injury to arteria palatine major (99,100). In addition, at the recipient site, thick grafts may result in an unaesthetic bulky tissue profile (99, 101). In a study, FGGs of 0.9 mm thickness have been proven to be functionally sufficient regardless of the healing on denuded alveolar bone or a periosteal bed (102). Very thin grafts of 0.5 to 0.6 mm thickness have also been reported to show an excellent tissue blending during widening of the KT zone (100). Thin grafts re-vascularize and heal faster than thick ones (6, 83, 92). Gordon et al. (91) showed that healing of 0.75 mm thickness grafts was completed in 10.5 weeks, while 1.75 mm thicker grafts lasts 16 weeks or more.

Hall and Mörmann (103-105) examined FGG healing according to their thickness. In their study, grafts were grouped as ultra-thin (0,5-0,8 mm) grafts, thin (0.9-1.4 mm) grafts and intermediate thick (1.5-2 mm) grafts. Ultra-thin grafts were the fastest healing group as vascularization was rapid with a better color matching. Since the wound depth in the donor area was shallow, the patient complaint was also less.

2.3.4. General Information about the Dimensional Changes of FGG after the Procedure

Shrinkage of FGG after the procedure is a well-known clinical event due to many reasons (44, 106-108). Various studies have reported a broad range of percentages (12-48) of shrinkage occur during post-operative period and the obtained KT remained stable after 6 to 12 months (4, 109-118).

After stabilization of FGG, recipient bed may decrease in vertical dimension by the contraction of the wound and reinsertion of muscles leading to inadequate keratinized gingival tissue formation (119-120). Hatipoğlu et al. stated that the gingival tissue biotypes in the recipient site may be related to the dimensional changes in the horizontal and vertical direction (110). Claffey and Shanley (121) said that among three defined gingival tissue biotypes (thick, medium and thin), the thin biotype had a higher tendency to shrink in terms of recipient bed compared to the thick biotype suggesting further controlled studies (122). Other factors having an impact on the surgical outcomes aiming to create sufficient zone of KT are related to the distruption of the continuity or delay of graft vascularization which are both effective in graft shrinkage. These factors may be listed as;

- Suturing without adequate bleeding control
- Loosely adapted FGG (52)

- Keeping the graft in the extraoral environment for a longer period of time
- Thickness of the graft (6, 44, 100, 106-108, 112, 113, 124).

Suturing without adequate bleeding control or bleeding after stabilization of the graft can cause a hematoma that may form underneath the graft that disrupts the nourishment of the graft (6, 125,126).

Holbrook and Ochsenbein (52) stated that loosely adapted grafts that occur due to various factors such as the suturing technique, anatomical factors, and the correction of the graft after removal from the palate show more shrinkage. The graft should be fixed to the recipient bed with a minimum number of sutures so as to prevent the movement of the graft during the healing process while not damaging it.

A substantial factor that increases the shrinkage of the graft is keeping it in the extra-oral environment for a long period of time or elongating its stabilization time. In this way, depending on the time elapsed, drying occurs in the graft content and the vascular structures contract (127).

FGG maintenance in general depends on the formation of collateral circulation from the recipient bed, the thin blood clot for tensile strength and wound stability without excess contraction of both recipient bed and the individual graft tissue. Individual graft tissue thickness is considered as a critical factor for the graft shirinkage (6, 110).

Many studies investigated the relationship between graft thickness and shrinkage. For thin grafts average 45 – 47% shrinkage was reported after first post-operative month (44, 106-108). Furthermore, for approximately 1 mm thickness grafts shrinkage was reported as 25% while for 0,5-0,6 mm grafts shrinkage was detected as 12% (106, 108, 100). Mörmann et al. (128) investigated 4 groups on their study; 0.37 mm, 0.56 mm, 0.76 mm grafts harvested by ‘Mucotome’ and approximately 0.92 mm harvested by scalpel. Shrinkage percentages were reported as 45%, 44%, 38% and 30%, respectively. While 0.76 and 0.92 groups showed no difference, 0.37 and 0.56 groups showed statistically significantly more shrinkage than 0.92 mm group. Also during healing period thicker than optimal grafts showed a later vascularization, which may cause more shrinkage. It was concluded that 0.9 – 1.5 mm grafts could be thought as optimal thickness, while thinner and thicker grafts show more shrinkage (109, 110).

Hatipoğlu et al. (110) assessed the changes in vertical and horizontal dimensions of the graft and graft surface area after FGG procedure. In this study, 15 patients with insufficient KT in mandibular incisor area were treated with FGG using 5/0 silk sling sutures. The dimensions of the graft were measured by a periodontal probe and then the

graft surface area was calculated. Re-evaluation of dimensions and the graft area were performed at baseline and days 10, 21 and 180. Horizontal dimensions were detected as 11.74mm ± 1.83 at baseline and 10.40mm ± 1.35 at day 180. Vertical dimensions were observed as 6.80mm ± 1.42 at baseline, 5.67mm ± 1.03 at day 10, 5.40mm ± 0.97 at day 21 and 5.00mm ± 1.00 at day 180. The graft area was initially calculated as 80.53mm^2 ± 27.76 and 52.13 mm^2 ± 12.65 at day 180. Although there were no statistically significant changes found in horizontal dimensions, a statistically significant reduction in vertical dimensions was detected between baseline and each measurement time point, except day 10. The calculated graft area value significantly decreased at 180. day when compared the baseline value (35%).

Silva et al. (113) evaluated the changes of FGG dimensions and donor-site healing in smokers and non-smokers. Ten smokers and 12 non-smokers who had inadequate KT in the anterior area of the mandible were treated with FGG using 5/0 nylon suspensory periosteal sutures in form of letter 'W'. The graft areas were evaluated at day 0, 7, 15, 30, 60 and 90. At post-operative day 90; the vertical and horizontal dimensions as well as surface area of FGG decreased by 44%, 25% and 58% in smokers and 31%, 22% and 44% in non-smokers, respectively. Although the research failed to show any significant differences between the groups, it was observed that smokers are more prone to delayed epithelization at donor-sites with a tendency to higher amount of shrinkage.

Çiftçibaşı et al. (129) evaluated the changes of horizontal and vertical dimensions and the surface area of FGG in 3-months period. In this one armed study, 30 patients underwent FGG operation to create an adequate KT zone underneath the gingival recessions. Using 4/0 nylon sutures grafts were stabilized t recipient bed. Assessments are recorded at baseline, 1st and 3rd months postoperatively. The graft area was measured by multiplying the width and length of the graft. At baseline, 1 month and 3-months, horizontal dimensions were observed as 6.88mm ± 0.91, 6.44mm ± 1.05 and 6.09mm ± 1.06 and vertical dimensions were reported as 13.41mm ± 2.47, 12.50 ± 2.44 and 12.03mm ± 2.16, respectively. Both vertical and horizontal dimensions reduced significantly at post-operative 1st and 3rd months in comparison to the baseline with similar changes in both horizontal and vertical dimensions in contrast to other related studies. However, thegraft shrinkage value as surface area was observed to be significantly higher in baseline and 1 month interval than in 1 and 3 month interval (12% vs 8%).

De Resende et al. (130) compared clinical outcomes, shrinkage and aesthetic

perception after the application of FGG or acellular dermal matrix (ADM) in a split-mouth study for gingival augmentation purposes. In both groups, 5/0 vicryl sutures were used to fixate the graft or ADM. After 6 months, shrinkage values of 12.41% and 55.7% observed in FGG and ADM groups, respectively. Clinical outcomes showed no difference except for recession depth, which was higher in the ADM group. Aesthetic outcomes were observed to be better in the ADM group. FGG shrinkage was given as 12.4%.

Günpınar et al. (114) compared the differences of graft shrinkage after the application of the FGG surgery with or without low-level laser therapy (LLLT). Thirty patients with gingival recessions Miller class I or II were treated with the aim of creating an adequate KT zone underneath the gingival recessions. The patients were randomly divided into the LLLT (n=15) and placebo groups (n=15). Re-evaluations were made at 1, 3 and 6 months post-operatively. The graft surface areas were 71.15 mm^2 ± 18.27 at baseline, 63.03 mm^2 ± 17.46 at 3 months (12%) and 69.59 mm^2 ± 16.34 at 6 months (3%) in the test group, 76.67 mm^2 ± 10.95 at baseline, 60.45 mm^2 ± 12.65 at 3 months (12.8%) and 60.02 mm^2 ± 14.76 at 6 months (12%) in the control group. The graft shrinkage was reported to be significantly lower in the test group compared to the control group at the third and sixth months. Additionally, in terms of visual analog scale (VAS) scores and analgesic consumption, there was a statistically significant difference between groups in favor of LLLT group.

2.4. Cyanoacrylates

An adhesive can be described as a material which applied to materials or surfaces to attach them together and resist their separation. Adhesives are the simplest, handy, practical and cheapest of all materials and techniques for attaching one material to another. It contains glue, cement, paste, etc. and these terms can be used interchangeably (131).

2.4.1. General aspects of adhesives

Adhesion can be described technically as attraction of materials by means of the bond formed between two surfaces. The joined materials are commonly referred to as substrates or adhesives (132, 133). A connection forms between the adhesive and the contacting surfaces of the materials. It is possible to explain this connection in the form of physical and chemical bonds. The force created by the adhesion molecules and the

molecules of the material sticking together holds the adhesive and the material together and resists their separation from each other. This sticking is defined as adhesion. The adhesive that connects the two surfaces also has a pulling power between its molecules. The power that keeps the adhesive molecules together without breaking against the externally applied forces is called cohesion. Adhesion and cohesion provide sticking between materials and surfaces (132, 133).

Adhesives have been used for many centuries to combine materials. Even so it has only been approximately 80 years since the scientific discipline and technology of adhesion and adhesives evolved significantly, and a major improvement took place in the middle of the 1940s. The primary reason for this is that the adhesives can be used in numerous different applications promoting the research and improvement of new, upgraded materials (131–133).

In the past, animal and plant originated materials were used to produce adhesives. Nowadays, adhesives are composed of a mixture of organic and inorganic polymeric materials. Organic polymers are responsible for the adhesive property. The ingredients in adhesives can be listed as follows:

- Polymeric substance,
- Catalytic, hardener,
- Adhesion promoter,
- Solver and diluent,
- Reaction accelerator, inhibitor and dilatory substances,
- Modifying substances,
- Filling materials and antioxidants

Although these substances are ingredients of an adhesive, it is not mandatory to contain all these substances together (134).

2.4.2. Cyanoacrylate adhesives

Cyanoacrylates are acrylic adhesives. Acrylic adhesives fall into the subgroup of thermoplastic adhesives. Thermoplastic adhesives are prepared in solution, dispersion or emulsion and solid forms. In solution and dispersion forms of adhesives, the thermoplastic material remains on the surface and provides adhesion as the liquid phase

leaves the system.

Cyanoacrylates are monomers modified with 2-cyanoacrylate, polymethacrylate, polyacrylate, polyvinyl acetate and cellulose esters. Industrially, 2-cyanoacrylate ester adhesives are made from methyl, ethyl, octyl and butyl 2-cyanoacrylate. Adhesion takes place at room temperature and the addition of catalyst is not necessary. In general, the humidity of the air and the moisture on the surface initiate the reaction, and the polymerization is completed in a very short time (134).

2.4.3. Cyanoacrylate as tissue adhesive

Cyanoacrylate was first synthesized by Alan Ardis in 1949 (135,136). When the tissue-adhesive effect of cyanoacrylate was discovered by Eastman Kodak Company in 1951, extensive related studies have been started on this subject. For the first time, Coover used cyanoacrylate in surgery as a tissue adhesive in 1959. Later, studies have shown that by increasing the carbon atoms in the side chain of the molecule, its toxic and carcinogenic effects on the central nervous system and living cells can be minimized (137). Many formulated cyanoacrylates such as methyl-ethyl cyanoacrylate, octyl cyanoacrylate, N-butyl-2 cyanoacrylate have been used over the years.

Although methyl and ethyl cyanoacrylate are well bonded, they are known as the most histotoxic cyanoacrylates. In animal studies, they have been found to be toxic in pharmacological doses (135). Later, octyl and butyl cyanoacrylates synthesized with long alkyl chains were developed. Thus, it has become available in the clinical application with its slow disintegration in a long time period (138).

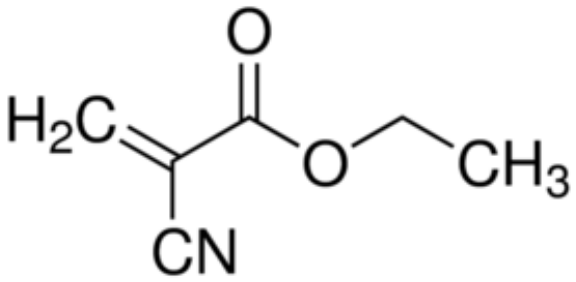

Figure 2.4. Chemical formulation of butyl cyanoacrylate

Butyl cyanoacrylate is a bacteriostatic, biodegradable and hemostatic biological adhesive, that has a long half-life and good tissue compatibility, as well as strong adhesive

properties in non-dry humid environments. In many studies comparing adhesives and sutures for fixation, similar results have been reported in wound infection and aesthetic scores (139-141).

2.4.3.1. The Use of Cyanoacrylates in Medicine

N-butyl cyanoacrylate has a wide range of applications in the medical field. It has been used in pediatrics (142-144), ophthalmology (145–147), general surgery (148,149), gastroenterology (150), obstetrics (151)(152), plastic surgery (153–158) and dentistry (113, 116, 118, 159, 160-163) as a tissue adhesive for decades (134, 137, 140, 142, 143, 145, 151).

Studies have revealed that cyanoacrylate derivatives prevent the development of infection in the application area with bactericidal and bacteriostatic effects (164–166). It has been reported that they cause negligible mild submucosal inflammation compared to other synthetic substances. Researchers have shown that N-2-butyl cyanoacrylate and ethyl 2-cyanoacrylate tissue adhesive are not contaminated with microorganisms. In one study, ethyl 2-cyanoacrylate tubes have been inoculated with high concentrations of bacteria and claimed to be free of contamination (167). Adhesives containing cyanoacrylate can be used safely as they do not carry a risk of bacterial or fungal contamination (8), and they have antimicrobial properties specifically for gram positive microorganisms. The antimicrobial properties of cyanoacrylates and growth inhibition against gram-positive bacteria have also been reported in a recent study (168). Although there is strong evidence for their antimicrobial properties, the mechanism of action remains unknown. Initially, it has been thought to be related to breakdown products of cyanoacrylate, even though short chain derivatives break down faster, longer chain derivatives have more antimicrobial effect.

The use of tissue adhesives reduces the number of sutures to be applied, thus reducing trauma to the tissue. It is used in different organs and structures in cases where suturing techniques and materials are not possible or insufficient. Differently from the use of conventional suturing techniques, with the use of cyanoacrylate, advantage is provided in terms of not requiring additional treatment, preventing operative contamination, reducing operation time and anesthesia (169).

2.4.3.2. The Use of Cyanoacrylates in Dentistry

The research on the use of cyanoacrylates in dentistry started in 1960s with toxicity studies (170, 171).

Greer (172) evaluated histotoxicity by using butyl cyanoacrylate as an oral hemostatic agent on rats. In the study, the upper jaw molar teeth were removed, and cyanoacrylate was applied to deep regions of sockets in one group and to a superficial layer of sockets in another group. In both groups, bone formation and tissue healing occurred however in the group applied to the deep region, foreign body reaction was observed, and giant cell tissue response developed against the adhesive, whereas in the group applied to the superficial layer, foreign body reaction and healing delay were less. new bone formation was seen in all sockets. No neoplastic differentiation was shown in both groups

Levin (173) stated that when cyanoacrylates used as a periodontal paste on the surface of the biopsy area in individuals who underwent oral biopsy, the healing was normal and uneventful with no side effects. In oral ulcers, cyanoacrylate applied to the surface of movable mucosa does not adhere tightly compared to the immobile tissues and falls 2 days after the application with the movement of the mucosa. The patients stated that this two-day period was quite comfortable and painless.

The effectiveness of 3-0 silk sutures and cyanoacrylate tissue adhesive in the flap closure procedure after surgical extraction of third molar teeth was compared in one study (174). While the effectiveness of both approaches was similar, the application time was shorter and the hemostatic effect was found superior in the cyanoacrylate group.

In a case study on rabbits, during the maxillary sinus augmentation process, approximately 1.5 cm wide sinus mucosa perforations were fixated with cyanoacrylate. Two weeks later, new epithelial formation was observed in the perforation zone (175).

In one clinical case report, an avulsified tooth in a 14-year-old patient was reimplanted and splinted to neighboring teeth with orthodontic wire and cyanoacrylate. When the tooth was evaluated thirty months later, no abnormal mobility, root resorption and ankylosis symptoms were observed (176).

2.4.3.3. The Use of Cyanoacrylate in Periodontal Surgery

In the 1960s, researchers first tried to use cyanoacrylates for their hemostatic effects in extraction sockets and tongue injuries in animal models. With the successful results obtained, studies have been conducted on its use in periodontal surgery, especially because the application period is very short, it does not impair healing and show any toxic

effects.

Miller et al. (177) evaluated the toxic effect of cyanoacrylate adhesive on wound healing following mucogingival flaps. While the application of cyanoacrylate tissue adhesive under the flap induced a foreign body reaction, the application outside the flap showed similar results with the suture group.

Forrest et al. (178) performed various periodontal procedures using butyl cyanoacrylate and compared it with concomitant conventional methods. In this study, 85 patients underwent open access flap procedures; 160 patients were treated with apically positioned flap (AFP); 140 patients had laterally positioned flap (LPF) and 27 patients were treated with FGG. The results indicated that cyanoacrylate application was more painless and comfortable. Clinicians who performed the surgery stated that the application of cyanoacrylate takes a shorter time than suturing, but sometimes the application in the posterior region can be more difficult. It was said to be quite practical, especially in patients with FGG. When the areas were evaluated in terms of healing, it was stated that the areas treated with adhesive were better in the first month, but the tissues became clinically similar after the second month.

A group of researchers from Michigan made a split mouth study on monkeys. In the test group, the modified Widman flap was stabilized with cyanoacrylate, whereas in the control group, sutures were applied (16, 179). Histological samples were collected at 14 days, 35 days and 180 days. Clinically and histologically, less inflammation was observed in the adhesive areas in the early stages of healing (up to 4 weeks). Beyond 4 weeks no difference was found between the two groups In biometric tests, it was stated that cyanoacrylate was not as durable as silk sutures (16, 179).

Hoexter et al. (180) compared butyl-cyanoacrylate adhesives and conventional suturing in a FGG case report for creating a KT zone. In the test group, the FGG was fixed with transparent scotch tape and cyanoacrylate was dropped on the part of the scotch that coinciding the tooth surface, while in the control group, the FGG was sutured. Periodontal dressing was then applied on the graft in both groups. Clinical results showed no difference in terms of the obtained KT amount.

Jaeger (181) compared cyanoacrylate and conventional sutures to stabilize FGG in a split mouth study on 14 patients. Clinical parameters (PPD, recession depth and keratinized tissue width) and operation time were evaluated. After 6 years of follow-up period there were no significant difference in any of the parameters. The only difference between the two groups was that the operation time was significantly shorter in the

cyanoacrylate group.

In a similar study comparing the effect of silk sutures and butyl cyanoacrylate on the mucosa after upper incisor root resection, it was revealed that the post-operative first day edema and pain were significantly higher in the suture group, but there was no significant difference on the 3rd, 7th, 14th days. When the groups were compared by clinical observation in terms of scar formation on the 21st day, it was observed that more scar tissue was formed in the suture group. Histologically, similar inflammatory findings were reported (182).

Perez et al. (183) treated 100 patients with root resection, periodontal surgery, extraction and ulcers by using topical cyanoacrylate or 3/0 silk sutures. Clinical comparison between two groups showed no significant difference in terms of clinical parameters. On the other hand, researchers reported that cyanoacrylate application is better in terms of hemostasis, ease of application, shorter operative time, and patient comfort during operation along with patient perception.

Kulkarni et al. (184) performed flap operations on 24 patients in areas with deep periodontal pockets. In the same patient, the flap was stabilized with cyanoacrylate in one of the surgical fields, while 3/0 silk sutures were used in the other. Plaque and bleeding scores were significantly higher on the 7th day in the suture group. Histological findings were evaluated by biopsies on the 7th, 21st days, and 6th weeks. The inflammatory reaction was found significantly higher in the suture group on the 7th day. However, no significant difference was found between the two groups on the 21st day and 6th week clinically and histologically.

Barbosa et al. (109) investigated the dimensional changes of FGG which were stabilized with two different techniques as mucoperiostal suturing and ethyl cyanoacrylate adhesive. Twenty-four patients with insufficient keratinized gingiva and Miller I and II gingival recessions in anterior mandibular area were randomly assigned into 2 groups. In the test group (n = 12) ethyl cyanoacrylate was used for stabilization whereas silk sutures were applied in the control group (n = 12). Dimensional changes were calculated in day 15, 30, 45 and 90. In the test group, the graft width and length were calculated as 12.4 ± 2.6 mm and 6.5 ± 0.6 mm at baseline and 10.6 ± 2.4 mm and 4.1 ± 1.0 mm at day 90. In the control group, the baseline length and height was measured as 13.1 ± 2.3 and 6.3 ± 0.9 mm and 12.5 ± 2.2 and 3.7 ± 0.6 mm at day 90. The results demonstrated no significant differences in vertical and horizontal dimensions at any observation periods between the groups. The authors concluded that cyanoacrylate usage

did not alter the healing process of FGGs.

Gümüş et al. (118) compared three different stabilization techniques for FGGs in terms of the shrinkage, operation time, clinical parameters as plaque index (PI), Gingival Index (GI), KT, recession and patient centered outcomes. Forty-five patients with insufficient keratinized tissue in the anterior region of the lower jaw were divided into 3 groups: conventional 5/0 propilen suture group (n= 15), butyl-cyanoacrylate group (n= 15) and microsurgery group (n= 15). Post-operative evaluation was recorded at the 1st, 3rd and 6th months. The shrinkage of grafts at 6th month for surface area was observed to be 15.101 ± 6.552 mm^2 in the conventional group, 8.261 ± 2.334 mm^2 in the cyanoacrylate group and 14.182 ± 6.738 mm^2 in the microsurgery group. Operation times were 37.33 ± 2.13 min, 26.87 ± 2.13 min, and 44.13 ± 3.46 min in the conventional, cyanoacrylate and microsurgery groups, respectively. Graft shrinkage was statistically lower in the cyanoacrylate group accompanied with shorter operation time. VAS values were reported to be significantly lower in the cyanoacrylate group during the first 5 days. There were no statistically significant differences between the other two groups (118).

Goel et al. (160) studied the clinical parameters that were obtained with two different FGG stabilization techniques. In the test group, grafts were stabilized with butyl-cyanoacrylate and 5/0 silk sutures in the control group. The clinical parameters: PI, GI, gingival recession depth, CAL, KT width and gingival tissue thickness were evaluated at baseline, 3 and 6 months. No statistically significant differences were shown in terms of any clinical parameters. The researchers added that the application was easy with no side effects and operative time seemed to be shorter. They concluded that cyanoacrylate usage may be an alternative to sutures in the stabilization of FGGs.

Aljasser et al. (116) compared the use of butyl-cyanoacrylate and 4-0 vicryl sutures for the stabilization of FGG on 22 patients regarding the clinical parameters of KT width, gingival tissue thickness, percentage of shrinkage and pain using VAS scoring. In this split mouth study, the extent of shrinkage was assessed via periodontal probe by multiplying horizontal and vertical measurements of the graft. No statistically significant differences were observed between the groups in terms of any evaluated parameters.

FGG is an easy, successful, safe, and predictable surgical procedure. These properties make FGG the gold standard for the treatment of inadequate KT zone. It is undesirable for FGGs to excessively shrink in the postoperative period. The available literature reveals controversial results for dimensional changes of FGGs. In addition,

patient perception has become one of the most important factors for clinical maintenance, especially in the recent years. A pain-free period in the recipient area will not only increase the comfort of patients, but also make them more satisfied with the result of the operation.

In the light of the current knowledge based on literature review, different studies showed controversial results depending on many factors. The aim of this randomized, controlled clinical study was to evaluate the effects of fixation with cyanoacrylate application versus 5/0 propylene sutures on FGG shrinkage, patient perception and operation time excluding all known contributing factors as much as possible.

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3. MATERIALS and METHODS

3.1. Patient Selection

Individuals involved in this study were selected among the patients who applied to Periodontology Clinics of Yeditepe University Dental Faculty and Hospital.

The selection of individuals was made according to the following criteria:

Inclusion criteria:

1- Presence of ≤1 mm attached gingiva and/or Miller type I gingival recession ≤2 mm involving one to four lower anterior teeth

2- Vital teeth in the surgical area.

3- 18 years old or older patients

Exclusion criteria:

1- Medications or antibiotics used in the last 6 months

2- Pregnancy or lactation

3- Smoking

4- Previous surgical periodontal therapy

5- Orthodontic forces to the related teeth

The study plan was explained to the patients who met the selection criteria by giving detailed information about periodontal diseases, microbial dental plaque, oral hygiene, the importance of keratinized tissue, and the periodontal treatments. An informed consent form (Appendix1) was obtained before the procedures.

The study protocol was evaluated by the Ethics Committee, Yeditepe University, Istanbul, Turkey and approved on 15.05.2019 / 1020 (Appendix2), and after admission to the Ministry of Health, Pharmaceuticals and Medical Devices Agency, the approval was received on 10.03.2020 with 68869993-511.06-E.62839 issue. (Appendix3)

3.2. Study Groups

Group 1 (Test): Stabilization of FGG on recipient bed by n-butyl-cyanoacrylate tissue adhesive

Group 2 (Control): Conventional stabilization of FGG on recipient bed by sutures

3.3. Sample Size and Randomization

The G Power software program (version 3.1.9.2) was used to determine the sample size. The power analysis was made according to a recent study (114). The effect size was 1.11, 80% statistical power, common standard deviation of 9 and 5% Type I error. The power analysis results indicated that 11 subjects in each group were sufficient for this study, therefore, 12 patients were treated in each group considering 10% drop-out.

The test and control groups were randomly assigned according to a computer-generated randomization table (www.randomizer. org). The patients were placed in the grouping system as shown in the randomization table (Table 1) according to the order of application date.

Table 3.1. Randomization Table

Patient No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Group No.	2	2	2	1	1	1	2	2	1	2	1	1
Patient No.	13	14	15	16	17	18	19	20	21	22	23	24
Group No.	2	1	1	2	1	2	2	1	2	1	2	1

3.4. Study Design and Flow Chart

The study was designed as an examiner-blind, parallel, randomized controlled clinical trial.

The flow-chart of the research is shown in Figure 3.1. At baseline, the patients received periodontal and radiographic examination. Those who met the initial inclusion criteria received non-surgical periodontal treatment and demonstrated a full-mouth plaque score (FMPS) of ≤ 20% and full mouth bleeding score (FMBS) of ≤ 20% (185–188).

All surgical procedures were performed by the same investigator (K.B). FGG was applied in both groups. While FGG was stabilized with n-butyl-cyanoacrylate tissue adhesive in the test group, sutures were used in the control group. No medication was prescribed postoperatively. The sutures were removed one week after surgery and patient-based evaluation forms were collected from the patients at the post-operative 7 day (daily evaluation). Vertical height and total graft area measurements were made on the 1st, 3rd and 6th months postoperatively based on clinical photographs.

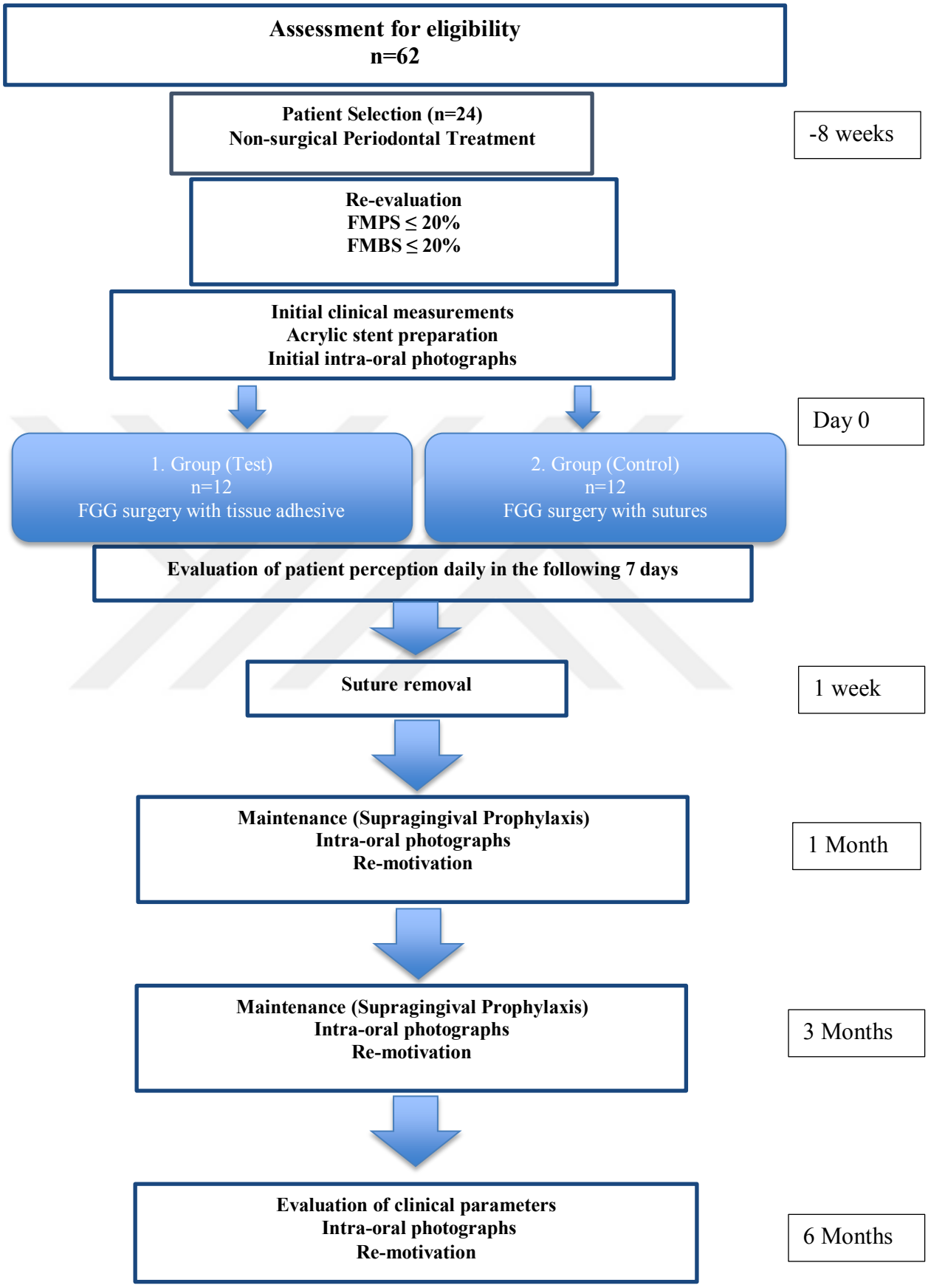


Figure 3.1. Flow Chart

3.5. Clinical Indices and Measurements

All clinical periodontal indices and measurements including FMPS, FMBS, probing depth (PD), and keratinized tissue (KT), vertical recession (VR) were recorded at day 0 and 6-months by the same blinded examiner (E.Ö.K) with a manual 15 mm periodontal probe[1]. In order to prevent any inaccuracy, all measurements were made in an arranged order. All data were recorded on a custom made clinical form (Appendix 4).

3.5.1. Full Mouth Plaque Score

FMPS was determined dichotomously (+/-) as presence or absence of plaque by using a periodontal probe. The percentage of total tooth surfaces (mesiobuccal, buccal, distobuccal and palatal midpoint) (185, 186) presenting plaque accumulation was calculated.

3.5.2. Full Mouth Bleeding Score

FMBS was also recorded dichotomously (+/-) with a periodontal probe and was calculated as the percentage of total surfaces (mesiobuccal, buccal, distobuccal and palatal midpoint) with bleeding on probing (185, 186).

3.5.3. Keratinized Tissue

The height of KT was measured with the same periodontal probe at the mid-buccal point of the involved teeth at the mandibular surgical area as the distance between the mucogingival junction (which determines the alveolar border of keratinized tissue) and the gingival margin.

3.5.4. Vertical Recession

Vertical recession of the involved teeth at the surgical area were measured using the same periodontal probe at the mid-buccal point as the distance between the cemento-enamel junction and the gingival margin.

[1] 15 UNC Color Coded Probe, University of North Carolina

3.5.5. Probing Depth (mm)

Full mouth PDs were measured with the use of the same periodontal probe from 4 points of tooth surfaces (mesio-buccal, mid-buccal, disto-buccal and palatal midpoint), as the distance between the gingival margin and the bottom of the gingival sulcus. Furthermore, PD measurements of the mid-buccal point of the involved teethat the surgical area were performed.

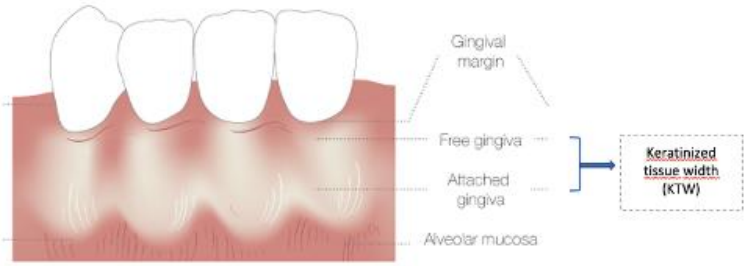


Figure 3.2. Schematic view of keratinized tissue height

3.6. Clinical Procedures

3.6.1. Non-Surgical Periodontal Therapy

At -8 weeks; the patients who met the initial inclusion criteria of the study, were given oral hygiene instructions. While Modified Stillman technique demonstrated for teeth with keratinized tissue deficiency or recession, Bass technique for the rest of the mouth were recommended (189, 190). The patients were also instructed to perform interdental cleaning by dental floss. After oral hygiene instructions, non-surgical periodontal therapy consisted of full-mouth mechanical instrumentation was applied by using ultrasonic devices[2] and Gracey curettes[3] (191, 192). Polishing by rubber con and polishing paste was then performed. Each patient was re-motivated for brushing and the use of dental floss in every visit. Eight weeks after non-surgical treatment, FMPS and FMBS, as well as other selected periodontal parameters were measured at the day of the surgery.

[2] Ultrasonic Scaler, Woodpecker UDS-J, China
[3] Gracey, SG 5/6, 7/8, 11/12, 13/14, Hu-Friedy Ins. Co., USA.

3.6.2. Preparation of Acrylic Stent for Donor Site

The dimensional standardization of FGG was provided with an individual acrylic stent. Acrylic stents were used during the surgery.

Alginate impression[4] was taken in each patient. Plaster models were prepared in Yeditepe University Dental Hospital Orthodontic Laboratory. An orthodontic wire[5] of 13 mm length was placed in each acrylic stent to guide the horizontal dimensions of the graft.

Figure 3.3. The acrylic stent

3.6.3. Surgical procedure

All patients were operated by applying local anesthesia[6] on the donor and recipient sites. The recipient bed was prepared in both groups with the conventional technique (6).

3.6.3.1. Preparation of Recipient Bed

Firstly, a horizontal incision was made on the mucogingival line with a scalpel[7]. A supraperiostal recipient bed was prepared by means of partial-thickness flap. Care was taken to keep the scalpel parallel to the bone to avoid any damage on the periosteum during splitting of the soft tissues to create a crescent shape as exposed connective tissue bed. All fibers and muscle pulls were eliminated by means of dissection. A proper size recipient bed was prepared for placing an approximately 13x8 mm graft (Figure 3.2). Loose and mobile connective tissues covering the recipient bed were removed by using

[4] *Impreceed, GC Dental,* IL, USA
[5] *Dynaflex*
[6] Ultracain DS Fort 2 ml, Aventis Pharma Istanbul, Turkey
[7] Scalpel Blade 15, Swann-Morton Ltd., Sheffield, England

surgical scissors. The flap margin was stabilized by 3 periostal sutures apically using 3/0 silk suture[8]. Hemostasis was achieved with wet gauze sponge compression.

3.6.3.2. Free Gingival Graft Harvesting

As the donor site, the palatal region of upper 1st premolar to 2nd molar was selected. After the local anesthesia, the acrylic stent was adapted in place and a horizontal incision which determines the horizontal length of the graft was made at least 2 mm apically from the gingival margin. Thereafter by guidance of the periodontal probe, the vertical width of the graft was measured as ≈8 mm at the mid-point of the horizontal incision to harvest a crescent shaped graft tissue. During harvesting, the scalpel was kept parallel to the palatal surface to maintain a thickness of 1-1.5 mm, measured with an endodontic reamer[9] and an endoblock[10] (193). Following harvesting, bleeding control was done applying one-minute compression of wet gauze sponges to the palatal donor site.

The graft was visually inspected whether there was any adipose tissue underneath. (Figure 3.3) and placed onto the recipient bed immediately after harvesting. In both groups; a periodontal dressing[11] was applied at palatal wound areas to reduce post-surgical patient morbidity.

3.6.4. Stabilization of the Graft

3.6.4.1. Stabilization of Graft in the Control Group

The grafts were stabilized coronally with a minimum number of sutures. Using 5/0 propilen[12] sutures, the grafts were firmly adapted and stabilized with two sutures. Before and after graft stabilization, compression was applied for 1 minute with wet gauze sponge, to provide hemostasis (194) (Figure 3.10).

3.6.4.2. Stabilization of Graft in the Test Group

In the test group, the stabilization of the grafts was achieved by butyl-cyanoacrylate[13] tissue adhesive. Wet gauze sponge compression was made carefully before and after graft placement to achieve hemostasis, to avoid any blood accumulation underneath the graft to prevent jeopardization of the cyanoacrylate material and to avoid

[8] 3/0 Silk Suture, Doğsan Ltd., Trabzon, Turkey
[9] *SVD Reamer,* Istanbul, Turkey
[10] *SVD Endoblock,* Istanbul, Turkey
[11] Coe-Pak, GC Dental, IL, USA.
[12] Dogsan LTD., Trabzon, Turkey
[13] Periacryl®, Glustitch, Canada.

any contact to the area after adhesive application (194). The graft was fixed through a manufactural straw ensuring to get 0.2 mL of butyl-cyanoacrylate in every use. The application was made to the borders of the graft starting at the coronal border. Excess material was absorbed with a wet gauze sponge. During polymerization process, special care was given to avoid any contact with the surgical area (Figure 3.20).

Figure 3.4. Baseline view of recipient site in the control group

Figure 3.5. Preparation of the recipient bed in the control group

Figure 3.6. Baseline view of donor site in the control group

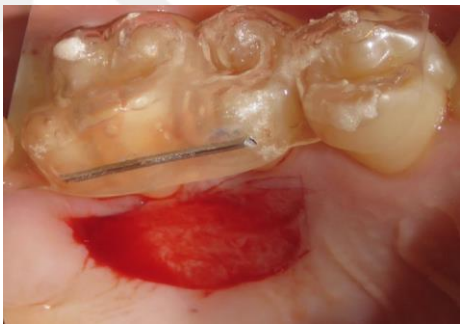
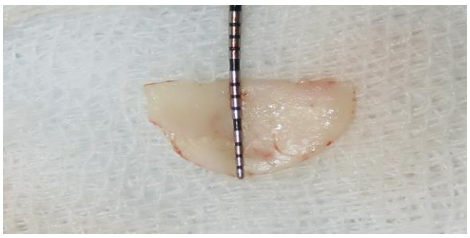


Figure 3.7. Immediately after graft harvesting in the control group



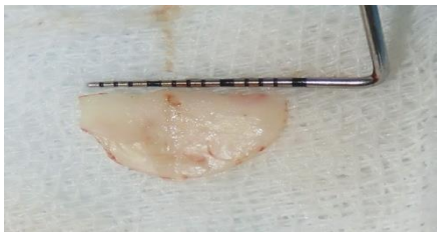
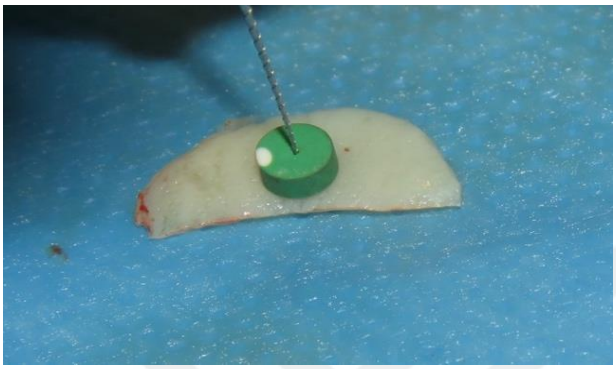


Figure 3.8. Horizontal and vertical dimensions of the graft



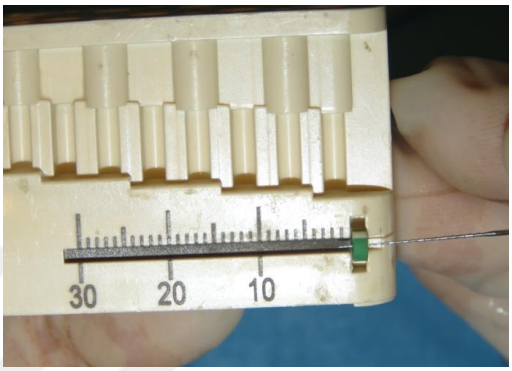


Figure 3.9. Thickness measurement of the graft

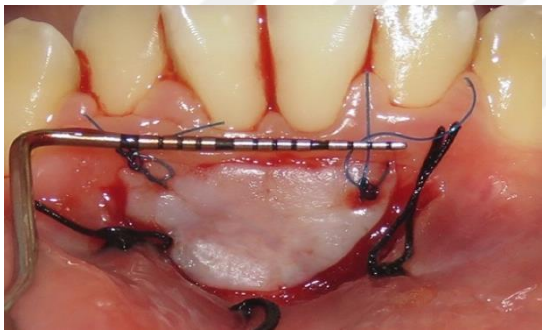


Figure 3.10. Graft stabilization in the control group

Figure 3.11. 1-month follow-up of the control group

Figure 3.12. 3-months follow-up of the control group

Figure 3.13. 6-months follow-up of the control group

Figure 3.14. Baseline view of recipient site in the test group

Figure 3.15. Preparation of the recipient bed in the test group

Figure 3.16. Baseline view of donor site in the test group

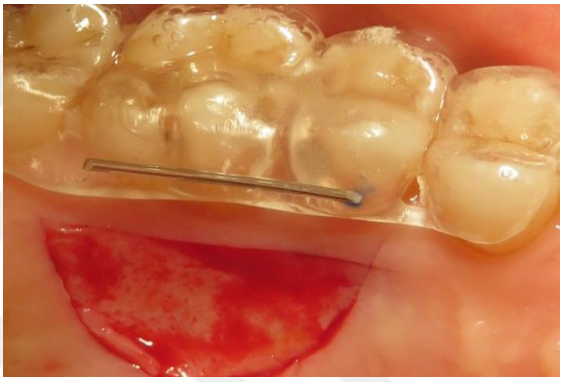


Figure 3.17. Immediately after graft harvesting in the test group

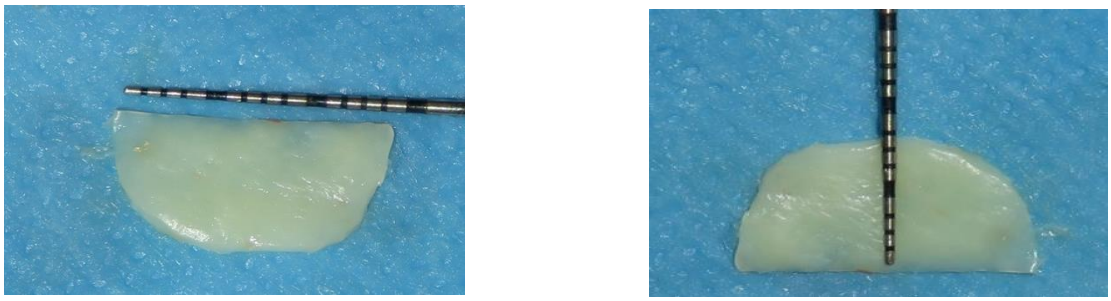


Figure 3.18. Horizontal and vertical dimensions of the graft

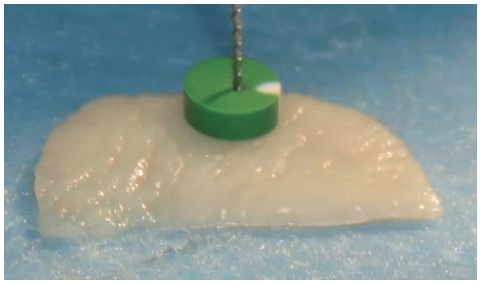


Figure 3.19. Thickness measurement of the graft

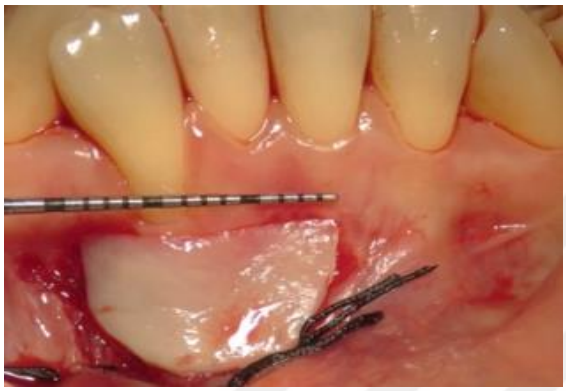


Figure 3.20. Graft stabilization in the test group

Figure 3.21. 1-month follow-up of the test group

Figure 3.22. 3-months follow-up of the test group

Figure 3.23. 6-months follow-up of the test group

3.7. Clinical Photographs

KT height, graft surface area and graft shrinkage assessments were made based on clinical photographs. In all of the postoperative appointments, clinical photographs were taken by the same periodontist using the same digital camera[14] with standardized parameters (dark chamber, ISO 125, aperture f/7.1, shutter speed 1/60 s, distance 31.4 cm). Nikon's R1C1[15] wireless close-up speedlight system with twin flash was used. The camera was held with vertical angle to operation area, and a standardized periodontal probe was placed on the soft tissue parallel to the operation site for relative calculation purposes.

3.8. Determination of Operation Time

A standardized timekeeper[16] was used at all operations. The timekeeper was started at the beginning of the first horizontal incision, and it was stopped right after the stabilization of the gingival graft. The operation time for each patient was noted.

3.9. Post-surgical care and other Precautions

Post-operative instructions regarding the infection control and home care were given pin written hand-outs. The patients were recommended to discontinue of using toothbrush and interdental devices full mouth at the first day of operation and around the surgical sites until removal of sutures (day 7). They were instructed to consume only soft foods, avoid salty, spicy and acidic foods during the first week, excessive lip and cheek movements and trauma around the surgical site. No medication was prescribed. The patients were informed about Visual Analogue Score (VAS), and a standardized paper was given to all patients to note their scores at each day for 7 days. An appointment was arranged at day seven to remove the sutures and periodontal dressing. The patients were recommended to brush the surgical site with a sensitive toothbrush. Following that all patients were re-evaluated on 1, 3 and 6 months.

14 Nikon d7500, Nikon INC, Tokio, Japan
15 Nikon R1C1, Nikon INC, Tokio, Japan
16 Delta SW 305, Delta Dış Tic. Ltd. Şti, Istanbul, Turkey

3.10. Data Collection for Evaluation of FGG Dimensional Changes

The vertical height of KT and total graft surface area were assessed. The clinical photographs were taken immediately after harvesting and at 1, 3 and 6 months follow-ups. The images were transferred to a java-based analysis software[17]. The digital measurements were made based on the reference of the periodontal probe for calibration purpose on each image. After the 1 mm region on this periodontal probe was marked, the relative vertical area and the area of the graft were evaluated separately. Each measurement was repeated twice to evaluate the intra-class correlation coefficient (ICC) and then their averages were taken for statistical analysis.

Feedback forms were prepared to evaluate the post-operative pain and discomfort. A VAS chart with equal intervals between "0" and "10" was prepared for the recipient area. Post-operative forms were given to the patients, and they were asked to mark the pain and discomfort value at the end of each day in the first week. All forms were collected on the day the sutures were removed.

The operation time was assessed with a standardized timekeeper. During the operations, the timekeeper was started with first horizontal incision and stopped right after the stabilization of the graft.

3.11. Statistical Analysis

Statistical analyses were performed using the SPSS software version 25. The descriptive analyses were presented using means, standard deviations, median, minimum, and maximum values for the continuous data. Frequencies and percentages were used for the categorical data.

The variables were investigated using Shapiro-Wilks test to determine if the variables were normally distributed. In case of the normal distribution, two independent sample t-test was used to compare the two groups. The evaluations were as follows: inter-group comparisons of age, initial periodontal parameters, dimensional graft parameters, VAS parameters and operative time. If the variables were not normally distributed, Mann-Whitney U test was used. For normally distributed data, change in the measurements over time within the groups (intra-group comparisons) was investigated using ANOVA for repeated measures.; Greenhouse-Geisser correction was applied when

[17] ImageJ, National Institute of Health, Maryland, USA

the sphericity assumption was violated. Bonferroni test was performed to test the significance of pairwise differences for multiple comparisons.

For not normally distributed data, change in the measurements over time within the groups was investigated using Friedman test. The Wilcoxon test was employed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. For variables that were normally distributed, the change in the measurements between baseline and 6 month was investigated within the groups using paired samples t test. For the variables that were not normally distributed, for changes of measurements between baseline and 6 months within the groups, Wilcoxon's test was used. Fisher exact's test was utilized to compare the categorical variables. Intra- and inter-observer agreements were determined by intra-class correlation (ICC). A 5% type-I error level was used to infer a statistical significance.

4. RESULTS

4.1. Demographic Results

Twenty-four patients with inadequate KT height and/or presenting Miller Type I gingival recession with a diagnosis of gingivitis were treated between January 2019 and March 2020. There were two drop-outs, one in each group during the post-operative follow-up period. The average age of the individuals in the groups and the gender distribution within the groups are shown in Table 4.1. The age and gender distributions of the groups were homogeneous without statistically significant difference.

Table 4.1. Average age and gender distribution of the patients.

	Test Group n=11	**Control Group n=11**	**p Value**
Age (Mean±SD)	36.63 ± 10.00	41.81 ± 14.70	0.345[a]
Age Range	19-50	19-64	
Female (Proportion) (%)	9/11(81.8%)	9/11(81.8%)	1.000[b]
Male (Proportion) (%)	2/11(18.2%)	2/11(18.2%)	

a: two-sample independent t test; b: Fisher exact test; $p < 0.05$

4.2. Baseline Parameters of the Surgical Area

Baseline periodontal parameters of the surgical area of the patients in the test and control groups are shown in Table 4.2. No significant differences were detected between the groups in terms of initial KT, PD and VR before treatment.

Table 4.2. Baseline parameters of the surgical area in the test and control groups

	Test Group **Mean+SD**	**Control Group** **Mean+SD**	**p Value**
KT (mm) **4 teeth at the surgical area** **(Range)**	2.05 ± 0.56 (1,00-2,75)	1.73 ± 0.71 0,75-3,00	0.262[a]
KT (mm) **teeth with mucogingival defect**	0.64 ± 0.36	0.70 ± 0.39	0.631[b]
PD (mm)	1.20 ± 0.33	1.19 ± 0.32	0.936[a]
VR (mm) **4 teeth at the surgical area**	0.72 ± 0.53	0.87 ± 0.44	0.489[a]
VR (mm) **teeth with mucogingival defect**	1.65 ± 0.57	1.45 ± 0.55	0.393[b]

a: two-sample independent t test, b: Mann-Whitney u test; $p < 0.05$

4.3. Full Mouth Plaque Score, Full Mouth Bleeding Score, and Full Mouth Probing Depth

The mean FMPS, FMBS, and FMPD values and standard deviations of the groups at baseline (day 0) and after the treatment (month 6) are shown in Table 4.3. There were no statistically significant differences between the test and control groups at baseline and 6 months full-mouth periodontal parameters. At baseline, the patients enrolled to the study in both groups had similar FMPS, FMBS, and FMPD values and all patients maintained optimal oral hygiene level throughout the study confirmed by 6 months measurements. Intra-group differences were statistically significant in both groups at 6 months ($p<0.05$). The inter-group comparison for intra-group changes (baseline-6 months) was not found statistically significant.

Table 4.3. Intra- and inter-group comparisons of FMPS, FMBS, and FMPD at baseline and after 6 months

		Test Group Mean+SD	Control Group Mean+SD	p Value
FMPS (%)	Baseline	14.68 ± 0.77	14.78 ± 1.08	0.803[a]
	6 months	13.70 ± 0.78	13.84 ± 0.53	0.626[a]
	change	0.98 ± 0.73	0.94 ± 0.86	0.911[a]
	p value	**0.002[b]**	**0.005[b]**	
FMBS (%)	Baseline	8.60 ± 1.79	7.79 ± 2,03	0.334[a]
	6 months	7.14 ± 1.74	6.65 ± 2,01	0.552[a]
	change	1.46 ± 1.14	1.13 ± 1.26	0.535[a]
	p value	**0.002[b]**	**0.014[b]**	
FMPD (mm)	Baseline	2.75 ± 0,70	2.48 ± 0.55	0.343[a]
	6 months	2.59 ± 0,70	2.40 ± 0.54	0.499[a]
	change	0.29 ± 0.18	0.23 ± 0.13	0.217[c]
	p value	**0.007[b]**	**0.007[b]**	

a: two-sample independent t test b: paired samples t-test, c: Mann-Whitney u test $p < 0.05$

4.4. Keratinized Tissue, Probing Depth, Vertical Recession of the Surgical Area and Individual Teeth with Mucogingival Defects

4.4.1. Keratinized Tissue

The mean and standard deviations for KT height of the individual teeth with mucogingival defects and surgical area of the groups at baseline and 6 months after treatment are shown in Table 4.4 and Table 4.5. In intra-group comparison, there were statistically significant gain between the values at baseline and after 6 months for each group in both comparisons ($p < 0.05$). The inter-group comparison of the intra-group changes revealed no statistically significant difference for both comparisons.

4.4.2. Vertical Recession

The mean and standard deviations of VR values of the individual teeth with mucogingival

defects and surgical area of the groups at baseline and 6 months after treatment are shown in Table 4.4 and Table 4.5. In intra-group comparisons, a statistically significant decrease was observed at 6 months for each group in both comparisons ($p < 0.05$). In the inter-group comparison in terms of surgical area, a statistical difference was detected in intra-group changes in favor of the control group. Thus, the reduction of VR in the control group was significantly higher than that of the test group ($p < 0.05$). In inter-group comparison of individual teeth with mucogingival defects, no statistically significant difference was observed.

4.4.3. Probing Depth

The mean and standard deviations of PD values of the groups at baseline and after 6 months are shown in Table 4.4. In the intra-group comparison, a statistically significant decrease was observed for both groups at 6 months ($p < 0.05$). The reduction in PD for both groups was found similar, and the inter-group comparison of the intra-group changes revealed no statistically significant difference.

Table 4.4. Intra- and inter-group comparisons of KT, PD, and VR of the individual teeth at baseline and after 6 months

		Test Group Mean+SD	**Control Group Mean+SD**	**p Value**
KT (mm)	Baseline	0.64 ± 0.36	0.70 ± 0.39	0.631[a]
	6 months	5.85 ± 1.42	5.95 ± 1.40	0.667[a]
	change	5.21 ± 1.48	5.25 ± 1.33	0.940[a]
	p value	**0.001[b]**	**0.002[b]**	
VR (mm)	Baseline	1.65 ± 0.57	1.45 ± 0.55	0.393[a]
	6 months	1.05 ± 0.49	0.75 ± 0.26	0.089[a]
	change	0.60 ± 0.45	0.70 ± 0.58	0.739[a]
	p value	**0.017[b]**	**0.014[b]**	

a: Mann-Whitney u test, b: Wilcoxon test, $p<0.05$

Table 4.5. Intra- and inter-group comparisons of KT, PD, and VR of the surgical area (4 teeth) at baseline and after 6 months

		Test Group Mean+SD	**Control Group Mean+SD**	**p Value**
KT	Baseline	2.05 ± 0.56	1.73 ± 0.71	0.262[a]
	6 months	4.79 ± 0.82	5.00 ± 0.60	0.514[a]
	Change	2.73 ± 0.85	3.26 ± 0.40	0.081[a]
	p value	**0.000[b]**	**0.000[b]**	
VR	Baseline	0.72 ± 0.53	0.87 ± 0.44	0.489[a]
	6 months	0.63 ± 0.49	0.68 ± 0.42	0.847[c]
	Change	0.09 ± 0.14	0.19 ± 0.11	**0.034[c]**
	p value	**0.034[b]**	**0.000[b]**	
PD	Baseline	1.20 ± 0.33	1.19 ± 0.32	0.936[a]
	6 months	0.90 ± 0.32	0.95 ± 0.22	0.705[a]
	Change	0,29±0,18	0,23±0,13	0,438[c]
	p value	**0.000[b]**	**0.007[b]**	

a: two sampled independent t test c: Mann-Whitney-u test, b: dependent samples t-test *p < 0.05

4.5. The Vertical Height and Graft Surface Area Parameters

The vertical height and total surface area of the graft are shown in Table 4.5. The intra-group multiple comparison of the vertical graft height and the total graft surface area parameters for both groups through the measurement times of baseline, 1st, 3rd and 6th

months revealed a statistically significant reduction ($p<0.05$). When the significance of pairwise differences for multiple comparisons were tested, there were significant differences in all time measurements (1, 3, 6 month) compared to baseline values for the two graft parameters in both groups ($p<0.05$).

The inter-group comparison of the vertical graft height and the total surface area values at the sequential measurement time points revealed no statistical differences ($p<0.05$).

Table 4.6. Mean ± standard deviation of vertical graft height and total graft area values at baseline and at 1st ,3rd and 6th months.

		Test Group	**Control Group**	**p value**
Vertical graft height (mm)	Baseline	8.00	8.00	
	1 Month	6.19 ± 0.90	6.23 ± 0.55	0.748[a]
	3 Months	6.17 ±1.04	6.26 ± 0.61	0.818[a]
	6 Months	5.91 ±0.94	6.51 ± 0.60	0.091[b]
	p value	**0.000[c]**	**0.000[d]**	
Total graft surface area (mm^2)	Baseline	98.00	98.00	
	1 Month	72.96 ± 22.15	81.46 ± 9.80	1.000[b]
	3 Months	72.26 ± 23.23	83.36 ± 13.19	0.184[a]
	6 Months	73.36 ± 21.37	82.67 ± 7.92	0.519[b]
	p value	**0.001[c]**	**0.001[d]**	

a: two sampled independent t test, b: Mann-Whitney u test, c: Friedman test d: ANOVA test, $p < 0.05$

4.6. Patient centered outcomes

The patient-based VAS evaluation for post-operative pain and discomfort is shown in Table 4.6. No statistically significant differences were observed between the two groups at any time point.

Table 4.7. VAS score evaluation in the test and control groups

		Test Group	Control Group	p value
VAS (0-10)	Day 0	4.00 ± 2.89	5.00 ± 2.09	0.365[a]
	Day 1	2.45 ± 2.62	4.54 ± 2.06	0.051[a]
	Day 2	2.27 ± 2.53	2.72 ± 1.19	0.300[b]
	Day 3	1.09 ± 1.57	2.18 ± 1.72	0.171[b]
	Day 4	1.00 ± 1.54	1.81 ± 1.40	0.217[b]
	Day 5	0.72 ± 1.34	1.00 ± 1.94	0.949[b]
	Day 6	0.18 ± 0.60	0.54 ± 0.93	0.478[b]

a: two independent samples t-test, b: Mann-Whitney u test, $p < 0.05$

4.7. Operative Time

The mean operative time in the control group was found significantly higher than the test group ($p<0.05$).

Table 4.8. Operative times of the test and control groups

	Test Group Mean±SD	Control Group Mean±SD	p Value
Operative time (h:m:s)	0:20:23 ± 0:02:08	0:26:15 ± 0:05:21	**0.005**

Two independent samples t test, $p < 0.05$

5. DISCUSSION and CONCLUSION

This randomized, controlled clinical study aimed to evaluate and compare the clinical and dimensional changes of FGGs, stabilized by using cyanoacrylate tissue adhesive versus 5/0 propylene sutures. No significant differences were observed regarding vertical graft height and total graft surface area changes. However, both groups showed significant clinical improvements. For the FGGs stabilized with sutures, the reduction in VR was significantly better at six months, whereas operation time was shorter with tissue adhesive application.

KT is of critical clinical importance since it resists mechanical, bacterial and surgical trauma, provides post-op wound integrity, prevents soft tissue recession, enables esthetic tissue manipulation, promotes creeping attachment, preserves papilla and eases oral hygiene procedures, eliminates muscle and frenum pull (99). However, controversial findings have been reported about the ideal KT zone and its effects on sustaining periodontal health (21-31). Although many studies have shown that patients with insufficient KT may maintain periodontal health in the presence of optimal oral hygiene (4, 25, 195, 196), thin gingival biotype may be less preservative in the presence of inflammation and recession. A recent systematic review (31) concluded that in cases of inadequate oral hygiene or the necessity of a sub-gingival restoration, a minimum of 2 mm KT is crucial. Thus, mucogingival therapy for soft tissue augmentation may be required according to the individual needs of the patients (197).

In this study, gingivitis patients presenting ≤1 mm attached gingiva and/or Miller type I gingival recession ≤2 mm on at least 1 to 4 lower anterior teeth are selected to widen the KT zone by using FGG surgical procedure as the gold standard method (27, 31, 36, 37). Involvement of 4 teeth as the length of surgical area is taken as a standard for the experimental design, no matter the teeth with muco-gingival problem vary between 1 to 4 in number. The mean KT width, measured on the whole surgical area, was found 1.73 ±0.71 mm in the control and 2.05 ± 0.56 in the test groups which seem initially high or sufficient. However, the perception of high mean KT values are associated with averaging the baseline KT measurements taken at the mid-buccal point of each four involved teeth at the surgical area with and without muco-gingival problem for standardization purposes.

Although FGG procedure is the most predictive and successful surgical technique

for the treatment of insufficient KT, it is inevitable for this technique to present some disadvantages such as 2 separate surgical sites and the palatal connective tissue left to secondary healing which in return cause postoperative patient discomfort, requirement of delicate postoperative care for the final graft success, and possible dimensional changes of transferred graft due to multiple doctor and patient factors. Graft stabilization is one of the most important factors for the successful treatment outcomes. As the conventional technique with sutures has been used in the stabilization of the graft for years, only a limited number of studies evaluated the alternative tissue adhesives in the literature (109, 115, 116, 118).

Tissue adhesives come up as a simple, practical, handy, quick to use and cheap material to fix and stabilize the soft tissues without causing any possible tissue trauma and graft displacement. No adverse effects or allergic reactions were seen in the previous studies supporting that butyl-cyanoacrylate is a safe material to be used on human tissues (109, 115, 116, 118, 198). In this study, butyl-cyanoacrylate tissue adhesive was used as an alternative procedure for FGG stabilization with sutures.

Owing to the fact that dimensional changes may be associated with FGG stabilization (52), all other possible factors that enhance graft shrinkage were eliminated as much as possible in this study to single out the effects of two stabilization techniques on graft shrinkage. Besides the dimensional changes, clinical periodontal parameters were further evaluated. There is paucity of information in the literature to conclude whether cyanoacrylate tissue adhesives can replace suturing techniques or prevent/reduce the graft shrinkage. Thus, we aimed to contribute to the literature by comparing tissue adhesives and conventional sutures in graft stabilization through the evaluation of parameters for dimensional changes of the graft as well as clinical healing on the recipient site.

No significant differences were detected between the groups regarding initial KT, PD and VR mean values at the surgical area involving four teeth at the mandibular anterior area. Also, no significant differences were found regarding initial clinical periodontal parameters of FMPS, FMBS and FMPD values ($p>0.05$).

Graft healing following the operation was unproblematic for both groups. In the intra-group comparisons, statistically significant improvements were observed for both groups regarding FMPS, FMBS, FMPD, KT, PD and VR at six months ($p<0.05$). In the test and control groups, mean PD reduction was 0.29 ± 0.18 mm and 0.23 ± 0.13, respectively. KT change was both evaluated as a mean value of four involved teeth at the surgical area on a patient level as well as of individual teeth presenting the muco-gingival

defect. Individual teeth KT change was detected as 5.21 ± 1.48 and 5.25 ± 1.33 for test and control groups, respectively. Mean KT gain of the teeth at the surgical area was 2.73±0.85 mm and 3.26±0.40 mm in the test and control groups, respectively. No statistically significant difference was found between the groups regarding PD and KT changes ($p>0.05$). Better oral hygiene scores were obtained in both groups during the follow-up time compared to baseline, confirming the maintenance of an optimal level of oral hygiene to exclude any negative effects of microbial dental plaque biofilm on healing. The presence of better oral hygiene could be due to the increase in KT zone improving oral hygiene level supported by the literature (24-25) or to the motivational effect of being under periodontal treatment in an experimental study. Gümüş et al. (118) in their study evaluated the KT width, measured as the distance between gingival margin and bottom edge of transplanted graft, immediately after the FGG operation, at 1, 3 and 6 months as 5.5±0.44 mm, 4.92±0.59 mm, 4.76±0.62 mm, 4.77±0.77 mm in the test and 5.66 ± 1.00 mm, 4.74 ±0.89 mm, 4.68±1.01mm, 4.55±1.01 mm in the control groups, respectively. KT decrease between immediate post-op and 6 months was 0.79 ±0.58 mm and 1.12±0.93 mm for test and control groups, respectively. Researchers did not take the initial KT values into consideration as baseline. This is different from our methodology and the difference in methodology explains the statistically significant "KT decrease" instead of "increase" within both groups at each evaluation period compared to the immediate post-op measurements ($p<0.05$), since the measurements include the vertical graft shrinkage values added onto the previous width of KT before the surgery. There is no way for direct comparison of our results with this study. AlJasser et al. (116) evaluated KT change with the same methodology. KT values for test and control groups were made immediately after the operation, at days 15, 30, 60, 90, 120 as 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.09 ± 1.02 mm, 3.09 ± 1.02 mm and 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.14 ± 1.04 mm, 3.09 ± 1.02 mm, 3.09 ± 1.02 mm, respectively. Results were comparable in both groups and no statistically significant difference was observed between groups regarding any period. With similar approach as in our study, Goel et al. evaluated the KT value at baseline and after six months and reported the KT gain as 0.91±0.46 mm, 1.37±0.43 mm in the test and control groups, respectively. In inter-group comparison, no statistical difference was found consistent with our findings ($p>0.05$). However, no details in the materials and methods regarding the initial KT values or the graft dimensions were given in the study to enable the

comparison of our results or the introduction of any comments on the low amounts of KT gain obtained.

In the present study, the main purpose of the FGG application was to increase the KT zone without any root coverage intention. However, as a matter of fact VR decrease was seen in both groups ($p<0.05$). Mean VR decrease covering the teeth on surgical area was found 0.09 ± 0.14 in the test group stabilized with tissue adhesive and 0.19 ± 0.11 mm in the control group revealing a statistically significant difference in favor of the control group where the FGG was stabilized using conventional sutures ($p<0.05$). Improved oral hygiene together with augmented KT may affect so-called 'creeping attachment' leading to decrease in mean VR height at six months(20)(46)(64). However, VR decrease in individual teeth covering the teeth presenting either recession or insufficient amount of KT was detected as 0.6 ± 0.45 and 0.7 ± 0.58 in the test and control groups without a significant difference. The loss of significance may be due to the total number of teeth taken together as teeth with mucogingival defects, not only the recessions. Gümüş et al. (118), also reported a significant difference in mean values of maximum 2 involved teeth (with severe gingival recessions or inadequate KT) between the groups regarding intra-group VR changes between baseline and six months. VR was also evaluated in the study by Goel et al., presenting decreases of 2.04 ± 0.49 mm and 2.91 ± 0.84 mm in the test and control groups including only teeth (the number of involved teeth was not given) with severe recessions at the surgical area, respectively. Researchers declared that although no significant difference was found between the groups, recession decrease was found higher in the control group ($p<0.05$). Better improvements may also be explained by the mechanical stabilization in the control group compared to the chemical stabilization in the test group in which some unexplained soft tissue interactions may be expected. However, in contrast to these findings favoring sutures, Barbosa et al. (109) reported no statistical difference in their study between any measurement time points.

In our study, according to our inclusion criteria of involving four teeth at the mandibular anterior surgical area, graft dimensions were standardized to approximately 13 mm x 8 mm as the length and height. This initial standardization led us to make a safe comparison between the groups as much as possible. An inadequate KT zone is mostly seen in the anterior mandibular region with or without gingival recession, and the mandibular anterior region is the easiest area to obtain proportional clinical photographs

appropriate for software analysis.

FGG shrinkage is a well-known phenomenon in the postoperative period, which is calculated as the difference of total graft surface area between measurement time points. In the literature, the total graft surface area is evaluated using a periodontal probe and caliper (193). Recently, a software program, computing the pixel amount of the marked graft area(118) is in use. This evaluation technique is sensitive and used only in one of the previous study (118). Unlike most of the previous studies in the literature (4, 5, 6, 27), we also used the software program in our study instead of multiplying the length and height of the graft dimensions. In the present study, the total graft surface area was expected to be 104 mm^2 with 13 x 8 mm dimensions. Gümüş et al. (118) harvested 5 x 10 mm sized graft and the software predicted 45 mm^2 of surface area instead of 50 mm^2 (118). Similarly, in our study, the program calculated the initial total graft surface area as 98 mm^2. The total graft surface area values and the percentages of the test and control groups at baseline, 1, 3 and 6 months were 98 mm^2 (100%), 72.96 ± 22.15mm^2 (74,44%), 72.26 ± 23.23 mm^2 (73,73%), 73.36 ± 21.37 mm^2 (74.85%) and 98 mm^2 (100%), 81.46 ± 9.80 mm^2 (83.12%), 83.36 ± 13.19 mm^2 (85,06%), 82.67 ± 7.92 mm^2 (84.30%), respectively. In our study, intra-group sequential measurements showed statistically significant differences ($p<0.05$) in every time point compared to baseline, compatible with the previous studies in the literature as expected (4, 6, 44, 100-120, 129). Inter-group comparisons showed no statistically significant differences in terms of dimensional parameters of total graft surface area ($p>0.05$). Similarly, Barbosa et al. (109) reported that there was no statistically significant difference regarding percentages between cyanoacrylate tissue adhesives and sutures at any time point ($p>0.05$). In their study, comparisons were made on the measurements performed by a periodontal probe at baseline, on days 15, 30, 45, 90 and results were detected as (70.9% vs 67.4%), (60.9% vs 59.0%), (54.5% vs 57.1%) and (54.5% vs 57.1%) in cyanoacrylate and suture groups, respectively. AlJasser et al. (116) revealed no statistically significant differences in their split-mouth study in terms of total graft surface area difference as shrinkage ($p<0.05$). Shrinkage was reported at days 15, 30, 60, 90, 120 as 0%, 12.5%, 20.8%, 30.5%, 36% and 0%, 25%, 25%, 26.5%, 28% in test and control groups, respectively. On the other hand, Gümüş et al. (118) compared cyanoacrylate and conventional suture groups at baseline, 1, 3, 6-months intervals and reported total graft surface area results as 45.83 ± 8.76 mm^2 (100%), 41.71 ± 8.76 mm^2 (89.80%), 39.18 ± 9.02 mm^2 (84.80%), 37.57 ± 8.56

mm^2 (81.47%) and 45.38 ± 11.38 mm^2 (100%), 34.87 ± 7.26 mm^2 (76.84%), 32.81 ± 7.56 mm^2 (73.28%), 30.28 ± 7.28 mm^2 (67.50%) in cyanoacrylate and conventional suture groups, respectively. In contrast to our study, their cyanoacrylate group showed significantly less shrinkage than the control ($p<0.05$). Barbosa et al. (109) and our studies revealed parallel findings of no significant differences at any time points between the two groups, summarized as 54% vs 26% in the cyanoacrylate group and 57% vs 16% in the conventional suture groups, respectively. However, simple sutures were used in our study to stabilize the graft whereas Barbosa et al. (109) used mucoperiosteal sling sutures which were claimed to be less traumatic to the transplanted tissue. Moreover, a software program was used to assess the total graft surface area in our study as well as the intra subject calibration for the investigator who determines the graft borders before conducting software analysis, while Barbosa et al. (109) used only a periodontal probe for two dimensional assessment. The differences in percentages may further be due to our procedural special care before, during and after the FGG operation to eliminate the other possible factors enabling the shrinkage amounts. AlJasser et al. (116) also used a periodontal probe to assess graft dimensions. FGG shrinkage is expected to mostly occur during the postoperative 1 month (110)(129)(24); however, AlJasser et al. (116) stated a shrinkage percentage of 0% at day 15 for both groups complicating their results and assessment technique that were contrary to the literature. Gümüş et al. (118) reported a statistically significant result in favor of the test group, which is inconsistent with the findings of our study. This discrepancy may be due to many technical and methodological factors, such as the obvious differences in the determination of graft borders without calibration directly reflected to the evaluation of the software results, the long/short duration of the operation time reflected to the shrinkage amounts as well as the sample size. In our study when the patient-based data was further investigated, the presence of an exceptionally greater shrinkage (≈80%) in 2 of the patients in the test group may be reflected to the higher mean percent changes of the total graft surface area compared to the controls, which is certainly a matter of sample size limitation.

Vertical graft height was also evaluated besides total graft surface area taken as the primary outcome in this study due to its direct reflection to the total KT gain which is the most important clinical end point of the FGG surgery. Given the dimensional changes that occurred in vertical graft height assessed digitally on the standardized photographs, values of test and control groups were recorded at baseline, 1, 3 and 6 months as 8 mm (100%), 6.19 ± 0.90 mm (77.37%), 6.17 ± 1.04 mm (77.12%), 5.91 ± 0.94 mm (73.80%)

and 8 mm (100%), 6.23 ± 0.55 mm (77.87%), 6.26 ± 0.61 mm (78.25%), 6.51 ± 0.60 mm (81.37%), respectively. In the vertical graft height, the parameters for both groups through the measurement times of baseline, 1st, 3rd, and 6th months revealed a statistically significant reduction ($p<0.05$). The inter-group comparison of the vertical graft height at the sequential measurement time points revealed no statistical difference ($p>0.05$). Although there was no statistically significant difference, the change was found in favor of the control group measured as 18.63% vs 26.2% reduction in the test group. Barbosa et al. (109) also evaluated the vertical graft height parameter at day 0, 15, 30, 45 and 90 as 6.5 ± 0.6 mm, 5.0 ± 0.9 mm, 4.4 ± 0.9 mm, 4.1 ± 1.0 mm, 4.1 ± 1.0 mm and 6.3 ± 0.9 mm, 4.3 ± 0.6 mm, 3.9 ± 0.7 mm, 3.7 ± 0.6 mm, 3.7 ± 0.6 mm in the test and control groups (36.93% vs 41.30), respectively. These findings revealed no statistically significant difference regarding inter-group changes at any time point, while intra-group comparisons showed a statistically significant difference at every time point compared to baseline ($p<0.05$). We should note that there was no evaluation for the VH changes in the study by Gümüş et al. (118).

Evaluation of the patient-based VAS scores for postoperative pain and discomfort did not show statistically significant differences between the groups at any measurement time points. The mean VAS values of day 0 to day 6 were detected as 4.00 ± 2.89, 2.45 ± 2.62, 2.27 ± 2.53, 1.09 ± 1.57, 1.00 ± 1.54, 0.72 ± 1.34, 0.18 ± 0.60 and 5.00 ± 2.09, 4.54 ± 2.06, 2.72 ± 1.19, 2.18 ± 1.72, 1.81 ± 1.40, 1.00 ± 1.94, 0.54 ± 0.93 in test and control groups, respectively ($p>0.05$). Gümüş et al. (118) also evaluated the VAS parameter in their study and the test group showed statistically significantly better results during the first five days ($p<0.05$). In their study, researchers applied periodontal dressing on the surgical area after the operation in both groups. On the other hand, AlJasser et al. (116) also reported statistically better results in favor of the test group regarding VAS parameters on postoperative discomfort. In their study, there was a statistically significant difference between days two and six in favor of the test group ($p<0.05$). In our study, there was no significant differences between the patient perception. VAS parameter for discomfort is a patient-related variable related to the differences in individual perception as well as in analgesic and antibiotic administration leading to controversial results between the available studies (116, 118). Leaving the preference of analgesic consumption to the patient as in Gümüş et al. study (118), will certainly jeopardize the VAS score evaluation for patient perception. No analgesics and antibiotics were used in

our study to obtain a more reliable comparison between the groups.

Given the operative time parameters, the control group requiring sutures had significantly higher duration than the test group as expected ($p<0.05$). The operation time parameter was detected as 20.23 ± 2.08 min and 26.15 ± 5.21 min for the test and control groups, respectively. Similarly, Gümüş et al. (118) reported the operative time as 26.87 ± 2.13 min and 37.33 ± 2.13 min in the test and control groups, respectively ($p<0.05$) and the test group ended up with less graft shrinkage. The consistent findings obtained in both studies confirm the information in the previous studies in the literature that the use of cyanoacrylate naturally shortens the operative time (154, 155, 168, 169, 174)

Within the limits of this study, performed with great care for the elimination of documented factors effecting the graft shrinkage to single out the effects of two stabilization techniques, butyl-cyanoacrylate tissue adhesives may be considered as an alternative to conventional suturing for stabilization of the FGGs based on the current findings of similar dimensional changes and clinical improvements in both approaches.

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7. APPENDICES

T.C. YEDİTEPE ÜNİVERSİTESİ	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.

TANIMLAMA

Araştırmanın Adı / Protokol numarası

Keratinize doku yetersizliğinde uygulanan serbest dişeti greftlerinde cyanoacrilate kullanımının greft başarısına etkisi

Araştırma Konusu

Alt çene ön bölgede bulunan keratinize doku yetersizliklerinin serbest dişeti greftleri ile tedavisinde verici bölgeden alınan dokunun alıcı bölgeye dikiş veya cyanoacrilate denilen doku adezivi ile stabilize edilmesinin greftin başarısına etkisi

Araştırmaya Katılımcı Sayısı

40

Bu araştırmanın

Amacı

Keratinize doku yetersizliğinin tedavisinde kullanılan 'Serbest Dişeti Grefti' protokolünde cyanoacrilate denilen doku yapıştırıcılarının dikiş uygulamasıyla yapılan klasik yönteme göre faydalarını değerlendirmek

Süresi

6 ay

İzlenecek Yöntem / Yöntemler

Hastalara kendi ağızlarında Modifiye Bass fırçalama yöntemi, diş ipi ve/veya arayüz fırçası kullanımı anlatılacaktır. Günde 2 kez dişlerini bu tekniğe göre fırçalamaları ve fırçalamayı takiben arayüz temizliği yapmaları istenecektir.

Ağız içi fotoğrafları çekilecektir. Tüm ağızdan klinik ölçümler alınacaktır. İzlenecek cerrahi protokol öncesi ağız sağlığını sağlamak için Başlangıç Periodontal tedavi uygulanacaktır. 1 hafta sonra kontrole çağırılacak ve yeterli düzeyde ağız hijyenini sağlayabilen hastalar çalışmaya dahil edilecektir.

Klinik ölçümleri yapılan her iki gruptaki hastalar ameliyattan önce greft genişliğinin stabilizasyonunun sağlanması için üst çeneye hazırlanacak olan içerisine 0.7 cm çapında ortodontik tel yerleştirilmiş SX dişli plak yapılacaktır. İzlenecek cerrahi protokol kapalı zarf tekniğine göre yapılacak olup ameliyat günü belirlenecektir ve hastalar 20 kişilik 2 gruba ayrılacaktır. Test grubunda damaktan elde edilen keratinize dişeti doku yapıştırıcısıyla stabilize edilirken, kontrol grubunda geleneksel yöntem olan dikiş ile stabilizasyon sağlanacaktır.

Araştırma Sonunda Beklenen Fayda

Keratinize doku miktarında artış

Alternatif Tedavi Veya Girişimler
Hayvansal kaynaklı materyal ile keratinize doku elde edilmesi

Araştırma Sırasında Karşılaşılabilecek;

Riskleri	*Rahatsızlıklar*
a) Greft başarısızlığı	a) Operasyon sonrası ağrı
b)	b) Kanama
c)	c)
d)	d)
e)	e)
f)	f)
g)	g)

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

Aşağıdaki özel durumlara ait katılımcı var mı?

	EVET*	HAYIR
Çocuk		
Mahkum		
Gebe		
Mental yetersizlik		
Sosyoekonomik eğitim olarak yetersiz		

*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.

ONAM (RIZA)

T.C. YEDİTEPE ÜNİVERSİTESİ	KLİNİK ARAŞTIRMALAR ETİK KURULU BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

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.

Söz konusu araştırmaya, hiçbir baskı ve zorlama olmaksızın kendi rızamla katılmayı kabul ediyorum.
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 bilgiler

Bilgilendirilmiş Gönüllü Onam Formu asgari olarak yukarıda belirtilen başlıkları içermelidir.

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15- 1821 **30/01/2020**
Konu: Klinik Araştırmalar
Etik kurul Başvurusu hk.

İlgili Makama (Kübra Burcu)

Yeditepe Üniversitesi Diş Hekimliği Fakültesi Prof. Dr. Bahar Ezen Kuru'nun sorumlu araştırmacı olduğu **"Serbest Dişeti Greftlerinde Cyanoacrylate Kullanımının Greft Başarısına Etkisi"** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası **(1807)** kayıt Numaralı KAEK Başvuru Dosyası, Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **29.01.2020** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isimi belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir (**KAEK Karar No: 1162**).

Prof. Dr. Turgay ÇELİK

Yeditepe Üniversitesi
Klinik Araştırmalar Etik Kurulu Başkanı

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

NORMAL

Sayı : 68869993-511.06-E.62839 10.03.2020
Konu : 2019-215(Onay)

Sayın Prof. Dr. Bahar EREN KURU

İlgi : 04.03.2020 tarihli ve E.119481 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	Serbest Dişeti Greftlerinde Cyanoacrylate Kullanımının Greft Başarısına 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: 2,0
BGOF tarihi / versiyon no	29.01.2020 V: 2,0
ORF tarihi / versiyon no	29.01.2020 V: 2,0
Araştırma Broşürü tarihi / versiyon no	-
Proje Yürütücüsü	-

Bu kapsamda yukarıda ayrıntıları verilen çalışma ile ilgili olarak;

- Araştırmanın başlamaması, iptali veya sonlandırılması halinde tarafımıza bilgi verilmesi,
- Araştırma süresince ortaya çıkan advers olayların/etkilerin tarafımıza bildirilmesi,

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

- 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

Araştırmanın Açık Adı	**"Serbest Dişeti Greftlerinde Cyanoacrylate Kullanımının Greft Başarısına 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 BÜTÇESİ	29.01.2020	2	Türkçe ☒ İngilizce ☐ Diğer ☐
	İŞ AKIŞ ŞEMASI	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	☒	
KARAR BİLGİLERİ	**Karar No:1162**	**Tarih: 29.01.2020**	

Yukarıda bilgileri verilen **"Serbest Dişeti Greftlerinde Cyanoac ullanımının Greft Başarısına Etkisi"** klinik araştırmanın başvuru dosyası ile ilgili belgeler aras ın /çalışmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş ve uygun b anuş olup araştırmanın/çalışmanın başvuru dosyasında belirtilen merkezlerde gerçekleştirilmesin 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

14.02.2020
ASLI GELDİR

Prof. Dr. Tu C İK
Yeditepe Ü i KAEK Başkanı

Araştırmanın Açık Adı	**"Serbest Dişeti Greftlerinde Cyanoacrylate Kullanımının Greft Başarısına 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 İlişki		Katılım *	
Prof. Dr. Turgay Çelik (Etik Kurul Başkanı)	Tıbbi Farmakoloji	Y.Ü. Eczacılık Fakültesi	E☒	K☐	E☐	H☒	E☒	H☐
Prof. Dr. Funda 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 Ekşi	Genel Cerrahi	Y.Ü. Tıp Fakültesi	E☒	K☐	E☐	H☐	E☐	H☐
Buket Dirgan	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. Azize 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. Funda Kartufan	Anestezyoloji ve Reanimasyon	Y.Ü. Tıp Fakültesi	E☐	K☒	E☐	H☐	E☐	H☐

*:Toplantıda Bulunma

ASLI GİBİDİR

Prof. Dr. T[illegible]ay ÇELİK
Yeditepe [illegible]iversitesi KAEK Başkanı

Araştırmanın Açık Adı	"Serbest Dişeti Greftlerinde Cyanoacrylate Kullanımının Greft Başarısına Etkisi "
VARSA ARAŞTIRMANIN PROTOKOL KODU	

ETİK KURUL BİLGİLERİ	ETİK KURULUN ADI	Yeditepe Üniversitesi KAEK (2012-KAEK-70)
	AÇIK ADRESİ:	
	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 ☐

14.02.2012 ASLI GİBİDİR

Prof. Dr. Turgay Ç[illegible]
Yeditepe Üniver[illegible]si KAEK Başkanı

YEDİTEPE ÜNİVERSİTESİ

PERİODONTOLOJİ ANABİLİM DALI HASTA KARTI

Hastanın Adı Soyadı:..... Cinsiyeti:..... Doğum Tarihi: ...../...../.....
Meslek: .....Tel:..... Kayıt Tarihi: ...../...../.....
☐ Başlangıç ölçümü ☐Yeniden değerlendirme ☐ Recall Hekimi:.....

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 ☐Yemek yerken ☐Kendiliğinden ☐Yok
Dentin Hassasiyeti	☐Var ☐ Soğuk ☐ Ekşi ☐ Tatlı ☐ Sıcak ☐ Dokununca ya da fırçalamada (Değeri VAS skalasına göre 1-10) : ..... ☐Yok
Dişetinde iltihabi şekil bozukluğu	☐Ödemli ☐Fibrotik ☐Ödemli + Fibrotik
Mukogingival problem	☐Var ☐Sığ vestibül ☐Yetersiz yapışık dişeti ☐Keratinize dişeti ☐Dişeti çekilmesi ☐Yok
Dişeti çekilmesi	☐Generalize ☐Lokalize Diş no:..... Nedeni: ☐Travmatik ☐Periodontitis ☐Yaşlanma
Ağız kokusu/ Kötü tat hissi	☐Var ☐Yok
Dişlerde yer değiştirme	☐Var, Diş no:..... ☐Yok
Dişlerde sallantı	☐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 aralıklılarla sigara kullanan (adet/gün, hafta, ay) ☐≤ 5adet/..... ☐≤ 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 ilaçlar ve süresi	
Allede genel hastalıklar	
Allede 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 PLANı:

PERT.P.038-F.01Rev 0,27.9.2016

YEDİTEPE ÜNİVERSİTESİ

PERİODONTOLOJİ ANABİLİM DALI ÖLÇÜM KARTI

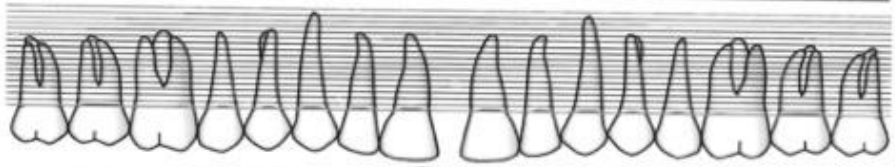
Hastanın Adı Soyadı: ..... Cinsiyeti: ..... Doğum Tarihi: ...../...../.....

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

☐ Başlangıç Ölçümü ☐ Yeniden değerlendirme ☐ Recall Hekimi: .....

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

BUKKAL



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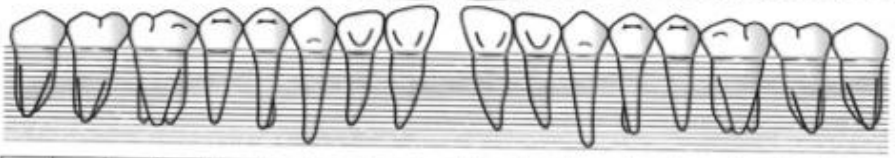
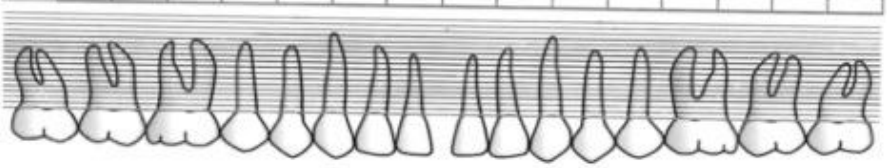


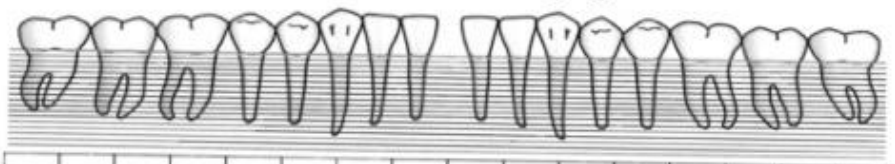
	18	17	16	15	14	13	17	12	11	21	22	23	24	25	26	27	28
Plak İndeksi (PI)																	
Gingival İndeks (GI)																	
Gingival marjin																	
Cep Derinliği																	
ındalamada kanama (SK)																	
Furkasyon																	

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

BUKKAL



LİNGUAL



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

ORTALAMA SONDALAMA DERİNLİĞİ: ..... mm. ORTALAMA KLİNİK ATAŞMAN SEVİYESİ: ..... mm. ORTALAMA PI: ..... ORTALAMA GI: ..... % SONDALAMADA KANAM

PERT.P.08-F.01Rev 0.27.9.2016

8. CURRICULUM VITAE

Personal Informations

First Name	Kübra	**Last Name**	Burcu Yıldırım
Birth Place	[redacted]	**Date of Birth**	[redacted]
Nation	[redacted]	**Identity Number**	[redacted]
E-mail Address	[redacted]	**Phone Number**	[redacted]

Educational Background

Degree	**Science**	**Name of the Foundation**	**Graduation Year**
Doctorate	Periodontology	**Yeditepe University**	2022
Post Graduate			
License	Dentistry	**İstanbul University**	2015
High School	-	Pertevniyal High School	2010

Foreign Languages	**The Point of Foreign Language**
English	88 (YDS)

#If there are exams (KPDS, ÜDS, TOEFL; EELTS etc) that are achieved more than one, all results should be written.

Business Experience (Rank back to past)

Duty	Foundation	**Duration (Year - Year)**

Computer Knowledge

Program	**Using Ability**
Excell Program	Very well
Word Program	Very well

***Evaluate as very well, well, in-between, weak.**