PLATELET-RICH FIBRIN TO PRESERVE ALVEOLAR BONE SOCKETS FOLLOWING TOOTH EXTRACTION; A RANDOMIZED CONTROLLED TRIAL

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MASTER OF SCIENCE

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GRADUATE SCHOOL

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THIS THESIS HAS BEEN APPROVED TO BE A PARTIAL FULFILLMENT
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MASTER OF SCIENCE
IN DENTISTRY

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Kanokporn Areewong

หัวข้อวิทยานิพนธ์	ผลของเพลทเลทริชไฟบรินต่อการสร้างกระดูกใหม่ในเบ้าฟันภายหลังถอนฟัน การทดลองแบบสุ่มในคลินิก	
ผู้เขียน	นางสาวกนกพร อารีวงศ์	
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บทคัดย่อ

บทนำ ภายหลังการถอนฟันกระดูกเบ้าฟันจะมีการเปลี่ยนแปลงขนาดและรูปร่างอยู่เสมอ การละลายของกระดูกเบ้าฟันจะเกิดขึ้นอย่างรวดเร็วในช่วง 8 สัปดาห์แรกภายหลังการถอนฟัน ปริมาณการละลายของกระดูกเบ้าฟันอยู่ที่ประมาณร้อยละ 50 ทั้งในแนวความกว้างและความสูง ซึ่ง 2 ใน 3 ของการละลายทั้งหมดจะเกิดขึ้นภายใน 3 เดือนแรกภายหลังการถอนฟัน

จากการศึกษาในปัจจุบันพบว่าการทำการอนุรักษ์กระดูกเบ้าฟันภายหลังการถอนฟันช่วยลดการละลายตัวของจากการศึกษาในปัจจุบันพบว่าการทำการอนุรักษ์กระดูกเบ้าฟันภายหลังการถอนฟันช่วยลดการละลายตัวของกระดูกเบ้าฟัน ทำให้คงสภาพของสันกระดูกเดิมได้มากกว่าเมื่อเทียบกับกลุ่มที่ไม่ได้รับการอนุรักษ์กระดูกเบ้าฟัน ซึ่งประโยชน์ที่ตามมาคือ ทำให้มีกระดูกเพียงพอในการฝังรากเทียม รับแรงจากฟันเทียม ลดการเปลี่ยนแปลงรูปร่างของใบหน้า และลดความจำเป็นในการปลูกกระดูกสันเหงือกในภายหลัง การอนุรักษ์เบ้าฟันสามารถทำได้หลายวิธี และมีวัสดุหลากหลายในการนำมาเติมในแผลถอนฟัน ทั้งกระดูกจากตัวเอง จากสิ่งมีชีวิตอื่น หรือวัสดุสังเคราะห์ อย่างไรก็ตามขั้นตอนการทำยังคงยุ่งยากซับซ้อน และมีค่าใช้จ่ายสูง ทำให้ไม่สามารถใช้ได้อย่างแพร่หลายในคนทั่วไป

เพลทเลทริชไฟบริน (Platelet-Rich Fibrin, PRF) มีกรรมวิธีการผลิตที่ง่าย มีต้นทุนการผลิตต่ำ สามารถสกัดได้จากเลือดของผู้ป่วยเอง โดยนำมาปั่นที่ความเร็วต่ำ และนำมาใช้ได้ทันทีโดยที่ไม่ต้องมีการเติมสารต้านการแข็งตัวของเลือด (Anticoagulant) ใด ๆ ซึ่งในเพลทเลทริชไฟบรินประกอบไปด้วย growth factor ต่าง ๆ ที่เป็นประโยชน์ต่อการเจริญเติบโตของเนื้อเยื่อ ทั้งนี้มีการศึกษาการนำเพลทเลทริชไฟบรินมาใช้ในการอนุรักษ์เบ้าฟัน พบว่าส่งผลดีต่อการหายของแผล ช่วยลดอาการปวด และ

อาการแทรกซ้อนหลังถอนฟันได้ แต่ยังไม่มีหลักฐานแน่ชัดที่แสดงถึงการละลายของกระดูกที่ลดลงหรือช่วยในกระบวนการสร้างของกระดูก อาจเนื่องมาจากจำนวนตัวอย่างน้อย และระยะเวลาติดตามผลสั้นเกินไป

ดังนั้นงานวิจัยนี้จึงมีจุดประสงค์ที่จะศึกษาเพิ่มเติมถึงผลของการใช้เพลทเลทริชไฟบรินในการอนุรักษ์เบ้าฟัน โดยเน้นในผลแง่ของการสร้างกระดูกใหม่ในเบ้าฟัน

วัสดุอุปกรณ์และวิธีการ การศึกษานี้ผู้ทำการศึกษาเปรียบเทียบปริมาณการสร้างกระดูกใหม่ในกระดูกเบ้าฟันภายหลังถอนฟันด้วยวิธีการอนุรักษ์กระดูกขากรรไกรโดยใช้เพลทเลทริชไฟบรินเปรียบเทียบกับการปล่อยให้เกิดการหายของแผลเองตามธรรมชาติ โดยจะมีการเก็บตัวอย่างกระดูกภายหลังจากถอนฟันนาน 8 สัปดาห์ไปตรวจประเมินทางอนุกายวิภาคศาสตร์เพื่อประเมินปริมาณกระดูกที่ถูกสร้างขึ้นใหม่โดยใช้โปรแกรม FIJI

ผลการศึกษา มีผู้เข้าร่วมการศึกษานี้ทั้งหมด 33 คน โดยคิดเป็นฟันในกระดูกเบ้าฟันทั้งหมด 36 ซี่ กระดูกที่ถูกสร้างขึ้นใหม่ในเบ้าฟันและมีปริมาณเพียงพอให้เก็บไปทำการวิเคราะห์มีทั้งหมด 28 ซี่ กระดูกเบ้าฟันที่เหลืออีก 8 ซี่ ไม่สามารถเก็บตัวอย่างกระดูกไปศึกษาได้เนื่องจากการสร้างกระดูกที่บริเวณส่วนกลางของกระดูกเบ้าฟันยังไม่เพียงพอ อัตราส่วนของกระดูกที่ถูกสร้างขึ้นใหม่ต่อพื้นที่ทั้งหมดในกลุ่ม PRF คือ 31.33 ± 18 ในกลุ่มควบคุมคือ 26.33 ± 19.63 ในแต่ละกลุ่มจะมีการวิเคราะห์อัตราส่วนกระดูกที่ถูกสร้างขึ้นใหม่ต่อพื้นที่ทั้งหมดเปรียบเทียบระหว่างเพศของผู้เข้าร่วมการศึกษา กลุ่ม PRF อัตราการสร้างกระดูกใหม่ต่อพื้นที่ทั้งหมดในเพศชายคือ 28.84 ± 20.41 ในเพศหญิงคือ 33.82 ± 16.05 กลุ่มควบคุมอัตราส่วนกระดูกที่ถูกสร้างขึ้นใหม่เปรียบเทียบกับพื้นที่ทั้งหมดในเพศชายคือ 28.71 ± 23.88 ในเพศหญิงคือ 33.82 ± 16.55 เมื่อวิเคราะห์ข้อมูลด้วยโปรแกรม SPSS โดยใช้สถิติ independent sample T-test พบว่าอัตราการสร้างกระดูกใหม่ในเบ้าฟันในกลุ่ม PRF ไม่แตกต่างจากกลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($P = 0.431$) เปรียบเทียบระหว่างเพศชายและหญิงในกลุ่ม PRF และกลุ่มควบคุมก็ไม่พบความแตกต่างทางสถิติอย่างมีนัยสำคัญเช่นกัน (ในกลุ่ม PRF $P = 0.573$, ในกลุ่มควบคุม $P = 0.728$)

สรุปผลการศึกษา ด้วยข้อจำกัดในการศึกษาพบว่าการอนุรักษ์กระดูกเบ้าฟันด้วย PRF ไม่สามารถกระตุ้นให้เกิดการสร้างกระดูกใหม่ในอัตราที่แตกต่างจากการปล่อยให้แผลหายเองตามธรรมชาติได้อย่างมีนัยสำคัญทางสถิติ

Thesis Title	Platelet-rich Fibrin to Preserve Alveolar Bone Sockets Following Tooth Extraction; a Randomized Controlled Trial	
Author	Miss Kanokporn Areewong	
Degree	Master of Science (Dentistry)	
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ABSTRACT

Objectives: Alveolar socket preservation is performed immediately after tooth extraction. The aim of the procedure is to maintain alveolar ridge architecture to almost the same dimension as before the extraction. Platelet-rich fibrin (PRF) is an autogenous graft which can be used in soft tissue regeneration; this graft is user-friendly and inexpensive. However, the hard-tissue-regeneration property of PRF in alveolar socket preservation is still unclear. The purpose of this study was to compare the new bone formation ratio between using PRF as a socket preservation material and normal wound healing, by means of histomorphometric analysis.

Materials and methods: Thirty-six healthy volunteers with single-rooted teeth which need to be extracted and who were planned for dental implant placement were recruited. Minimally traumatic extractions were performed on all of the patients. Eighteen patients were treated with alveolar socket preservation using platelet rich fibrin, while the rest were left to heal naturally. Bone specimens were harvested from the central part of the former alveolar socket two months after the extraction process. Histomorphometric analysis of the area of new bone formation compared with total socket area was performed using FIJI software.

Results: Thirty-three volunteers (a total of 36 alveolar bone sockets) participated in this study. Twenty-eight bone specimens were collected; no new bone formation was found at the central part of the other eight alveolar bone sockets. The new bone formation

ratio was 31.33±18 in the PRF group and 26.33±19.63 in the control group. In each group, the new bone formation ratio was calculated separately for each sex. In the PRF group, the new bone formation ratio was 28.84±20.41 in males and 33.82±16.05 in females. In the control group, the new bone formation ratio was 28.71±23.88 and 25.14±18.21, in maless and females, respectively. There was no statistically significant difference in the new bone formation ratio either between the PRF and control groups (P = 0.431) or between the sexes in each group (P = 0.573 in the PRF group, P = 0.728 in the control group).

Conclusions: It may be concluded that the use of PRF in alveolar socket preservation does not enhance new bone formation after tooth extraction compared to normal wound healing.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

Introduction

1.1 Principles, Theories and Rationales

Major changes occur suddenly in alveolar bone following the tooth extraction process, especially in the first eight weeks of the healing process. [1] Almost half of the bone width is resorbed and some vertical dimension is also lost. Sixty-six per cent of the total resorption takes place in the first three months of healing.

One benefit of socket preservation is minimization of the loss of alveolar ridge volume after tooth extraction. [2] Another benefit is improved esthetics and function. Socket preservation provides bone volume, which enhances implant stability, maintains the contour of the alveolar ridge almost the same as before the tooth extraction and reduces the need for alveolar bone grafting procedures later. This procedure involves placing some biological material, such as autogenous bone, xenograft or synthetic biomaterial, into the alveolar socket. However, the process requires surgical skill, and the biomaterials involved are expensive.

Platelet-rich fibrin (PRF) was introduced in the 2000s; the fibrin provides a three-dimensional scaffold, which is rich in platelets, plasma proteins, and leukocytes involved in the healing and tissue regeneration processes. [4] PRF can be simply fabricated by collection of the patient's blood, which is then centrifuged at low velocity to separate the red blood cell portion without using any anti-coagulant agent. [3] PRF is rich in many important growth factors, promoting a wound-healing cascade. [4, 5, 6, 7] Its potential for bone remodeling or bone formation has not yet been adequately explored.

1.2 Purposes of this study

To compare new bone formation ratio between using PRF as a socket preservation material and normal wound healing using histomorphometric analysis.

1.3 Research question

Does PRF enhance new bone formation in socket preservation procedure after tooth extraction compared to normal wound healing of alveolar ridge?

1.4 Anticipated benefits

The benefits of human post-extraction socket preservation using of platelet-rich fibrin is resulting in significantly less vertical and horizontal contraction of the alveolar bone crest. This provide maximize ridge dimensions for the fabrication of a fixed, removable prosthesis and placement of a dental implant, esthetic obtaining, phonetic and functional outcomes.

1.5 Hypothesis

Null hypothesis:

There is no significant difference of new bone formation in socket preservation procedure with PRF after tooth extraction compared to conventional wound healing of alveolar ridge.

CHAPTER 2

Literature review

This literature review is divided into four parts as follows:

2.1 Wound healing

2.2 Platelets and its growth factors

2.3 Platelet-rich fibrin

2.4 Alveolar ridge preservation

2.1 Wound healing

Wound healing process consists of 4 important phases: hemostasis phase, inflammatory phase, proliferative phase, and remodeling phase, respectively. The process starts with the hemostasis phase or blood clotting phase to inhibit blood lost. After tissue damage followed loss by inflammatory phase. Various inflammatory cells migrate to the injury site to eliminate foreign bodies and micro-organisms around the wound area. Simultaneously, the cells also release cytokines to promote tissue reconstruction and angiogenesis. The proliferative phase is starting with repairing damaged tissue by fibroblasts and epithelial cells, newly formed capillary and granulation tissue will appear and gradually turn into matured tissue. [1, 2]

Protein molecules that play important roles in wound healing are often secreted from surrounding cells. Some molecules are floating in the bloodstream. Platelets, protein molecule secretory unit, are the starter of healing process, they are the first unit approaching the wound and activating clot formation cascade. [2]

Once tissue damage occurs, the endothelial cell will trigger platelets together with collagens to form platelet plug, afterwards, the bleeding is stopped followed by the beginning of damaged tissues healing. Later, platelets are activated, platelet's granules release several potential molecules such as platelet-derived growth factor (PDGFs), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF),

insulin-like growth factor (IGFs) and epidermal growth factor (EGF) to promote other stem cells and chemokines to the site of injury and repair damaged tissue. [1]

2.2 Platelets and its growth factors

Each phase of healing involves platelet's chemokines. These proteins help the healing proceeding smoothly. As mentioned previously, PDGF, which are released from alpha granules of platelets, this molecule regulates the functions of various cells, including fibroblast, inflammatory cells, smooth muscle cells, as well as causing contraction of the wound in the final stage. PDGF is very important for the soft tissue healing process. [3]

TGF-β is secreted from many sources, such as macrophages, platelets, and fibroblasts. It is responsible for all phases of healing, it stimulates cells migration, cell function and extracellular matrix production. Collagen and fibronectin are leading to the creation of granulation tissue and capillaries. [2]

VEGF secreted from platelets triggers coagulation process by activation of the function of Von Willebrand Factor which is including platelets adhesion, promoting vasodilation, induction and increasing vascular permeability in order to enhance cell migration to the wound. In addition, VEGF is the main controller of angiogenesis in wound healing proliferative phase. Capillaries will be formed at third day of wound healing.

IGFs is important to the cell cycle. It controls normal cell growth and cell maturation. Particularly, osteoblast are mainly stimulated by this chemokine. Furthermore, the releasing of IGFs are upon the level of growth hormone which has an influence in osteogenesis. PDGFs and EGFs, regulated by IGFs, deal with cellular proliferation in the healing event. [4]

EGFs control the signaling cascade in DNA synthesis and cellular proliferation such as protein kinase C and phosphorylation process. [5] Growth factors concentration is influential to the wound healing, the higher concentration the faster rate of healing. [2, 6, 7]

2.3 Platelet-rich fibrin

In 1997, Whitman and co-worker introduced Platelet gel or autogenous fibrin glue, which is the first generation of platelet concentrate. [8] It is a derivative product of platelet rich plasma (PRP), which combines with thrombin and calcium chloride. Importantly, Platelet gel has higher platelet concentration over 300 times than in normal condition. [9, 10]

Formulation of platelet concentrate bases on blood components density, thus, two centrifugation speeds were set differently. [11] First spin, this procedure proposes to isolate blood into platelet-poor plasma layer, platelet concentrated layer and red blood cells layer, orderly. In addition, coagulation cascade was inhibited by using anticoagulant agent. Second spin, centrifugation speed is decreased, platelets were then separated from the rest compartment. [8, 12] Thereafter, thrombin and Calcium Chloride, the coagulant agents, are added to activate the fibrin gel formation and platelets degranulation.

According to platelet properties mentioned above, Platelet growth factors are released to boost the healing process. [8] Clinically, Platelet concentrated applications are available in many treatment procedure such as hemostasis, thrombocytopenia treatment, chemotherapy and post-operative bleeding. [11]

Platelet-rich fibrin (PRF), the second generation of platelet concentration, was proposed by Choukroun. [13] (Fig. 1) Briefly, PRF manipulation, following protocol of the creator team, begins with at least 10 ml of blood collection which is immediately stored in glass tube. Afterwards, centrifugation process proceeds with 400 gram forces for at least 10 minutes. As a result, blood sample is segregated into 3 layers, poor cellular plasma which is at the most superficial part, the yellowish fibrin clot in the middle part of the tube, and red corpuscle at the bottom.

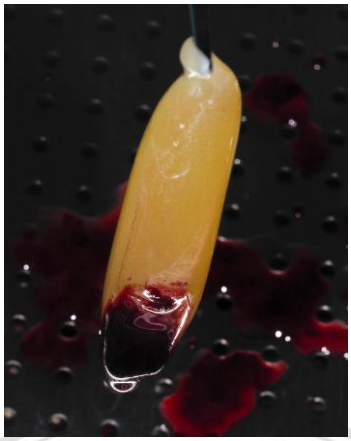


Figure 2.1 Platelet-rich Fibrin

Moreover, when blood is exposed to the glass surface, coagulation process of PRF is provoked instantly against the PRP. Fibrinogen turns into fibrin bulk. Platelet growth factors are released and trapped in the 3-dimensional fibrin network. This feature makes PRF a strong fibrin clot which gradually releases growth factors for a longer time than PRP. [14]

According to platelet characteristics, platelets are fountain for wound healing cytokines. Many studies suggested that PRF has efficacy in hard and soft tissue regeneration. [12, 15-17] Hence, PRF is introduced in many parts of dental treatment especially in surgical field. It has been used as a hemostatic agent and surgical adhesive for graft materials. [18]

Marx and co-worker observed facility of platelet concentrate as the supplement in bone graft. They concluded that platelet concentrate gives better result than in control group, significantly. In addition, another study claimed that growth factors in platelet concentrate speed up rate of bone formation and bone mineralization in first 6 months. [10]

Recently, Kim and co-worker cultured osteoblast with PRF. The activity of the cells was measured. The result showed progression of rate of osteoblast DNA synthesis and alkaline phosphatase activity. Authors concluded that the utility of PRF improves bone regenerative capacity. [19]

2.4 Alveolar ridge preservation

Currently, in implant dentistry, the obstacle in treatment is bony insufficiency for excellent dental implant position. Alveolar bone is formed to support tooth structures. Whenever tooth extraction procedure happens, bone remodeling begins to support new circumscribed condition. In accordance with the systematical review of Tan and co-workers in 2012, ridge resorption pattern is more prone to horizontal than to vertical dimension. [20]

Mean bone reduction in horizontal dimension after tooth loss after 6 months is 3.79±0.23 mm. (29 to 63 percentage), whilst vertical dimensional reduction is 1.24±0.11 mm, in buccal 0.84±0.62 mm, in lingual (11 to 22 percentage). Especially in the aesthetic restoration of dentistry, bone resorption in anterior teeth a serious problem. Consequently, there are many attempts to solve bone insufficient issue, thus alveolar ridge preservation was introduced.

Alveolar ridge preservation (ARP) is an attempt to counteract bone resorption process. The ARP concept is distinguished into 3 categories: preservation of soft tissue, preservation of hard tissue, preservation in both hard and soft tissue. [21]

A number of experts introduce various ARP techniques. The technique decision depends on severity of tissue lost. When only soft tissue preservation is required then the autogenous tissue graft is used. On the other hand, if hard tissue preservation is needed, bone-substitute materials protected with a membrane and primary closure are indicated. Lastly, combination of autogenous soft-tissue grafts and bone-substitute materials are recommended in both hard and soft tissue preservation. ARP simplifies dental implant treatment by reduction of dimensional changes in alveolar ridge and promotes new bone formation. [22, 23]

PRF's growth factors are the stimulating key for soft and hard tissue regeneration. [19] Besides using as supplement for other augmentation materials, PRF is used as a sole bone-substitute material in maxillary sinus floor elevation.

Mazor and co-workers [24] have shown radiographic analysis results which demonstrated dense bone-like tissue in the sinus after 6 months of healing, together with bone biopsies exhibited well-orderly arranged bone architecture.

Many studies observed roles of PRF in ARP, the systematic review and meta-analysis of Del Fabbro and Co-workers in 2017 [25] reported only one study evaluated the new bone formation percentage after using platelet concentrate in mandibular molar extraction by means of histomorphometric analysis after twelve weeks of extraction, more new bone formation was found in platelet concentrate group than in the control, significantly. [26]

At the same time, the systematic review by Castro and Co-workers [27] found four studies involving the usage of PRF in ARP. [28-31] Two radiologic assessment studies report higher bone density in PRF group than in the controls, whilst the other two studies stated no different bone healing capacity between PRF and control.

Recently, Du Toit and co-workers conducted randomized human histomorphometric analysis study. They investigated bone healing capacity of PRF with histological analysis in non-molar teeth after tooth extraction for ninety days. Their results showed no significant difference in amount of new bone formation when PRF (the autogenous graft material) was compared with natural wound healing. [32]

Up to date, the ability of PRF in bone forming stimulation is controversial, few randomized controlled studies are available. Besides, histomorphometric analysis with bone stain is another way which may show the effectiveness of PRF using in ARP.

Thus, the purpose of this study was to compare new bone formation ratio between using PRF as a socket preservation material and normal wound healing by means of histomorphometric analysis.

CHAPTER 3

Materials and methods

3.1 Materials

3.1.1 Blood collection set

3.1.2 Blood centrifugation machine (IntraSpin™, Intra-Lock, Nice, France)

3.1.3 PRF preparation set (Xpression™ box)

3.1.4 Piezotome (Implant™ center 2, Acteon®, France)

3.1.5 Surgical trephine bur (Komet Dental, Lemgo, Germany) 2-mm inner diameter and length at lease 6 mm.

3.1.1 Blood collection set: vacuum

Fig. 3.1 Vacuum tubes and plastic syringe with needle guage No. 18

3.1.2 Blood centrifugation machine (IntraSpin™, Intra-Lock, Nice, France)

Fig. 3.2 Blood centrifugation machine (IntraSpin™, Intra-Lock, Nice, France)

3.1.3 PRF preparation set (Xpression™ box)

Fig. 3.3 PRF preparation set (Xpression™ box)

3.1.3 Piezotome (Implant™ center 2, Acteon®, France)

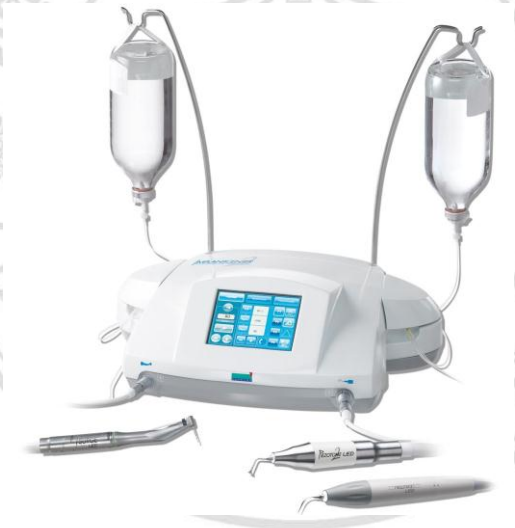


Fig. 3.4 Piezotome (Implant™ center 2, Acteon®, France)

3.1.5 Surgical trephine bur (Komet Dental, Lemgo, Germany)

Fig. 3.5 Surgical trephine bur (Komet Dental, Lemgo, Germany)

3.2 Methods

Population

Sample size calculation based on alpha error of 5% and a power of 80%. Thirty-six extraction sockets were divided into 2 groups:

1) PRF group, tooth extraction following with socket preservation with platelet-rich fibrin.

2) Control group, the alveolar sockets were left for spontaneous healing.

Foremost, a blinded third party took responsibility for the arrangement of each study group, randomly. Sealed envelopes contained group numbers (1 for PRF group, 2 for control group) was used for randomizing. The selection criteria for volunteers are shown in Table 1

Table 1 Selection criteria

Inclusion criteria	Exclusion criteria
General criteria: 1) Healthy volunteers above 20 year of ages, no any systemic pathologies may disturb implant placement procedure which are as follow: - Psychosis - Uncontrolled bleeding disorder - Intravenous injection of bisphosphonate medication - Previously received Head and neck radiotherapy - Heavy smoker (≥ 10 cigarettes per day in the last five years) 2) Volunteers physical status were considered as ASA classification I or II.	**General criteria:** 1) Any uncontrolled systemic disease (ASA class III or above) 2) Abuse of drugs or alcohol. 3) Demonstrate negative feeling towards implants and prostheses. 4) Poor oral hygiene 5) Unable to participate until the study is completed.

Treatment procedure was explained in detail to all volunteers. Informed consent form was signed before the study begin. An intra-oral examination and dental radiographs, (panoramic and periapical films) were taken conformed to the standard protocol. The study work flow is shown in Figure 3.6.

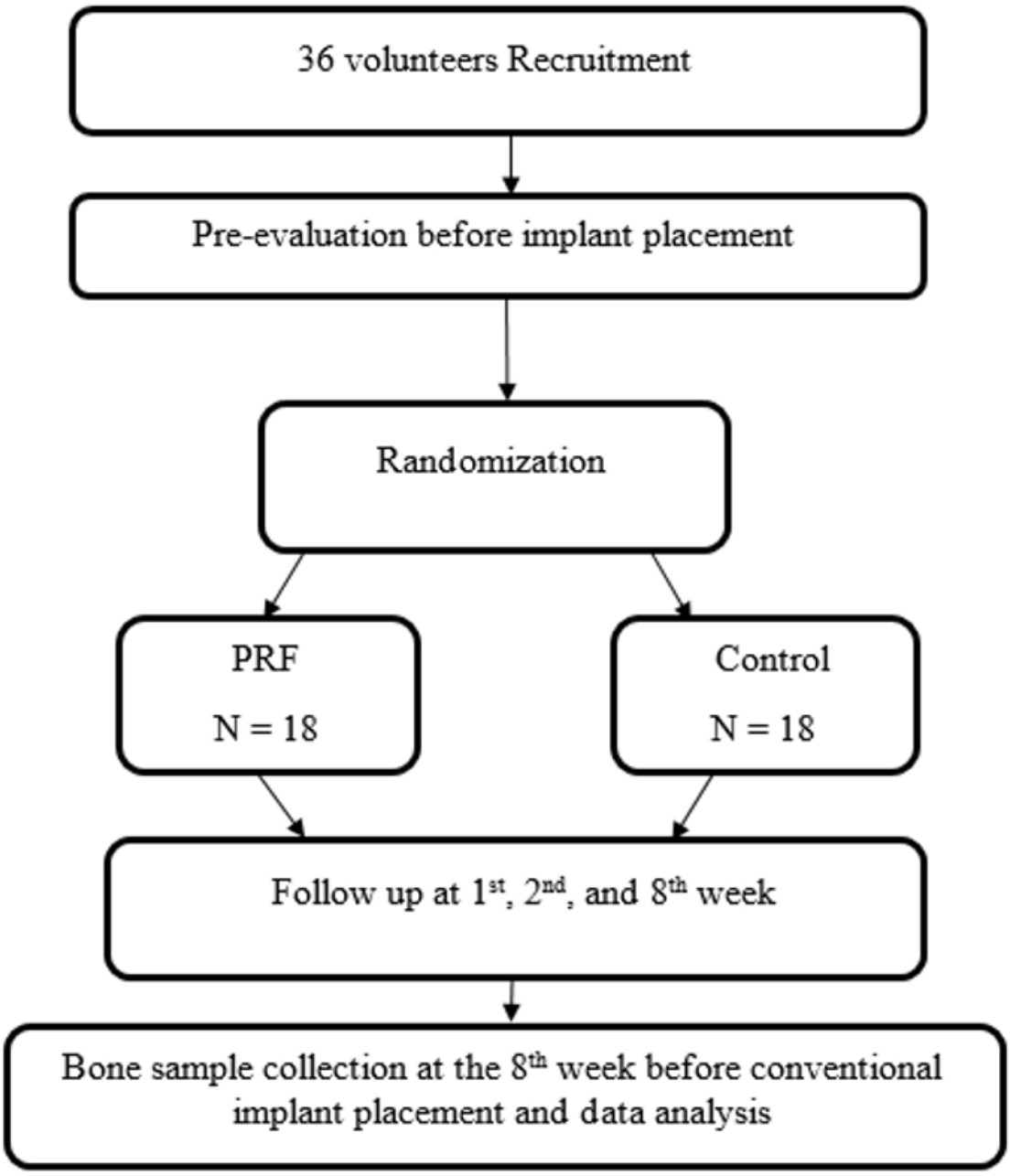


Fig. 3.6 Allocation of the sample population

PRF preparation

Following suggestion of Choukroun [13], blood was collected via common superficial veins within the cubital fossa including the median cubital, basilica, cephalic, and antebrachial veins along with their attendant tributaries. Ten milliliters of blood were drawn and put into a glass tube. The centrifuge device (IntraSpin™, Intra-Lock, Nice, France) speed were 2700 round per minute at least 12 minutes. Fibrin clot was formed at the middle of the tube between poor platelet plasma layer and red blood cell layer. A clot was taken out from glass tube by sterilized forceps and the lower red portion was cut. Xpression™ box was used to form a fibrin clot into fibrin plug. (Fig. 3.7)

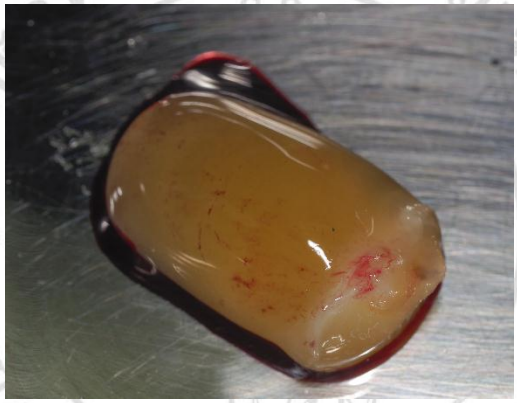


Fig. 3.7 Fibrin plug

Tooth extraction procedure

Local anesthetics containing 4 percentages articaine hydrochloride (Septanest® SP 1:100,000; Septodont Inc., Cedex, France) were used at the extraction site. Less traumatic extraction technique was performed. The periodontal ligaments were gently cut with piezotome (Implant™ center 2, Acteon®, France). Tooth was carefully mobilized using forceps without flap reflection. The granulation tissue was removed from alveolar bone socket following with normal saline solution irrigation.

The alveolar socket were treated differently in each group

- Control group, blood clots was left naturally within extracted sockets. The sockets were sutured with nylon by figure of eight method.
- PRF group, alveolar bone sockets were filled with PRF plug. The sockets were treated with the same technique as in control group.

Analgesic and antibiotic drugs were prescribed after the treatment procedure. Acetaminophen (500 mg.) were administered as pain relief. Amoxicillin (500 mg.) or clindamycin (300 mg.), for patients who has penicillin allergy, were suggested three times per day or two times per day respectively.

The healing events were followed up at 1st, 2nd and 8th week after tooth extraction. Any found complications were recorded.

Bone biopsy and histomorphometric preparation

After 2-month healing, new bone formation in alveolar ridge following tooth extraction was investigated using histomorphometric analysis. The alveolar ridge were scanned with CBCT before dental implant placement. The localization of the reference plane (sagittal section, axial section, and coronal section) were determined using surgical template.

Local anesthesia was administered at the site. Full mucoperiosteal buccal and lingual flaps were reflected. A surgical trephine bur (Komet Dental, Lemgo, Germany) 2-mm inner diameter and 6-mm length was used as pilot drill at the implant site, which was the central part of former alveolar bone socket. Bony core trapped within trephine bur was harvested and prepared for histological slide. The alveolar bone was prepared for appropriate-size of dental implant with 10 mm in minimum length. Primary stability of implant was assured using Resonance Frequency Analysis (RFA) (Fig. 3.8)

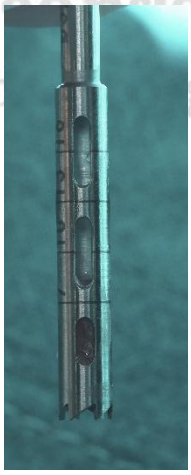


Fig. 3.8 Bone sample harvesting with trephine bur

According to Donath and Breune [33], the specimens were fixed with 10% formalin after that fixed bone was dehydrated with serial alcohol concentration (60%, 80%, 96%, and 100%). The specimens were rinsed and embedded in methylmetacrylate blocks. The polymerization blocks were cut using a 150-micrometre diamond disc with grinding machine along the longitudinal axis. Final thickness of the specimen was approximately 10-15 micron. The prepared specimens were stained with toluidine blue and basic fuchsin dye respectively.

Twenty-eight slides were captured by stereo microscope (Stemi 350, Zeiss, Jena, Germany) with 4X magnification for each specimen. New bone forming area and total area were calculated using FIJI software (*Fiji Is Just Image J,* version 2, GNU General Public License). [34] Ratio of new bone forming in alveolar socket was presented out with an equation below:

$$\text{Percentage of new bone area} = \frac{\text{new bone area}}{\text{total area}} \text{ x } 100$$

The data was determined by two independent examiners with intra-class correlation coefficient (ICC) calculated at 0.98.

Statistical analysis

SPSS software (SPSS version 17, SPSS Inc., Chicago, USA) was used to carry out the statistical analysis. Data were tested for normality by Kolmogorov-Sminov Test. The independent *t*-test was applied to compare the differences of those parameters between the two groups in normal distribution of data. Mann-Whitney U test was used in abnormal variation of data. The level of statistical significance was set at a $P<0.05$

CHAPTER 4

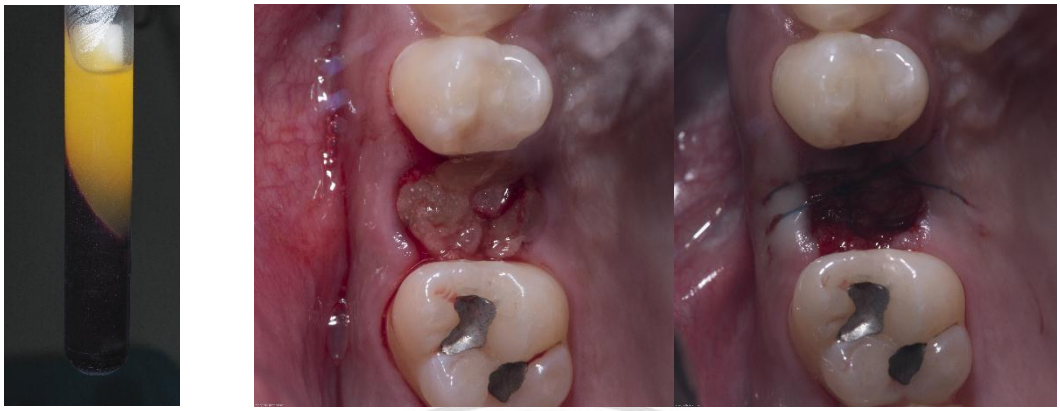
Results

In summary, thirty-three volunteers enrolled for the study. Thirty-six alveolar bone sockets were divided in to PRF group and control group equally (n = 18). In both groups 1 smoker was present. Demographic data of PRF group and controls are shown in Table 4.1.

Table 4.1 Presentation of demographic data and the distribution of the volunteers

	PRF	control	total
Number of alveolar bone sockets	18	18	36
Gender			
Male	9	6	15
Female	9	12	21
Age range			22-73
Mean age (years)			50.67
Smoking behavior	1	1	2

Volunteers mean age in PRF group was 48.17 and in control group 52.94 (overall minimum to maximum: 22 to 73, total mean age: 50.67), respectively. All alveolar sockets healed uneventfully. (Fig. 4.1 and 4.2)



A B C

Fig. 4.1 Presentation of alveolar ridge preservation using PRF.

A) Blood was separated into 3 layers, the PRF demonstrated yellow fibrin at the middle of the tube.

B) PRF was placed in alveolar socket after extraction procedure.

C) The socket was sutured to maintain PRF within place.

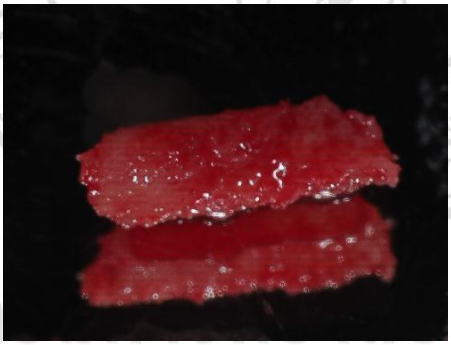


Fig. 4.2 Presentation of bone sample which was collected using trephine bur at the 8th week after tooth extraction.

New bone forming area was calculated comparing with total bony area (Fig. 4.3), the results are reported as percentage ratio. New bone formation was found in twenty-eight former sockets, the remaining eight alveolar sockets were found with no new bone formation at central of alveolar sockets (three cases in PRF group, five cases in control group). The data distribution was analyzed using Kolmogorov-Smirnov test, data was normally distributed in both groups. (P = 0.2 in PRF, and P = 0.093 in control)

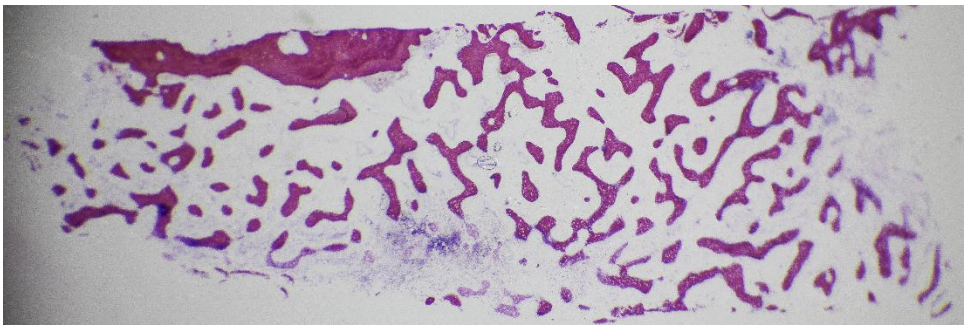


Fig. 4.3 Presentation of histological specimen stained with toluidine blue followed by basic fuchsin dye used for new bone formation ratio calculation.

Mean new bone formation ratio were 31.33 ± 18% in PRF group and 26.33 ± 19.63% in control group, respectively (Fig. 4.4)

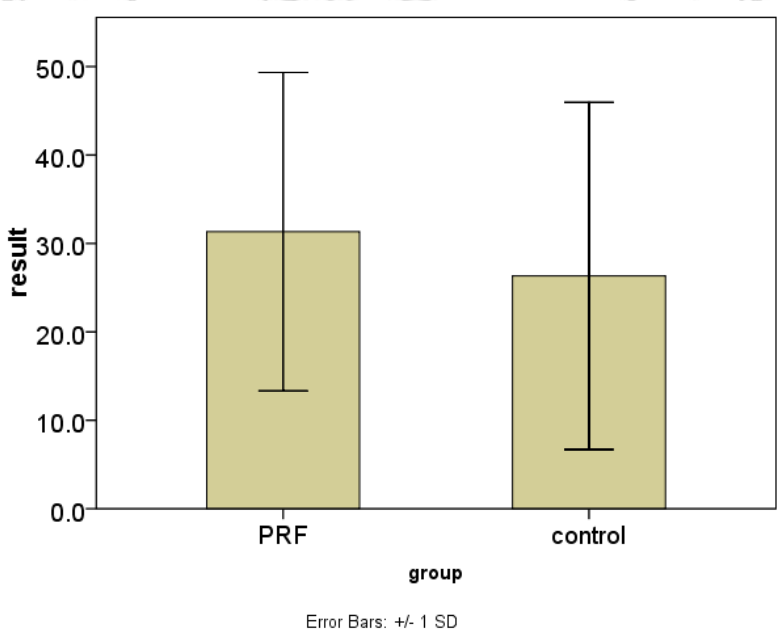


Fig. 4.4 Presentation of comparison of bone formation ratio in PRF group and control group

The results of data distribution were normal either in PRF group (P = 0.2 in male group, and 0.13 in female group) or in control group (P = 0.2 in both groups). Mean new bone formation ratio between male and female in each group were calculated. New bone

formation in PRF group was 28.84±20% in males and 33.82 ± 16.05% in females. Simultaneously, control group showed that new bone formation in males were 28.71 ± 23.88% and 25.14 ± 18.21% in females (Fig. 4.5 and 4.6).

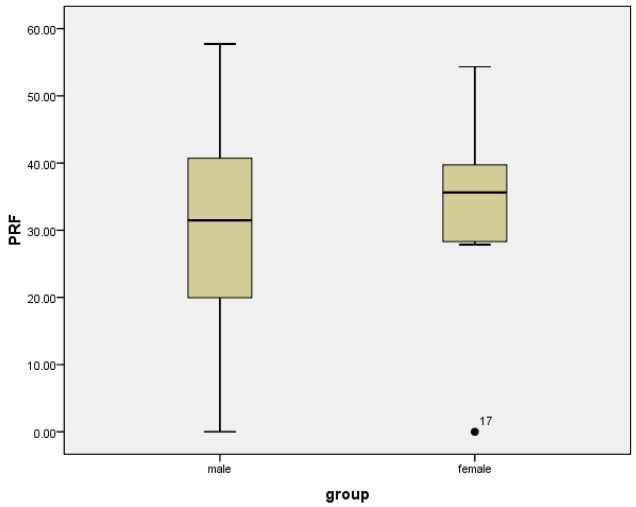


Fig. 4.5 Presentation of box plot graph showing mean new bone formation ratio of male and female in PRF group

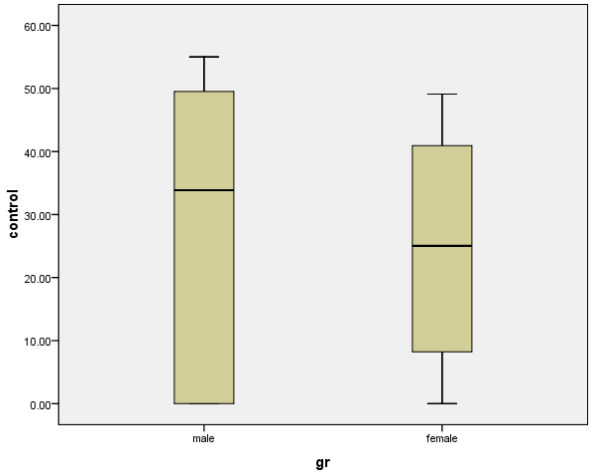


Fig. 4.6 Presentation of box plot graph showing mean new bone formation ratio of male and female in control group

There was no statistical significant difference of new bone formation between male and female patients either in PRF group (P = 0.573) or control group (P = 0.728).

All of the data were calculated with independent sample *t*-test, result demonstrated no statistical significantly different between PRF group and control group (P = 0.431). Concerning gender, the outcome showed no statistical difference of new bone formation ratio both in PRF group and control group. New bone formation in both PRF and control group are shown in Table 4.2.

Table 4.2 Presentation of statistical analysis of the data

	Mean bone formation	SD	P
Treatment modality			
PRF	31.33	± 18	0.431
Control	26.33	± 19. 63	
Gender PRF group			
Male	28.84	± 20.41	0.573
Female	33.82	± 16.05	
Control group			
Male	28.71	± 23.88	0.728
Female	25.14	± 18.21	

CHAPTER 5

Discussion

Conventionally, simple dental implant placement is usually conducted after tooth extraction for at least 3 months due to the occurrence of bone regeneration, however, residual bone after the completion of bone remodeling process is often insufficient for treatment. Araujo and Lindhy [35] confirmed that excessive bone resorption, especially at buccal plate, seems to be intense during the first 8 weeks after tooth extraction. Thus, complicated procedure was suggested and higher costs of implant placement are involved. Subsequently, alveolar bone preservation to maintain bone dimension at almost the original size.

A variety of materials are used in ARP, autogenous graft, xenograft, allograft, and alloplast. Normally, autogenous graft is a gold standard of material which has been used in the ARP, the usage of this autograft can reduce the cross-infection risk, when xenografts were used, and reduce treatment cost. Nevertheless, morbidity and risk of trauma after graft harvesting are always an issue. PRF is autogenous graft which was confirmed by several clinical studies that this type of platelet concentrate can accelerate wound healing and bone regeneration. [6, 10, 16]

As mentioned before, when tissue were damaged, the four phases of wound healing started, hemostasis phase, inflammatory phase, proliferative phase, and remodeling phase. Bone regeneration were regularly observed in first few weeks of wound healing process. According to the study of Cardaropoli and co-workers [36], they observed new bone regeneration events in dogs at 1, 3, 7, 14, 30, 60, 90, 120, and 180 days, authors stated that bone healing event were represented the series of tissue deposition. The series beginning with coagulum filled in the socket on first day, after 2 weeks of tooth extraction provisional connective tissue matrix were formed, followed by the formation of new bone on 8^{th} weeks, finally, new bone were mineralized and turned into lamellar bone after extraction procedure for three months. It can be concluded that woven bone, the

mineralized newly formed bone, was clearly noticed after tooth extraction for 8 weeks. Moreover, referring to the study of Choukroun and co-workers [37], they used PRF as a graft material in cystic cavity, within a period of 2 months, the defect was totally filled with the bone. Therefore, to confirm capacity of new bone regeneration of PRF, 8th week seems to be an appropriate time for the outcome observation in our study.

Observation methods in the PRF property are varying. A number of studies examined bone regeneration proportion with the assistance of radiology. Girish and co-workers [38] observed bone regeneration value of PRF comparing with natural wound healing by using serial radiographs (RVG) at immediate post-op, 1st month, 3rd month, and 6th month, they found higher mean pixels of new bone formation in each time intervals, however, there was no statistical significant difference between the two groups.

Another study by Alzahrani and co-workers [39] monitored the change in alveolar bone dimension after ARP with PRF using cast model analysis together with radiographic analysis via computer graphic software. The results showed a change of ridge dimension in test group is statistically less than the control group. Moreover, the average radiographic bone filled was greater than in the control significantly. In addition, a systematic review by Strauss and co-workers reported three histomorphometric studies. [40] Within the limits of the study they suggested using of PRF could enhance the alveolar ridge preservation.

Vice versa, a randomized clinical trial from Farina and co-workers [41] observed efficacy of platelet-rich growth factor (PRGF), one of platelet concentrate families, to stimulate early bone deposition on 4th and 8th week. The mean bone volume from radiographic analysis at 4-weeks in control group were 3.1 ± 3.4 mm^{3}and in PRGF group were 1.4 ± 2 mm^3, at 8-week the result showed 4.5 ± 2.7 mm^{3}in control and 3.2 ± 2.9 mm^3 in PRGF group, respectively. The results showed no statistical significantly difference either at 4-weeks or 8-weeks ($P > 0.05$). In addition to their study, histomorphometric analysis was conducted using the calculation of mean area of CD68+ cells staining, number of macrophage and giant cells. The results represented that there was a higher prevalence of the number of CD68+ cells in the PRGF group (97.8 ± 45.7 cells in 4-week group and 105.4 ± 93.9 cells in 8-week group) at both observation times compared to the control group (97.2 ± 159.1 cells in 4-week group and 105.6 cells in 8-

week group). However, the results showed that PRGF failed to promote bone formation in this period of time compared to the control group. ($P > 0.05$)

Alternatively, concerning to the study of PRF, Knapen and co-workers [42] conducted a study in rabbits to measure regenerative bone quantity subsequent to filling different biomaterials, which were L-PRF, bovine hydroxyapatite (BHA), the combination of BHA and L-PRF, and no material filled used as the control, into the prepared chamber of rabbit skull at three different time points which were 1 week, 5 weeks, and 12 weeks. Histomorphometric analysis results were presented in bone quantity percentages ratio. Authors found that bone quantity increased in co-ordination with time more than with the use of biomaterials, significantly. ($P < 0.0001$) However, bone formation quantity was not statistical significantly different between groups. ($P > 0.05$) They concluded that platelet fibrin has insufficient potential to stimulate more bone regeneration in the control group. Similar to our study, the null hypothesis assumed that there is no significant difference of new bone formation in socket preservation with PRF after tooth extraction compared to conventional wound healing. The statistic results showed no significant difference between two groups. Although, there are no statistic significant difference between the PRF and control group, the mean bone formation in PRF group is generally greater than control group.

In addition, wound healing is a multifactorial process. Among those factors tobacco is one of the important factors retarding the bone healing process. [1, 43] The study of Zhao and co-worker in 2018 [44], showed effects of smoking on human alveolar bone marrow mesenchymal stem cells (hABMMSCs). In 6 patients with dental implants, the osteogenic gene expression of hABMMSCs was reduced resulting in poor bone formation. Consequently, the success rate of implant treatment was significantly reduced. ($P < 0.05$). In our study, two smokers, which were randomly assigned to the different groups, demonstrated no new bone formation in central part of extraction sockets. This finding supported that smoking is an important factor affecting bone formation. However, more smokers are required for future studies.

Gender, one of the possible wound healing related factors, which may affect time consumption in wound healing cascade. According to Engeland and co-workers in 2006 [45], the clinical experiment measured wound healing condition using photographs in

first day of wound healing until 7th day. They found that wound healing in women was delayed compared to males (P=0.0008). However, our study showed no statistical significant difference in bone regeneration rate of PRF compared to control group in those males and females at 8th week period. This may need a more appropriate study design with more sample sizes in the future.

CHAPTER 6

Conclusions

Within the limitations of this study, it may be concluded that the use of PRF in alveolar socket preservation compared to natural bone healing are not showing statistically significant differences. The use of PRF may not enhances new bone regeneration in this treatment option. More clinical studies are required to prove the use of PRF in other clinical situation. The increasing use of PRF is commonly found more, especially in private practice. Though the benefit of using PRF is still controversial. The using of PRF is somehow assisted the dentist for wound covered. The regenerative effect of PRF or specific PRF is still required more studies to confirm the results.

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APPENDIX A

Ethical clearance

แบบรายละเอียดข้อมูลเสนอโครงการวิจัยเพื่อขอรับคำรับรองจากคณะกรรมการพิทักษ์สิทธิ์ สวัสดิภาพและป้องกันภยันตรายของผู้ถูกวิจัย คณะทันตแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

1. ชื่อโครงการวิจัย

(ภาษาไทย) การทดลองแบบสุ่มในคลินิกเพื่อเปรียบเทียบผลของเพลทเลทริชไฟบริ นต่อการสร้างกระดูกใหม่ในเบ้าฟันภายหลังถอนฟัน

(ภาษาอังกฤษ) The using of platelet-rich fibrin for alveolar bone socket preservation after tooth extraction: A randomized control trial study

2. สรุปย่อโครงการวิจัย (Project Summary)

เป็นการศึกษาผลของการสร้างกระดูกใหม่ภายหลังการถอนฟันในเบ้าฟันที่ได้รับการ อนุรักษ์ด้วยเพลทเลทริชไฟบริน ในผู้ป่วยที่มารับการถอนฟันก่อนใส่รากฟันเทียมที่ศูนย์ ความเป็นเลิศทางทันตกรรมรากเทียม คณะทันตแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ อายุ 20-55 ปี จำนวน 40 ราย ผู้เข้าร่วมจะได้รับการถอนฟันภายใต้ยาชาเฉพาะที่ แล้วสุ่มแบ่งเป็น 2 กลุ่ม ดังนี้

กลุ่มที่ 1 กลุ่มทดลองจะได้รับการใส่เพลทเลทริชไฟบรินในแผลถอนฟัน จำนวน 20 ราย

กลุ่มที่ 2 กลุ่มควบคุมจะมีเพียงลิ่มเลือดในแผลถอนฟันเท่านั้น จำนวน 20 ราย

ก่อนเย็บปิดปากแผลในทั้งสองกลุ่ม ถ่ายภาพรังสีเพื่อใช้อ้างอิง ภายหลังการถอนฟัน 8 สัปดาห์ทำการเก็บตัวอย่างเนื้อเยื่อกระดูกก่อนทำการฝังรากฟันเทียมโดยใช้หัวกรอขนาด เล็ก แล้วทำการตรวจประเมินทางอนุกายวิภาคศาสตร์เพื่อประเมินปริมาณกระดูกที่ถูกสร้าง ขึ้นใหม่

Fig. 1 Request form for certificate of ethical clearance of Human experimental committee, Faculty of dentistry, Chiang Mai University

เอกสารคำแนะนำแก่ผู้ถูกวิจัยหรืออนุญาต

(Patient or Subject Information Sheet)

ชื่อโครงการวิจัย การทดลองแบบสุ่มในคลินิกเพื่อเปรียบเทียบผลของเพลทเลทริชไฟบรินต่อการสร้างกระดูกใหม่ในเบ้าฟันภายหลังถอนฟัน

วัตถุประสงค์ของการวิจัย

เพื่อศึกษาผลของการใช้เพลทเลทริชไฟบรินในการอนุรักษ์เบ้าฟันหลังถอนฟันเปรียบเทียบกับการหายของแผลถอนฟันตามกระบวนการปกติ

ข้อมูลเกี่ยวกับการวิจัยโดยย่อ

เป็นการศึกษาผลของการสร้างกระดูกใหม่ภายหลังการถอนฟันในเบ้าฟันที่ได้รับการอนุรักษ์ด้วยเพลทเลทริชไฟบริน ในผู้ป่วยที่มารับการถอนฟันก่อนใส่รากฟันเทียมที่ศูนย์ความเป็นเลิศทางทันตกรรมรากเทียม คณะทันตแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ อายุ 20-55 ปี จำนวน 40 ราย ผู้เข้าร่วมจะได้รับการถอนฟันภายใต้ยาชาเฉพาะที่ แล้วสุ่มแบ่งเป็น 2 กลุ่ม ดังนี้

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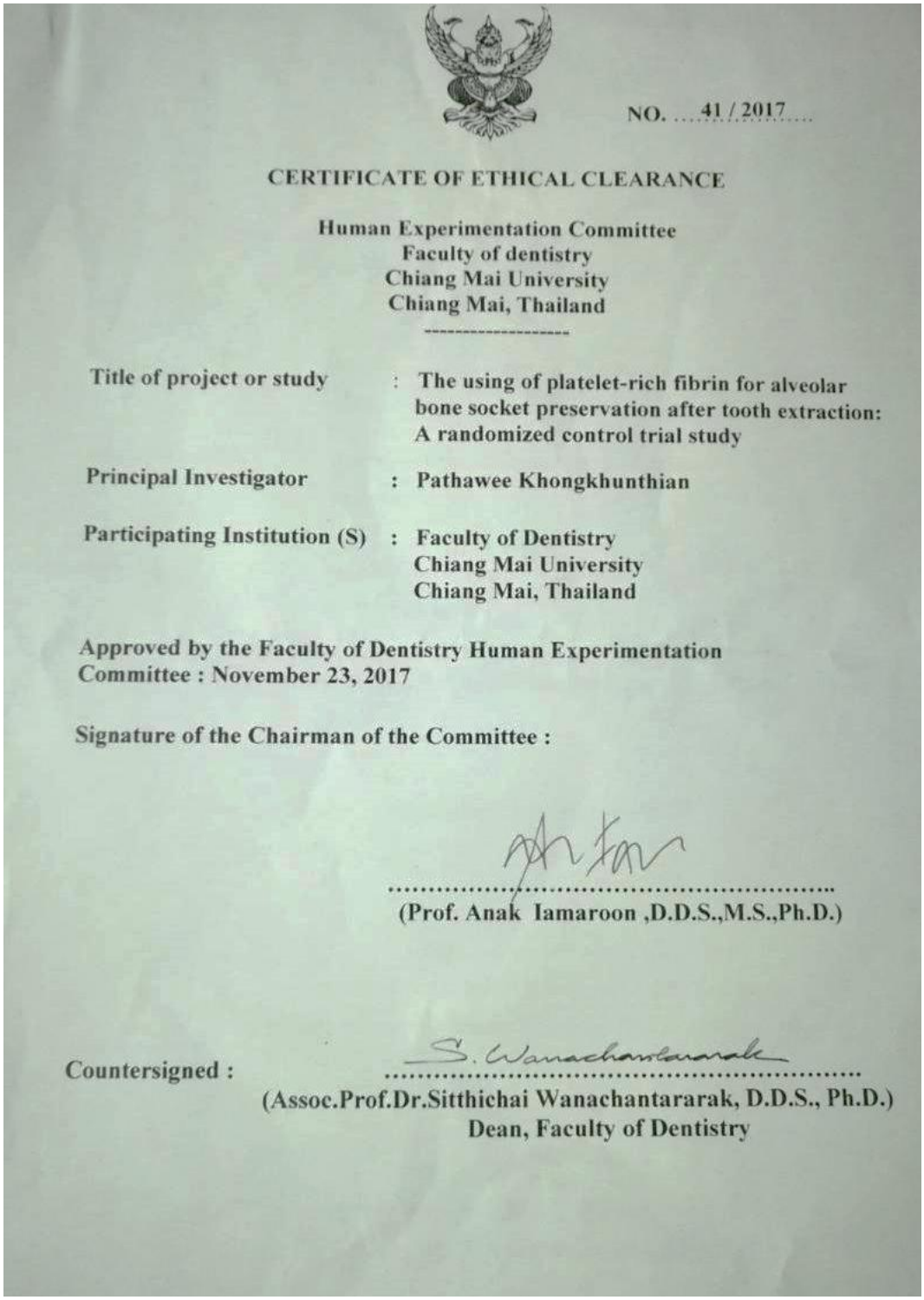
ก่อนเย็บปิดปากแผลในทั้งสองกลุ่ม ถ่ายภาพรังสีเพื่อใช้อ้างอิง ภายหลังการถอนฟัน 8 สัปดาห์ทำการเก็บตัวอย่างเนื้อเยื่อกระดูกก่อนทำการฝังรากฟันเทียมโดยใช้หัวกรอขนาดเล็ก แล้วทำการตรวจประเมินทางอนุกายวิภาคศาสตร์เพื่อประเมินปริมาณกระดูกที่ถูกสร้างขึ้นใหม่

ขอแสดงความนับถือ

ทญ. กนกพร อารีวงศ์

Fig. 2 Subjects information sheet



NO. 41 / 2017

CERTIFICATE OF ETHICAL CLEARANCE

Human Experimentation Committee
Faculty of dentistry
Chiang Mai University
Chiang Mai, Thailand

Title of project or study : The using of platelet-rich fibrin for alveolar bone socket preservation after tooth extraction: A randomized control trial study

Principal Investigator : Pathawee Khongkhunthian

Participating Institution (S) : Faculty of Dentistry
Chiang Mai University
Chiang Mai, Thailand

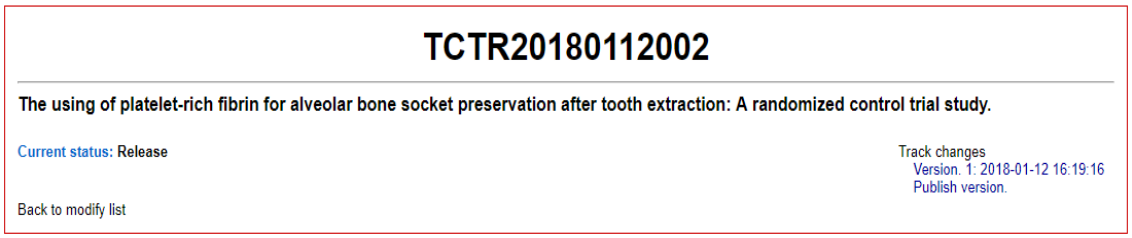
Approved by the Faculty of Dentistry Human Experimentation Committee : November 23, 2017

Signature of the Chairman of the Committee :

.....
(Prof. Anak Iamaroon ,D.D.S.,M.S.,Ph.D.)

Countersigned : .....
(Assoc.Prof.Dr.Sitthichai Wanachantararak, D.D.S., Ph.D.)
Dean, Faculty of Dentistry

Fig. 3 Certificate of ethical clearance from Human experimental committee, Faculty of dentistry, Chiang Mai University



TCTR20180112002

The using of platelet-rich fibrin for alveolar bone socket preservation after tooth extraction: A randomized control trial study.

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Version. 1: 2018-01-12 16:19:16
Publish version.

Back to modify list

Fig. 4 Certificate of ethical clearance from Thai clinical trials registry

APPENDIX B

Raw data of Histomorphometric image and Bone analysis

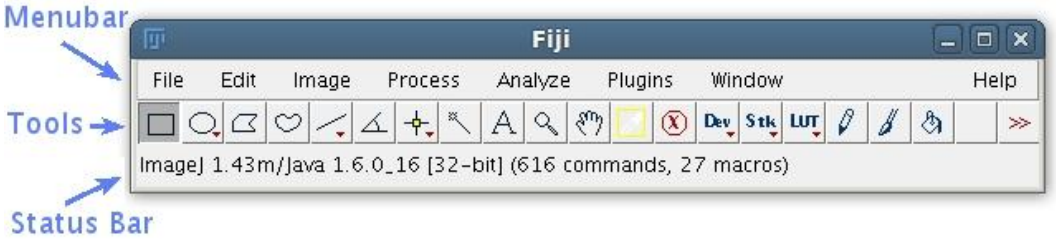

Fig. 5 Image J FIJI software

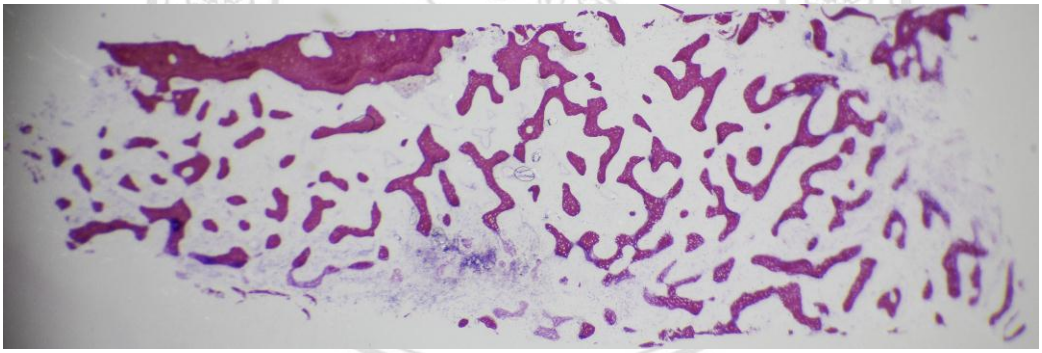

Fig. 6 Histomorphometric Image

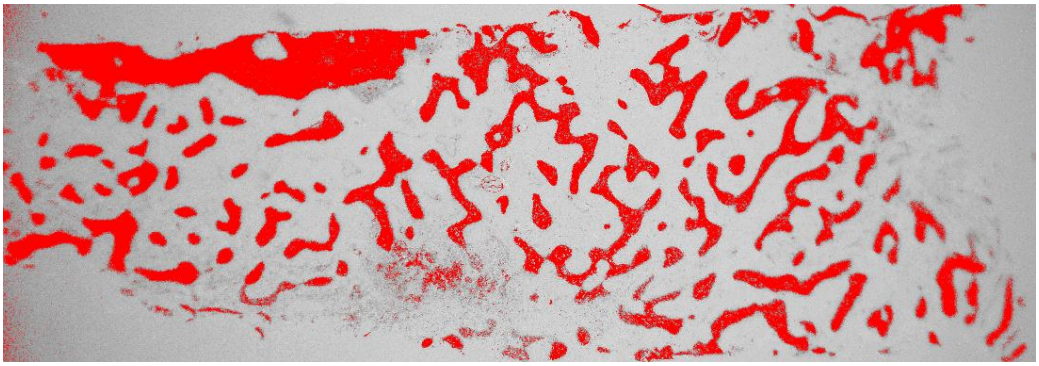

Fig. 7 Histomorphometric analysis presentation of new bone formation area by using Image J FIJI software

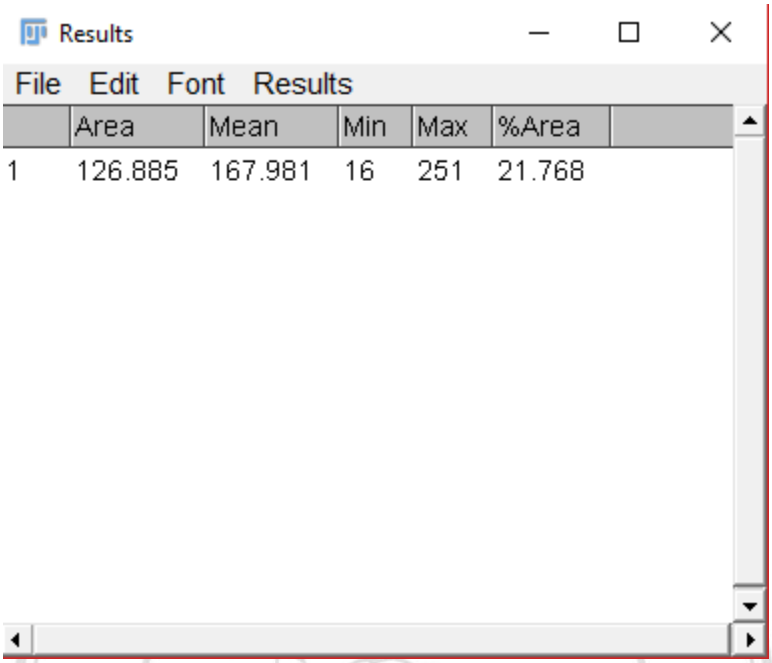

Fig. 8 Presentation of new bone formation percentage-area by using Image J FIJI software

APPENDIX C

Statistical analysis

Table 1 New bone formation ratio in PRF-group and control-group

PRF	1	2	3	4	5	6	7	8	9
new bone %	0	57.732	52.957	36.47	31.47	51.846	39.719	35.271	28.311
	10	11	12	13	14	15	16	17	18
	35.624	22.654	0	27.862	54.321	0	40.711	29.177	19.946
control	1	2	3	4	5	6	7	8	9
new bone %	36.43	30.249	0	45.868	55.018	49.529	49.114	23.439	0
	10	11	12	13	14	15	16	17	18
	45.45	0	0	22.212	26.642	36.082	0	16.461	37.477

Table 2 Independent Samples test of new bone formation ratio between PRF-group and control-group

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
result	Equal variances assumed	.659	.422	.797	34	.431	5.00517	6.27837	-7.75401	17.76435
	Equal variances not assumed			.797	33.747	.431	5.00517	6.27837	-7.75754	17.76788

t-test assumption is not significant, $p > 0.05$, therefore, it can be assumed that there is no different of bone formation efficacy between PRF-group and control-group. ($P = 0.431$)

Table 3 Independent Samples test of new bone formation ratio between sexes in PRF-group

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PRF	Equal variances assumed	.959	.342	-.575	16	.573	-4.97900	8.65774	-23.33259	13.37459
	Equal variances not assumed			-.575	15.159	.574	-4.97900	8.65774	-23.41571	13.45771

t-test assumption is not significant, $p > 0.05$, therefore, it can be assumed that there is no different of bone formation ratio between male and female in PRF-group. ($P = 0.573$)

Table 4 Independent Samples test of new bone formation ratio between sexes in control-group

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
control	Equal variances assumed	.722	.408	.354	16	.728	3.57067	10.07976	-17.79746	24.93880
	Equal variances not assumed			.322	8.021	.755	3.57067	11.07950	-21.96703	29.10836

t-test assumption is not significant, $p > 0.05$, therefore, it can be assumed that there is no different of bone formation ratio between male and female in control-group. ($P = 0.728$)

Table 5 Data of new bone formation ratio were checked for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. All data were considered to be taken from a normal distribution (P = 0.200 in PRF group and P= 0.093 in control group)

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PRF	.146	18	.200*	.920	18	.131
control	.188	18	.093	.891	18	.041

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

CURRICULUM VITAE

Author's Name Ms. Kanokporn Areewong

Date/Year of Birth 10 November 1986

Education

1993-1994	Primary school at Pattanawit Suksa School, Chiang Mai, Thailand.
1995-1996	Primary school at Anuban Phrae School, Phrae, Thailand.
1997-1998	Primary school at Anuban Phitsanulok School, Phitsanulok, Thailand.
1999-2004	Secondary school at Chalermkwan Satree School, Phitsanulok, Thailand.
2005-2010	Doctor of Dental Surgery (D.D.S.), Faculty of Dentistry, Naresuan University, Phitsanulok, Thailand.