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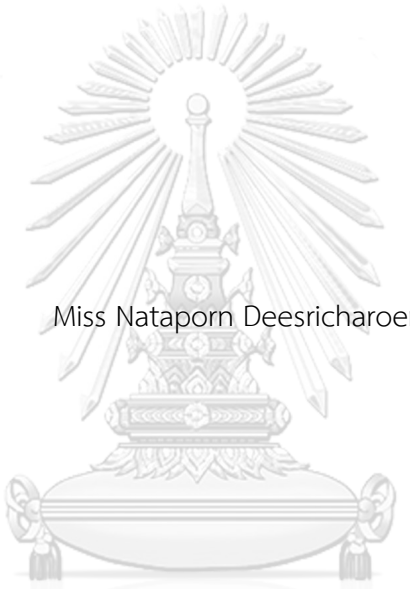
The effect of acemannan in implant placement with simultaneous bone graft in esthetic zone : a randomized controlled trial

Nataporn Deesricharoenkiat
Faculty of Dentistry

THE EFFECT OF ACEMANNAN IN IMPLANT PLACEMENT WITH SIMULTANEOUS BONE GRAFT IN ESTHETIC ZONE : A RANDOMIZED CONTROLLED TRIAL

Miss Nataporn Deesricharoenkiat



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การทดลองแบบสุ่มและมีกลุ่มควบคุมในการศึกษาผลของสารอะซีแมนแนนในว่านหางจระเข้ต่อการฝังรากเทียมร่วมกับการปลูกกระดูกบริเวณฟันที่ต้องการความสวยงาม

น.ส.ณฐพร ดีศรีเจริญเกียรติ

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Thesis Title	THE EFFECT OF ACEMANNAN IN IMPLANT PLACEMENT WITH SIMULTANEOUS BONE GRAFT IN ESTHETIC ZONE : A RANDOMIZED CONTROLLED TRIAL
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ณฐพร ดีศรีเจริญเกียรติ : การทดลองแบบสุ่มและมีกลุ่มควบคุมในการศึกษาผลของสารอะซีแมนแนนในว่านหางจระเข้ต่อการฝังรากเทียมร่วมกับการปลูกกระดูกบริเวณฟันที่ต้องการความสวยงาม. (THE EFFECT OF ACEMANNAN IN IMPLANT PLACEMENT WITH SIMULTANEOUS BONE GRAFT IN ESTHETIC ZONE : A RANDOMIZED CONTROLLED TRIAL) อ.ที่ปรึกษาหลัก : รศ. ทพ. ดร.พรชัย จันศิษย์ยานนท์, อ.ที่ปรึกษาร่วม : ศ. ทพ. ดร. พสุธา ธัญญะกิจไพศาล,อ. ทญ. ดร.วรรณาภรณ์ ชื่นชมพูนุท

บทนำ: อะซีแมนแนนเป็นสารสกัดที่พบได้ในว่านหางจระเข้ โดยสารนี้มีบทบาทสำคัญในการหายของแผลและกระตุ้นให้เกิดการสร้างเนื้อเยื่อใหม่ *วัตถุประสงค์การวิจัย:* การทดลองแบบสุ่มในงานวิจัยนี้มีวัตถุประสงค์เพื่อทดสอบดูประสิทธิภาพของอะซีแมนแนนในการส่งเสริมการสร้างกระดูกหลังจากฝังรากเทียมร่วมกับการปลูกกระดูก *วิธีดำเนินการวิจัย:* อาสาสมัครจำนวน 20 คนจะได้รับการสุ่มแบ่งออกเป็น 2 กลุ่ม (กลุ่มทดลองที่มีการปลูกกระดูกจากสัตว์ร่วมกับอะซีแมนแนน และกลุ่มควบคุมที่มีการปลูกกระดูกจากสัตว์เพียงอย่างเดียว) โดยผงอะซีแมนแนนมีขนาด 32.45 ไมโครเมตร อาสาสมัครทั้ง 20 คน จะได้รับการฝังรากเทียมร่วมกับการปลูกกระดูกตามกลุ่มที่ได้รับการสุ่มไว้ จากนั้นจะทำการวัดผลด้วยการถ่ายภาพรังสีโคนบีม (3 มิติ) ที่ระยะเวลาทันทีหลังการผ่าตัด และหลังจากการผ่าตัดไปแล้ว 3 และ 6 เดือนตามลำดับ ภาพรังสีจะถูกนำมาวัดปริมาณกระดูกด้านหน้ารากเทียมทั้งในแนวตั้ง และแนวนอนที่แพลตฟอร์มรากเทียม และที่ระยะห่างจากแพลตฟอร์มมา 2, 4, 6 และ 8 มิลลิเมตร ตามลำดับ *ผลการวิจัย:* ในกลุ่มทดลองที่ฝังรากเทียมและปลูกกระดูกจากสัตว์ร่วมกับอะซีแมนแนน มีการลดลงของกระดูกด้านหน้ารากเทียมน้อยกว่าในกลุ่มควบคุมที่ไม่มีอะซีแมนแนนอย่างมีนัยสำคัญในระยะเวลา 3 เดือน ทั้งในแนวตั้งและแนวนอนที่แพลตฟอร์มรากเทียม และที่ระยะห่างจากแพลตฟอร์ม 2, 4, 6, 8 มิลลิเมตร แต่ในระยะเวลา 6 เดือน ผลของทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญ บทสรุป: นับว่าอะซีแมนแนนเป็นวัสดุชีวภาพที่ปลอดภัย และมีคุณสมบัติในการกระตุ้นการสร้างกระดูกในระยะสั้นในการฝังรากเทียมร่วมกับการปลูกกระดูก การศึกษาเพิ่มเติมในอนาคตอาจมุ่งเน้นไปที่การติดตามผลระยะยาวในเรื่องของประสิทธิภาพและข้อดีของการใช้อะซีแมนแนนในการปลูกกระดูก

สาขาวิชา	ศัลยศาสตร์ช่องปากและแม็กซิลโลเฟเชียล	ลายมือชื่อนิสิต .....
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Nataporn Deesricharoenkiat : THE EFFECT OF ACEMANNAN IN IMPLANT PLACEMENT WITH SIMULTANEOUS BONE GRAFT IN ESTHETIC ZONE : A RANDOMIZED CONTROLLED TRIAL. Advisor: Assoc. Prof. Pornchai Jansisyanont, D.D.S., M.S., Ph.D. Co-advisor: Prof. Pasutha Thunyakitpisal, D.D.S., Ph.D., VANNAPORN CHUENCHOMPOONUT, D.D.S., Ph.D.

Background: Acemannan, a linear polysaccharide produced by Aloe vera has been shown to have important biological functions promoting wound healing and tissue regeneration. *Objective*: The aim of this randomized clinical trial was to investigate the impact of acemannan in guided bone regeneration (GBR) with simultaneous implant. *Materials and methods*: Twenty patients were randomly allocated to test-(Deproteinized bovine bone with Acemannan particulate with mean size of 32.45μm) and control groups (Deproteinized bovine bone only). Twenty implants were placed with simultaneous GBR. CBCT radiographic measurements were conducted immediately and at 3- and 6-months post-surgery. Vertical and horizontal dimensions of the buccal bone were measured at implant platform (0) and at points 2, 4, 6, 8 mm apically. *Results*: Volumetric reduction of vertical and horizontal buccal bone was significantly smaller in the test group at 3-month post-operation ($p<0.05$) for every position measured (0, 2, 4, 6, 8), but the difference was not statistically significant at 6 months. *Conclusion*: Acemannan is a safe and predictable biomaterial, which could potentially enhance short term clinical outcomes of GBR in relation to implant placement. Further studies would be required to document long term efficacy and advantages of its use as a supplement in bone regeneration.

Field of Study:	Oral and Maxillofacial Surgery	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....
		Co-advisor's Signature .....
		Co-advisor's Signature .....

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CHAPTER I

INTRODUCTION

1.Title:

The effect of acemannan in implant placement with simultaneous bone graft in esthetic zone: A randomized controlled trial

2.Background and Rationale:

Nowadays, dental implant placement becomes more popular and the number of patients has been increasing. Normally, after tooth extraction, patients have to wait for completely wound healing before doing surgery of dental implant placement. Following tooth extraction, the width and the height of alveolar bone will resorb about 25% or 4 mm during first year[1]. Tatum and Misch have observed a 40%-60% decreasing in alveolar bone width after the first 2-3 years post extraction[2]. Bone will continue resorb during the remainder for the rest of patients' life with annual resorption rate at least 0.5%-1%[3]. Following bundle bone theory, bundle bone contains thick collagen bundles which arranged parallel to each other, presents underneath the alveolar socket with approximately 0.5 mm in thickness and mostly locates at anterior teeth. The bundle bone will resorb after tooth extraction especially 2-3 mm at facial aspect[4]. Therefore, some cases with atrophic of labial bone of anterior maxilla have to be reconstructed with bone graft before or during implant placement. Bone augmentation procedure can be done before implant placement, but the procedure of implant placement has to be delayed at least 4 to 6 months for completely healing of the bone[5]. To reducing the time, the implant procedure trends toward the implant placement with simultaneous bone graft.

Implant placement with simultaneous bone graft has become more popular in case with labial or buccal bone defects. Carlos revealed that implant placement with bone augmentation and bioabsorable collagen membrane in immediate and

delayed implant placement showed good results in bone healing and primary stability of implant when it has sufficient soft tissue covered the implant[6]. For the long term stability and esthetic outcome, Buser reported a low risk of mucosal recession and presence of intact facial bone after implant placement with simultaneous bone augmentation[7]. In general, bone material comes from autogenous graft, allogenic graft, xenograft, and alloplastic graft. Deproteinized bovine bone's structure is similar to human bone, and it also has osteoconductive properties[8]. From Wong study, deproteinized bovine bone can increase the new bone formation and lead to heal the bone defects in white rabbits[9].

Aloe vera gel has been used for a long time in various industrials. For example, it has been used as components of foods, cosmetics, and medicine. Acemanan, extracted from Aloe Vera, plays an important role in immune-stimulating, antineoplastic and wound-healing action[10]. Moreover, it can stimulating bone marrow stromal cells proliferation and differentiation that inducing bone formation[11]. Due to its functional properties, many researchs use acemannan as an adjunctive material in many dental procedures. For example, Jansisyanont used acemannan sponges in post-extraction socket to stimulate bone healing[12]. Chantarawaratit used acemannan sponges to accelerate new alveolar bone, cementum and periodontal ligament formation in class II furcation defects of mongrel dogs[13]. Acemannan has potential to promote bone formation because it can stimulate bone marrow stromal cells proliferation, ALPase activity, expression of VEGF, BMP-2, Osteopontin, and Siaolopontin. These can stimulate bone formation and bone healing in Sprague-Dawley rats[11].

However, there has no clinical study about using acemannan as an adjunctive with deproteinized bovine bone in implant placement with simultaneous bone graft in esthetic zone. This study aims to prove that clinical and radiological outcome of acemannan with deproteinized bovine bone is better than deproteinized bovine bone alone.

CHAPTER II

REVIEWS OF RELATED LITERATURES

3.Review of Literatures:

3.1 Healing of extraction socket

There will be hard and soft tissue changes in dimension following tooth extraction. In a recent clinical study, Januario studied the morphological features of the alveolar process in the anterior maxilla in humans by using cone beam computed tomograms[14]. The study showed that all anterior tooth sites and the buccal bone plate in most locations was ≤1mm thickness (average thickness 0.5 mm). Therefore, tooth sites in the anterior maxilla have a thin buccal bone wall which probably contribute to its loss following tooth extraction. Another research of Van reported that clinical bone loss in width was greater than that of height[4].

According to several studies in animal and human, the healing of the alveolar socket after tooth extraction is divided into three phases: inflammatory phase, proliferative phase and bone modeling and remodeling phase. The inflammatory phase involves in blood clot formation and inflammatory cell migration immediately after exodontia. Within the proliferative phase, fibroplasia and woven bone formation form rapidly. Bone modeling and remodeling is the last phase of the socket-healing process. Bone modeling is the bone resorption. Bone remodeling is the replacement of woven bone with lamellar bone or bone marrow. After tooth extraction, the socket walls have bone modeling and remodeling that leading to a dimensional alteration of the alveolar ridge[15].

3.2 Simultaneous implant placement

According to Branemark original protocol, implant placement has to delay for 6 to 8 months after tooth extraction waiting for complete bone healing. After implant placement, implant has to be non-functional used 3 to 6 months for

osseointegration. That leads to long treatment time for replacing the extracted tooth[16]. To reduce the period between extraction and prosthetic insertion, there comes the immediate and early implant placement. Hammerle introduced the classification of implant placement in 4 type: type I immediate implant placement (after tooth extraction), type II early implant placement with soft tissue healing (4-8 weeks after tooth extraction): soft tissue completely cover the socket, type III late implant placement with substantial clinical and radiographic bone fill in the socket (12-16 weeks after tooth extraction), and type IV delayed implant placement with completely bone fill in the socket (>16 weeks after tooth extraction)[17].

In case of immediate or early implant placement, it may have the bony wall defect. To overcome this problem, bone augmentation is necessary. The procedure includes of implant placement with simultaneous bone augmentation in the same operation. From study of Artzi et al[18], they compared simultaneous with two-stage implant placement and guide bone regeneration by histomorphometry. The result showed both groups had similar osseointegration level over time. The concept of bone augmentation using xenograft and resorbable membrane in combination with early implant placement was shown in several clinical studies with successful results [7, 19]. In addition, simultaneous grafting with implant placement could correct the small or medium defect size of bone defect liked the study of Bach T Le[20].

3.3 Deproteinized bovine bone

There are many types of bone material such as autogenous graft, allogenic graft, xenograft, and alloplastic graft. A bone graft material has been used to prevent the intra-osseous defects after tooth extraction and facilitate the future implant placement. It should have at least one of three characteristics: 1. Osteogenesis (the graft material containing vital osteoblast for bone formation), 2. Osteoinduction (the ability of inducing osteoprogenitor cells to differentiate to osteoblasts), and 3. Osteoconduction (the graft material performs as a scaffold for new bone growth).

The gold standard for bone grafting is autogenous bone graft. Autogenous bone has all above properties, but also has limitation for using. It has limited bone quantity, donor site morbidity, and increasing risks of post-operative complication[21]. Deproteinized bovine bone graft has been extensively used as graft material in bone augmentation procedures[22]. Deproteinized bovine bone is one of the xenograft bone materials which derived from bovine bone. Some studies reported that molecules of deproteinized bovine bone have similar physical properties as human bone tissue. Therefore, the cancellous bone trabeculae creates conductive pathway in the new bone[23]. Moreover, the graft resorbs between 3 to 7 months interval creating space for new bone formation. This property accomplishes the osteoconductive characteristic[24]. Rothamel's study used a sintered, natural bone mineral (Cerabone®) for sinus floor elevation. The result showed good hard tissue regeneration of the sinus in all patients. Histology result showed complete osseous integration of Cerabone® in newly formed bone matrix[25]. Comparing between two commercial deproteinized bovine bone graft, BioOss® released calcium due to dissolution of material in water higher than Cerabone® in first 6 weeks. In x-ray images, BioOss® revealed significantly higher volumetric loss of initial graft size than Cerabone®. Thus, the rate of resorption of BioOss® was greater than Cerabone® after bone augmentation in 4 years follow-up[26]. Cerabone® may have advantages about acting as scaffold longer than BioOss®. This may allow more bone growth, formation, and remodeling for complete bone healing.

3.4 Acemannan

Acemannan is a linear polysaccharide of β-(1, 4)-linked polydispersed that found in the inner leaf gel of the aloe plant. Leucoplasts is a specialized cell that produce acemannan in the inner leaf gel. Acemannan composes of mannose, glucose, and galactose monomers in a 31:1:1 ratio[10, 27]. It has several therapeutic properties such as stimulate the process of immune response and wound healing.

And it also has anticancer activity[28]. It can stimulate the fibroblast of gingival tissue, synthesis growth factors, and induce secretion of several cytokines which modulate the wound healing. Some examples of growth factor are vascular endothelial growth factor(VEGF) which accelerate the angiogenesis, and keratinocyte growth factor which stimulate the growth of epithelium to cover the wound[29]. It can increase collagen synthesis and reestablish the vascularity of the burn tissues[30]. From the effectiveness of acemannan on bone formation, it can stimulate bone marrow stem cells proliferation and express the growth factors and mineralization that leads to induce the socket healing[11]. It increases the proliferation and differentiation of pulpal cells to be odontoblast and stimulates alkaline phosphatase enzyme, BMP-2, and dentinsialophosphoprotein to accelerate bone formation[29]. Fogleman injected acemannan extract into blood vessels and abdomens of mice and rats to determine the acute toxicity of acemannan. The results showed no significant signs of intoxicication and no deaths occurred in animal treated with single dose of acemannan injection. There were not considered adverse effects of acemannan[31].

In dentistry, Sajjad reported that acemannan reduced the pain and stimulated the healing of the aphthous ulcers, oral lichen planus, angular chelitis, and burning mouth syndrome. It's also used as denture adhesive, antiplaque and antibacterial agent[32]. Other study suggested that it promoted wound healing, managed immune response and performed as anti-inflammatory and antibacterial agent. It could be an alternative materials for the treatment of alveolar osteitis as alvogyl[33]. As its properties on bone formation, Boonyagul suggested acemannan stimulate bone marrow stromal cells proliferation and differentiation to osteoblasts to induce bone formation[11]. Godoy studied the effectiveness of acemannan on increasing bone surface, bone volume, and bone density. The results showed acemannan enhanced bone growth and bone regeneration in two- and three-dimensions with no inflammatory cells infiltration and no trace of acemannan sponge after 4 weeks[34].

3.5 The evaluation of bone formation

3.5.1 Clinical measurement

According to the study of Buser et al., the baseline clinical measurements intraoperative were defined as vertical distance from the implant shoulder to the alveolar crest (IS-AC), vertical distance from implant shoulder to the first bone-to-implant contact (IS-BIC) and horizontal defect width from the implant surface to the alveolar wall (HDW) (Figure1)[35]. For soft tissue parameters, they used modified plaque index (mPI), modified sulcus bleeding index (mSBI), probing depth (PD), and the width of keratinized mucosa (KM). These parameters were assessed with crowns placement at 3, 6, and 12 months. At 12 months examination, they removed screw-retained crowns and measured distance from the mucosal margin to the implant shoulder (DIM) by using a periodontal probe to the nearest millimeter at four locations in the implant site. For the esthetic outcome, they measured at 12 months by analyzing pictures following pink esthetic score (PES) and white esthetic score (WES)[36].

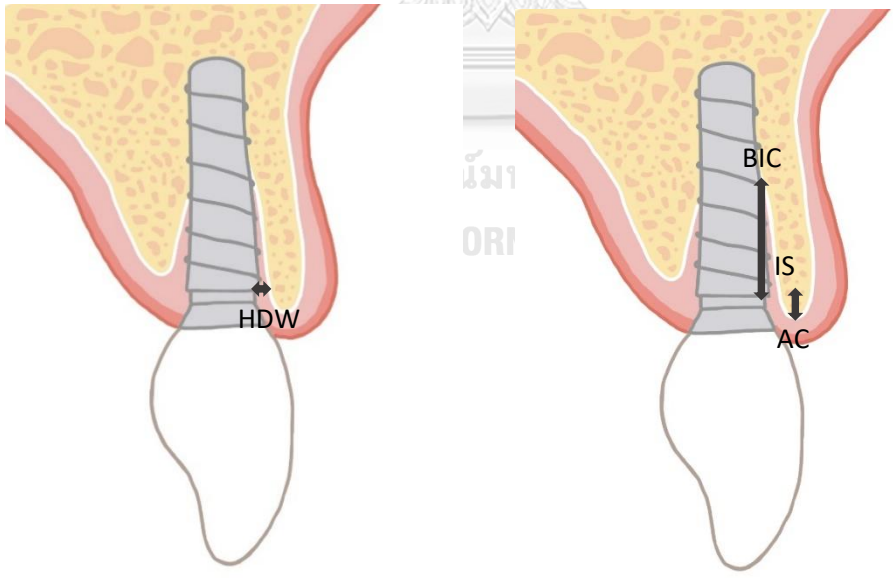


Figure 1: shows the baseline clinical measurements were defined as follows:

(I) vertical distance from the implant shoulder to the alveolar crest (IS-AC),

(II) vertical distance from implant shoulder to the first bone-to-implant contact (IS-BIC),

(III) horizontal distance from implant surface to labial bone

3.5.2 Imaging measurement

Cone beam computed tomography (CBCT) is an advanced imaging modality that was first used in 1990s[37]. Each image can provide information about hard tissue from head to neck in three-dimensional views. The reasons for the popularity of CBCT are its abilities of volumetric jaw bone imaging at reasonable doses and costs. For the implant rehabilitation, 3D dataset assists in diagnostic field and gives patient information for presurgical and treatment applications[38]. Roe[39] used cone beam computed tomography (CBCT) to evaluate horizontal and vertical dimensional changes of the facial bone after immediate implant placement at anterior maxilla. They selected the reference plane by adjusting 3 views of image. First, in the axial view, they rotated the image to the plane that vertical reference line perpendiculated the implant in the faciopalatal direction. Then, in the coronal view, they rotated the image until the implant's long axis was paralleled to the vertical reference line. And the last, in the sagittal view, they rotated the image until the occlusal plane was paralleled to the horizontal reference line. Then they got the axial cut plane (AC1) as reference plane for the next process (Figure2). On AC1, they could identify the implant center point (ICP) by drawing perpendicular line between faciopalatal and mesiodistal lines (Figure3).

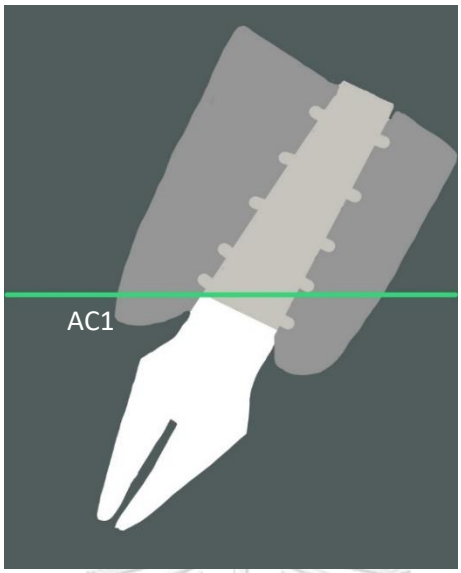


Figure 2: shows the axial cut (AC1) immediately apical to the abutment (center green line) is identified on sagittal view. *(adapted from study of Roe et al. 2012)*

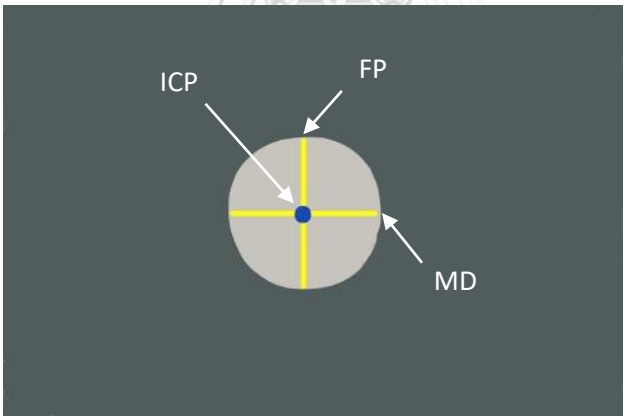


Figure 3: shows implant center point (ICP) was identified by drawing perpendicular lines at faciopalatal (FP) and mesiodistal (MD) at center of the implant. *(adapted from study of Roe et al. 2012)*

Then they measured the horizontal and vertical facial bone thickness. For the horizontal facial bone thickness (HFBT), they placed lines parallel to the implant platform (horizontal implant lines) at 1, 2, 4, 6, 9, and 12 mm apical to the implant platform and at the most coronal point of the facial bone. And measured on the line extending from the implant surface to the outer line of facial bone. The perpendicular distance from the implant platform (0) to the most coronal point of facial bone is the vertical facial bone level (VFBL) (Figure4)[39].

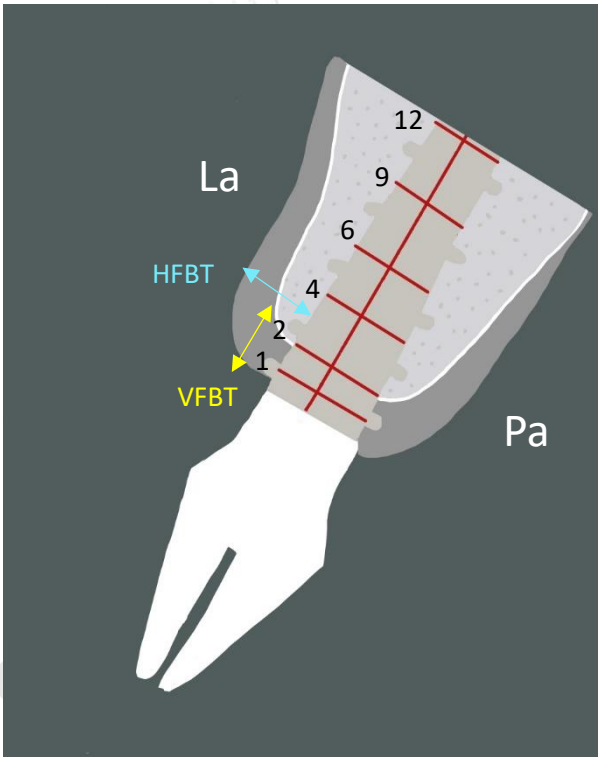
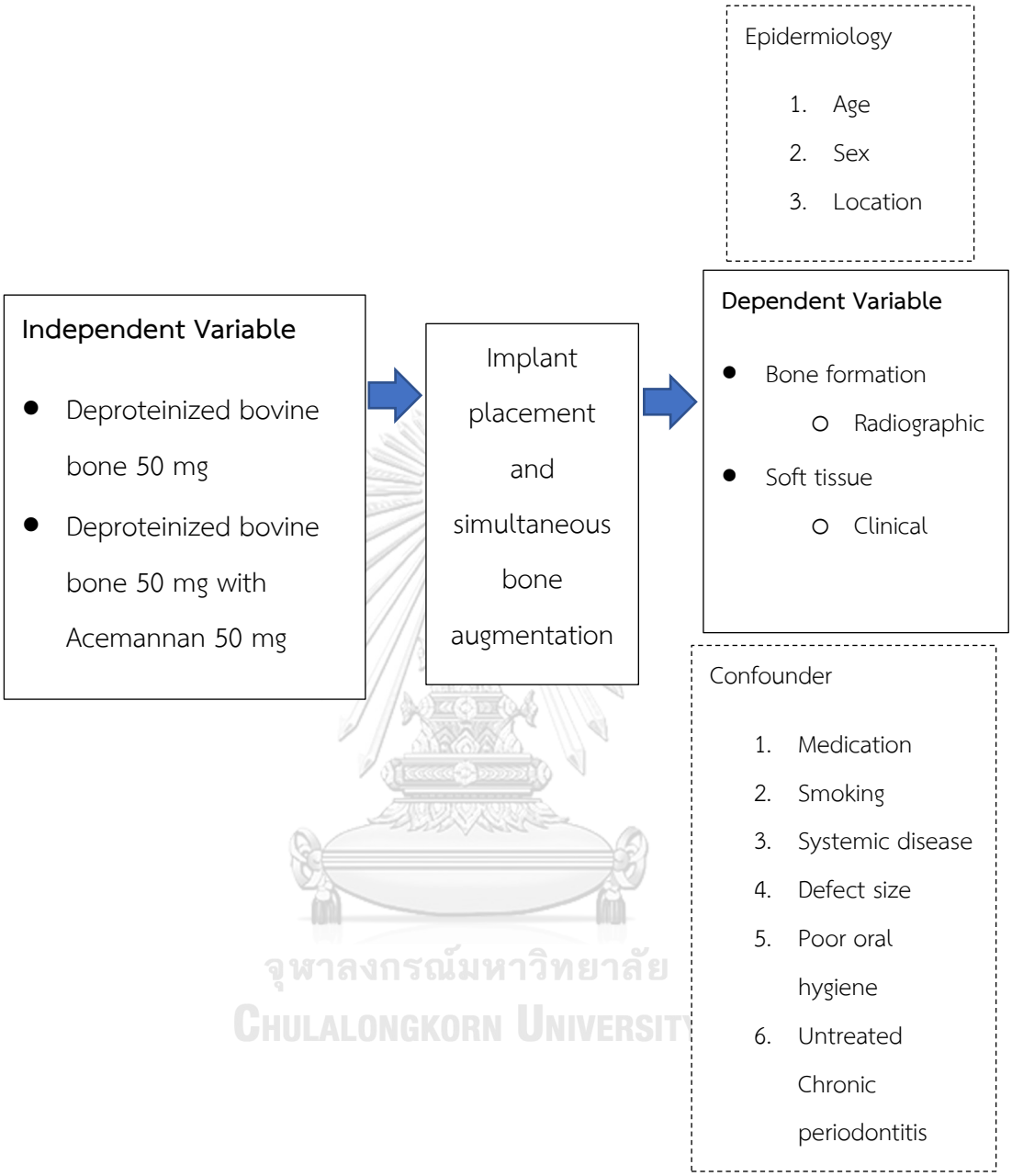


Figure 4: shows horizontal facial bone thickness (HFBT) at each level was measured on the line extending from the corresponding horizontal implant line to the outer line of facial bone. Vertical facial bone level (VFBL) was the perpendicular distance from the most coronal point of facial bone to the implant platform. *(adapted from study of Roe et al. 2012)*

4.Conceptual Framework:



5.Keyword(s):

- Acemannan
- Dental Implants
- Bone Regeneration
- Dental Esthetics

6.Research question:

Does Acemannan using with deproteinized bovine bone graft induce bone formation better than deproteinized bovine bone graft alone in implant placement with simultaneous bone graft in esthetic zone?

7.Research hypothesis:

Comparison between deproteinized bovine bone, Acemannan with deproteinized bovine bone has better clinical efficacy and radiological outcome in implant placement with simultaneous bone graft in esthetic zone.

8.Research objective:

To compare the outcome of bone formation and resorption of implant placement with simultaneous bone graft in esthetic zone between Acemannan using with deproteinized bovine bone graft and deproteinized bovine bone graft alone. Measuring vertical and horizontal bone width by periodontal probe in clinic and CBCT.

CHAPTER III

MATERIALS AND METHODS

9.Research methodology:

9.1 Study design

A randomized controlled trial, experimental and prospective study

9.2 Ethical consideration

The study clinical protocol approved by ethical committee of faculty of dentistry Chulalongkorn University (HREC-DCU 2019-057). Written consents were obtained from all subjects.

9.3 Sample size calculation

The sample size was calculated by using G*Power program (version 3.1.9.2 software) with mean and deviation from previous study of GI Benic, et al[40]. The estimation of sample size was based on type I error 5 % and study power 80%. From the calculation, the sample size for each group is 7 subjects. The sample size for each group was 10 for error or sample lost (Figure5).

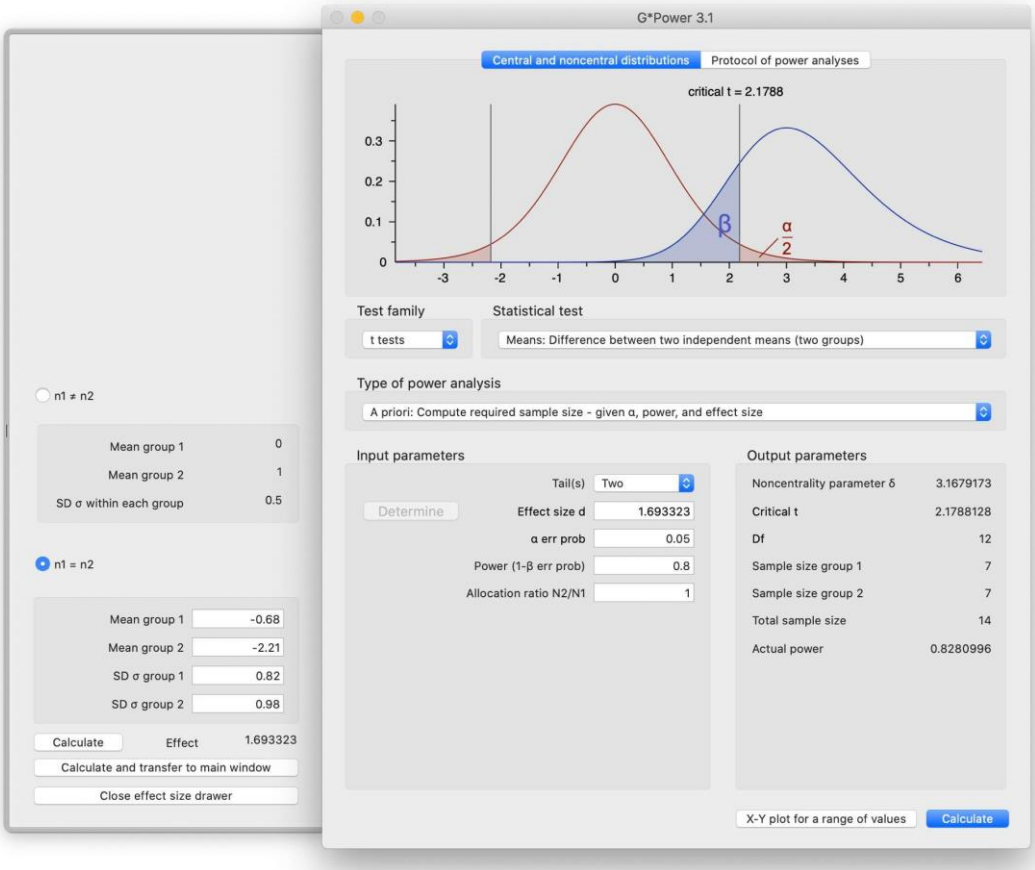


*Figure 5: shows sample size calculation by using G*Power program (version 3.1.9.2 software)*

9.4 Sample assignment

Participant were randomly assigned by using a computer-generated randomization into 2 groups:

1. Deproteinized bovine bone 50 mg. (control group)

2. Acemannan 50 mg. with deproteinized bovine bone 50 mg. (experimental group)

9.5 Participant

Patient who requires implant placement in esthetic zone at the department of oral and maxillofacial surgery, Chulalongkorn University was enrolled for the study. This study was prospective, randomized controlled trial study.

Inclusion criteria

1. Patient who has single edentulous area at anterior maxilla (central/lateral incisor) which had been extracted at least 2 months before operation and can achieve appropriate 3-dimensional positions of implant placement in esthetic zone.
2. Patient with age ≥ 20 years old.
3. Patient who has mild to moderate atrophy of bone. (loss of 25-50% bone width and bone height from radiograph)
4. Patient with sufficient keratinized gingiva.
5. Patient who are healthy or well-controlled systemic disease.

Exclusion criteria

1. Patient who had previously received bone graft on the site to be operated.
2. Smokers.
3. Patient with poor plaque control and untreated chronic periodontitis.
4. Patient with acute infection such as severe swelling, suppuration and abscess.
5. Patient who is pregnant or lactating.
6. Patient who has previously received radiation therapy in head and neck regions.
7. Patient who has received chemotherapy.

9.6 Intervention

Preparation of the Acemannan

Providing Aloe vera by a local herbal supplier in Bangkok, Thailand. Aloe vera was identified and the specimen was kept in the Museum of Natural Medicines, Faculty of Pharmaceutical Sciences, Chulalongkorn University (Bangkok, Thailand).

Extraction of acemannan from fresh Aloe vera pulp gel began with draining off the yellow sap from the rind and cleaning with deionized water. The clear pulp was homogenized with a polytron. Then, centrifuged and precipitated by using cold alcohol[41]. Acemannan was dialyzed using a 10,000 Da molecular weight cut-off semipermeable dialysis bag for 24 hours to remove small monosaccharides and protein, then lyophilized. The molecular weight of acemannan was examined by high-performance liquid chromatography (HPLC) technique, using reflective index detector from Shimadzu corporation, Kyoto, Japan. A Shodex sugar KS-804 column will be used to compare with a P-82 standard (Showwa Denko, Yokohama, Japan). The composition of monosaccharide and polysaccharide structure were analyzed by gas chromatography-mass spectroscopy (GC-MS) and Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy[11, 41]. The results were analyzed and compared with prior studies to confirm that polysaccharide extracted from fresh Aloe vera gel are acemannan. The amount of acemannan after extraction was approximately 0.2%.

To make acemannan into particles, the acemannan was pulverized by sterilized mortar and pestle. The size of particles was investigated under scanning capacitance microscopy (SCM). Then, acemannan particles were packed in the bottles and sterilized by ionizing radiation (Gammar rays). All the acemannan particles were kept in dry condition at room temperature, prepared for using in the experiment.

9.7 Surgical procedure

After tooth extraction, the socket was left for healing at least 2 months before doing surgery implant placement with simultaneous bone graft. All surgical procedures were performed under local anesthesia with 2% mepivacaine with 1:100,000 epinephrine. The procedure began with mucoperiosteal flaps at palatal crest and sulcular to facial aspect of adjacent tooth. The vertical incision was also performed. Elevating the flap and drilling the bone with Neodent® drills and following standard manual of Neodent®. Using bone-level implant of Neodent® implant with a platform diameter of 3.5, 4.0 mm. and length of 10.0 mm. The location of implant placement must far away from adjacent root surface at least 1 mm. Implants were placed by 3 operators that had been trained by the same dental specialist. Preparing resorbable collagen membrane (Jason membrane®) and collecting blood from patients for mixing with deproteinized bovine bone graft (Cerabone®) before placing the graft into the defect site of labial bone. Perforating bone around implant was made by using round bur to increase vascularization. Then, using bone scraping device to harvest autogenous bone to augment bone in the defect sites before placing graft materials. Deproteinized bovine bone graft or deproteinized bovine bone graft with acemannan 50 mg was placed following random assignment which prepared before the surgery. After that, the graft was protected by placing resorbable collagen membrane (Jason membrane®) and sutured primary closure with vicryl® 4-0 (Figure6-9).

All patients were instructed to rinse the mouth twice a day with 0.12% chlorhexidine solutions for 2 week and took amoxicillin 500 mg three times daily for 7 days or clindamycin 300 mg three times daily (in case of patients who has allergic to penicillin) and acetaminophen 500 mg 4 times daily for 3 days postoperatively. Sutures were removed and temporary prosthesis could be used after 2 weeks of operation.

After 3 months of healing period, dental implants were reopened with minimal flap operation for removing healing abutment and change to abutment for crown. Final prosthesis fixation was done by a prosthodontist 1 month after second surgery (Figure10-12).

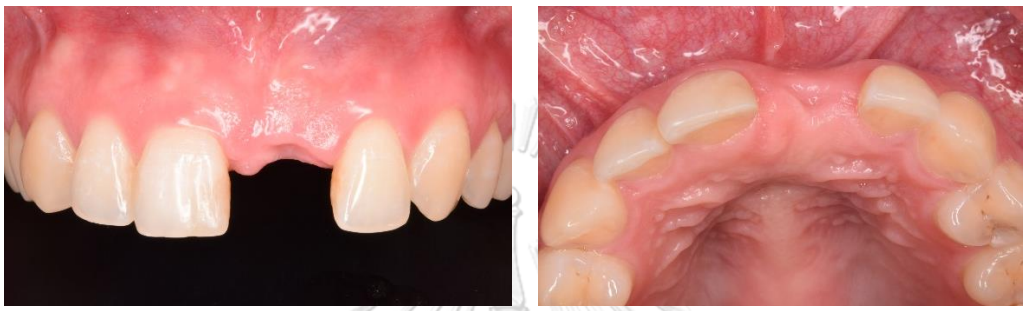


Figure 6: shows typical site.

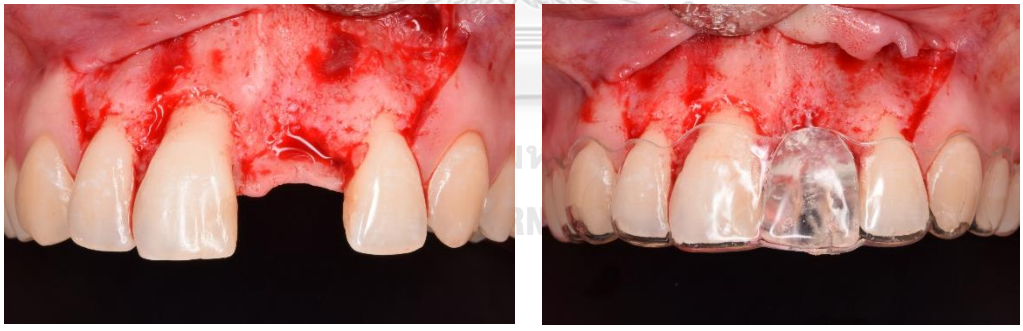


Figure 7: shows flap design and prosthetic guide placement to determine optimal implant position.

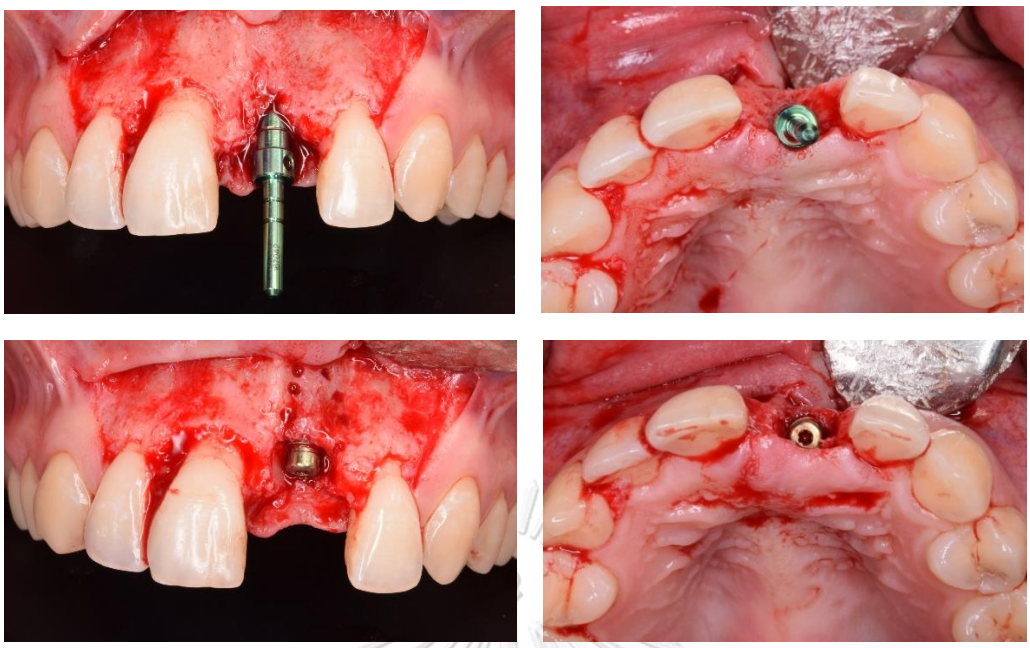


Figure 8: shows osteotomy preparation and implant placement.

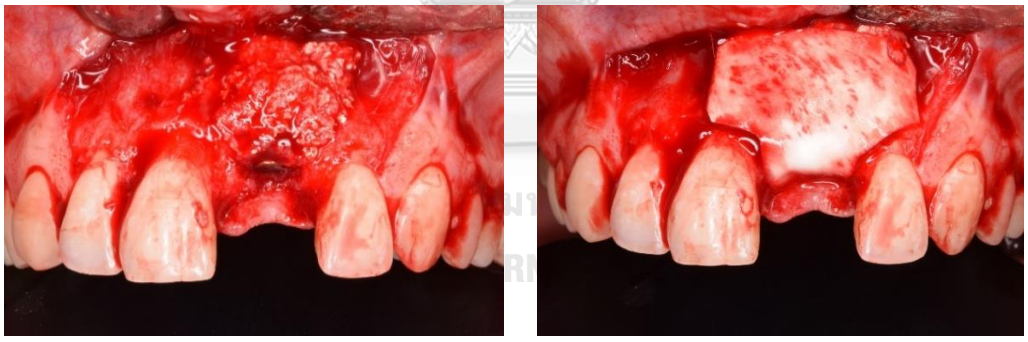


Figure 9: shows bone augmentation.

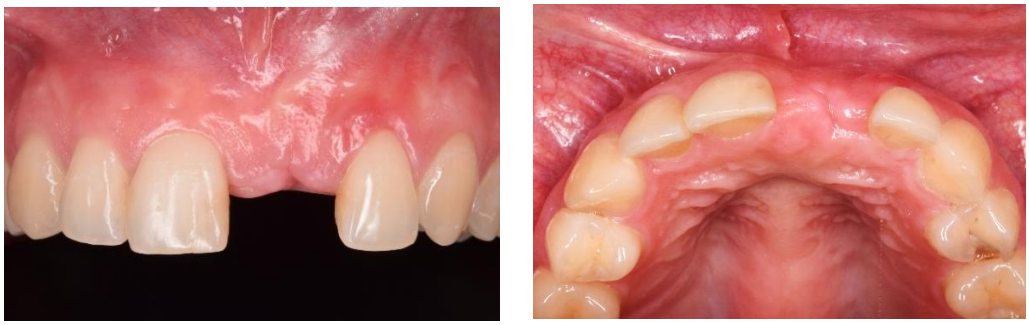


Figure 10: shows surgical site 3 months post-operation.

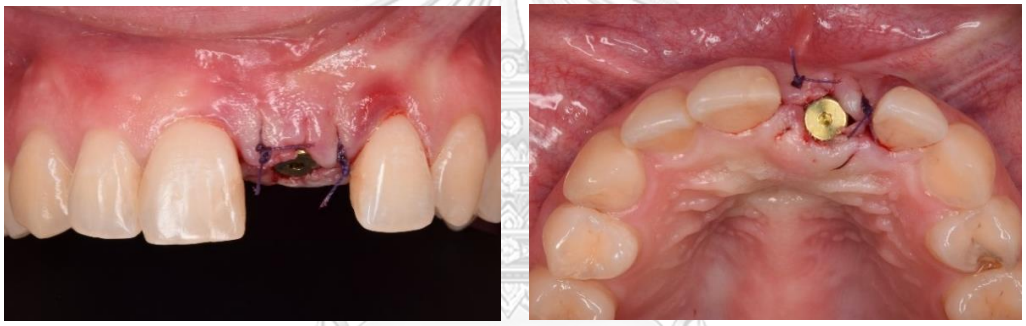


Figure 11: shows 2nd stage implant placement.

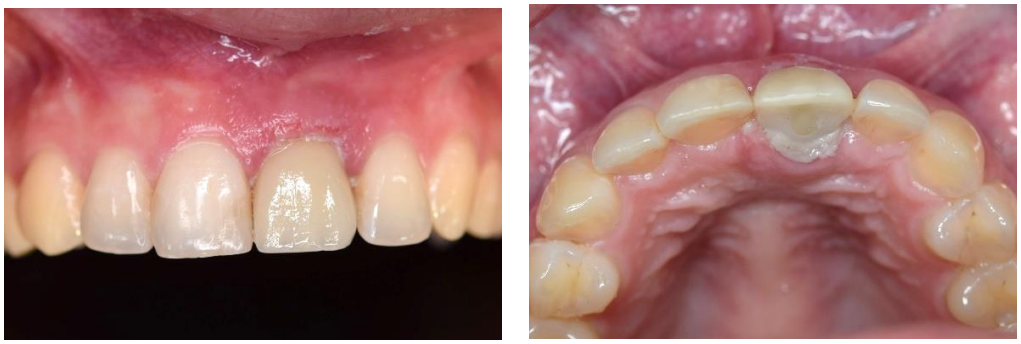


Figure 12: shows prosthetic restoration.

9.8 Picture of protocol

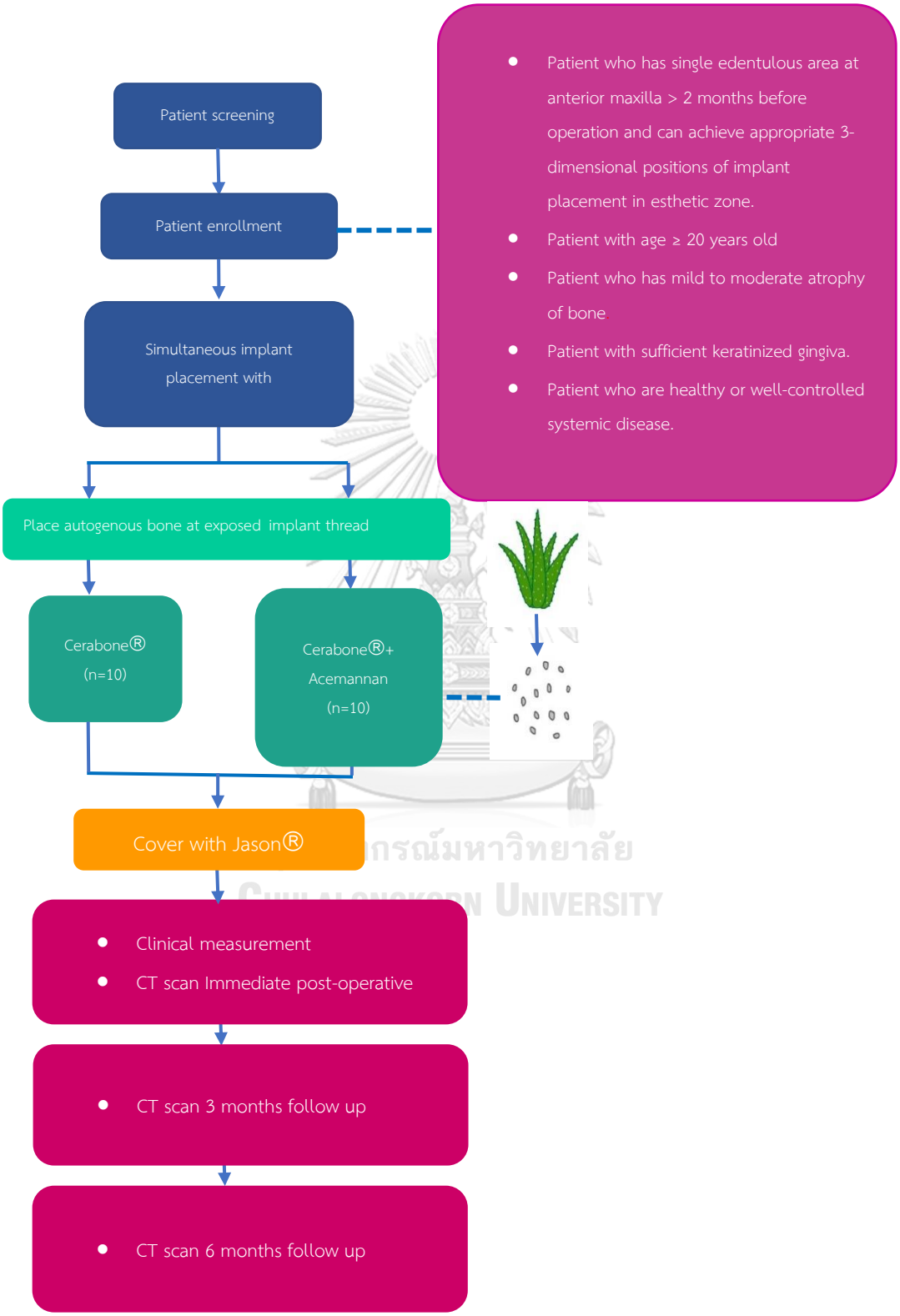


Figure 13: shows prosthetic restoration.

10.Measurement:

Measurement of bone formation

10.1 Clinical measurement

Placing probe and measure the vertical distance from the implant shoulder to the alveolar crest (IS-AC), vertical distance from implant shoulder to the first bone-to-implant contact (IS-BIC), and horizontal defect width from the implant surface to the alveolar wall (HDW) (Figure14). Each measurement was done twice and calculated the average value for the baseline. Width of keratinized mucosa was measured at pre-operative, 3 months, and 6 months follow-up. Probing depth was measured after prosthesis fixation.

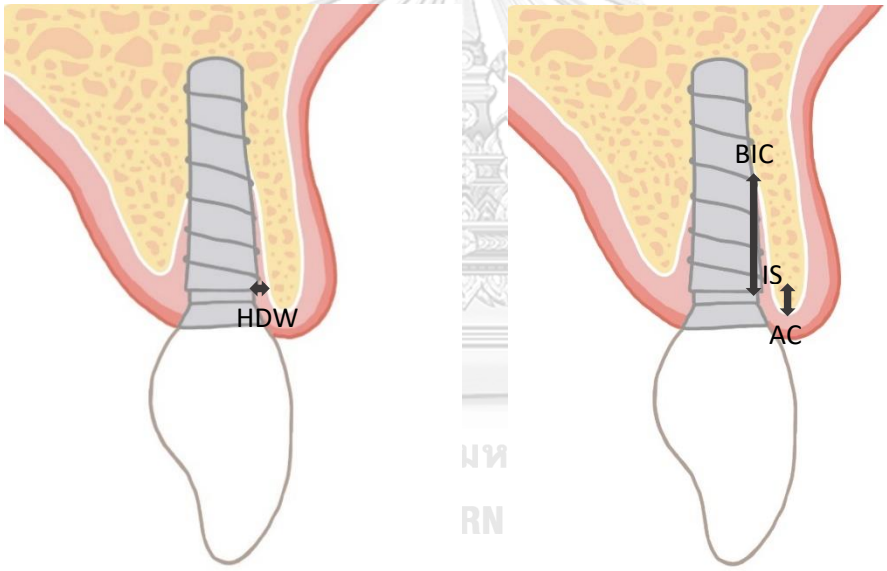


Figure 13: shows implant shoulder to the alveolar crest (IS-AC), vertical distance from implant shoulder to the first bone-to-implant contact (IS-BIC), horizontal defect width from the implant surface to the alveolar wall (HDW), and width of keratinized mucosa that use to measure.

10.2 Imaging measurement

Cone beam computed tomography (CBCT) was taken before implant placement for baseline measurement and treatment planning. Then, the CBCT was taken at immediate post-operative, 3 months, and 6 months post-operative to evaluate horizontal and vertical dimensional changes to the facial bone after implant placement with simultaneous bone graft at anterior region. All CBCT imaging were performed by a Accuitomo 170 (J. MORITA manufacturing Corp., Kyoto, Japan) with 90 kVp, 8.5-10 mA, 17.5 seconds of exposure time, and a field of view 10x10 cm. The images were reconstructed with a voxel size of 0.25 mm. All exposure parameters were properly fixed in each patient for every scan. The follow-up images at 3 months were differed from 6 months due to bone modeling and remodeling process. Using One Volume Viewer program to select the reference plane by adjust 3 views of image. First, in the axial view, the image was rotated to the plane that facio-palatal line of the implant perpendiculated the mesiodistal line. Then, in the coronal view, the image was rotated until the implant's long axis is parallel to the vertical reference line and perpendiculated mesiodistal line of implant. And the last, in the sagittal view, the image was rotated until the implant's long axis was perpendiculated to the horizontal reference line (Figure15). So, the axial cut plane was used as reference plane to identify the implant center point. Drawing perpendicular line between faciopalatal and mesiodistal lines to get implant center point.

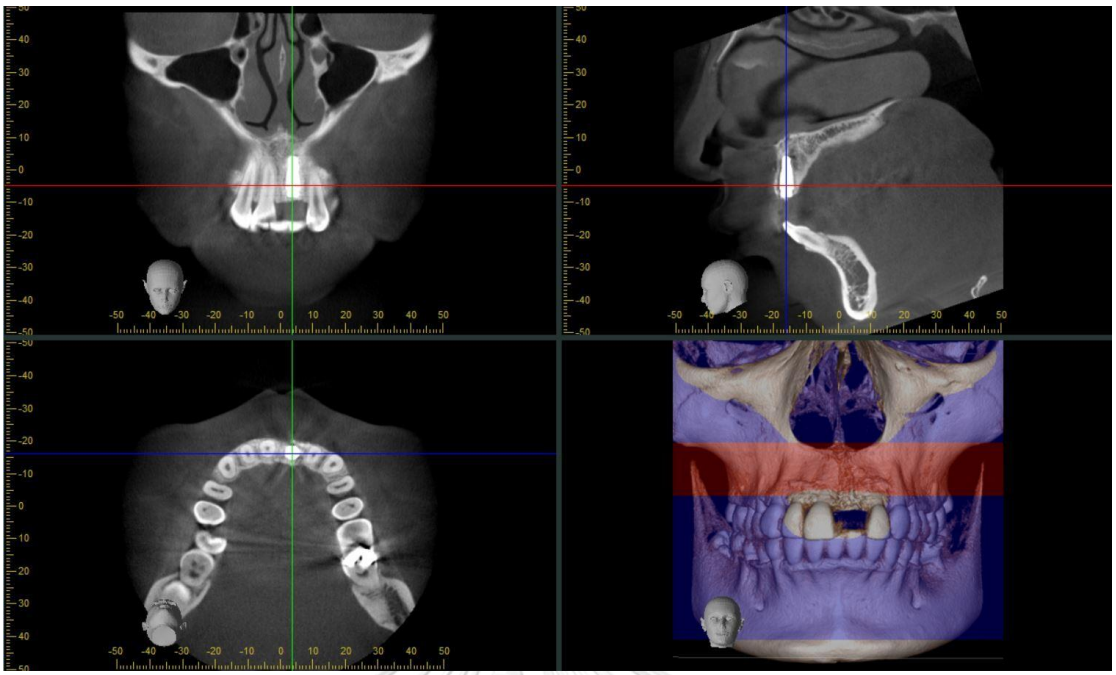


Figure 14: shows radiographic image shows reference line in 3 views: coronal, sagittal, and axial.

The horizontal and vertical facial bone were measured. The horizontal facial bone thickness (HFBT) was measured by using lines that parallel to the implant platform (horizontal implant lines) at 0, 2, 4, 6, and 8 mm from the implant surface to the facial bone. The vertical bone height was measured by using the perpendicular distance from the implant platform (0) to the most coronal point of facial bone (Figure16). Each measurement was done twice and calculated the average value for the baseline. Then, data were analyzed and compared dimensional change of vertical and horizontal bone height between 2 groups.

The dimensional change of vertical and horizontal facial bone height (VFBT, HFBT) between immediately, 3 months, and 6 months post-operation (ΔVFBT and ΔHFBT) of each group was determined as follows:

$\Delta VFBT_1 = VFBT_{3months} - VFBT_{immediate}$

$\Delta VFBT_2 = VFBT_{6months} - VFBT_{immediate}$

$\Delta VFBT_3 = VFBT_{6months} - VFBT_{3months}$

(same as ΔHFBT at 0, 2, 4, 6, and 8 mm.)

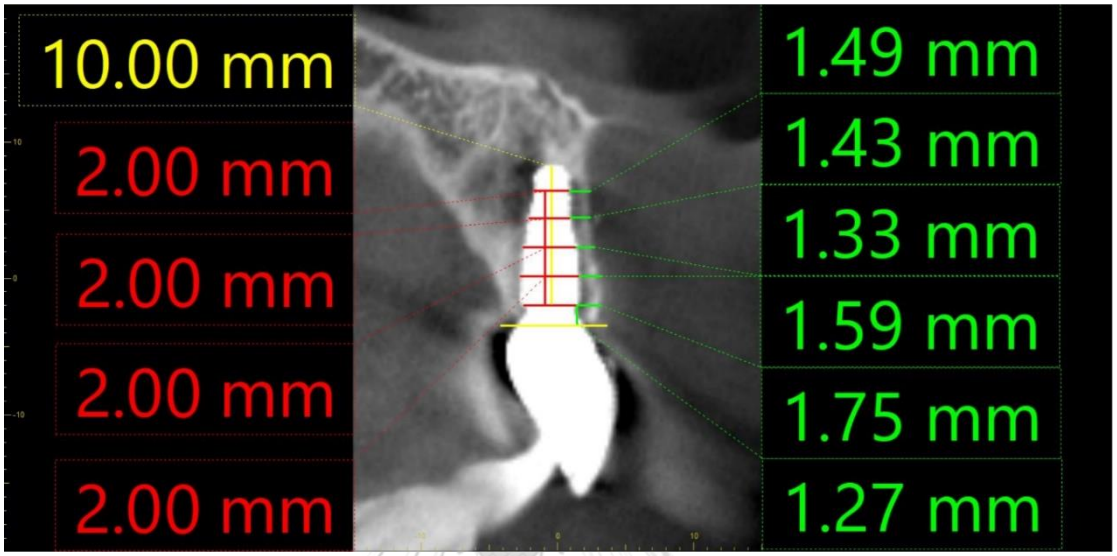


Figure 15: shows radiographic image in sagittal view shows vertical facial bone height and horizontal facial bone height at 0, 2, 4, 6, and 8 mm.

11.Statistical analysis:

Statistical analysis was performed by using SPSS. Using Shapiro-Wilk test to see distribution of the data. If the data were normal distribution, used independent t test and repeated ANOVA. But, if the data were not normal distribution, used Mann-Whitney U test and Friedman test. The differences were considered statistically significant when p-value was less than 0.05.

The statistical hypothesis:

In clinical measurement of bone formation

H_0: There was no difference in vertical and horizontal facial bone thickness between using Acemannan with demineralized bovine bone graft (Cerabone®) and demineralized bovine bone graft (Cerabone®) alone in implant placement with simultaneous bone graft.

H_A: There was difference in vertical and horizontal facial bone thickness between using Acemannan with demineralized bovine bone graft (Cerabone®) and demineralized bovine bone graft (Cerabone®) alone in implant placement with simultaneous bone graft.

In imaging measurement of bone formation

H_0: There was no difference in vertical and horizontal bone height between using Acemannan with demineralized bovine bone graft (Cerabone®) and demineralized bovine bone graft (Cerabone®) alone in implant placement with simultaneous bone graft.

H_A: There was difference in vertical and horizontal bone height between using Acemannan with demineralized bovine bone graft (Cerabone®) and demineralized bovine bone graft (Cerabone®) alone in implant placement with simultaneous bone graft.

CHAPTER IV

RESULT, DISCUSSION AND CONCLUSION

12.Result

According to Table1, the study participants composed of 20 subjects with averaged 50.50 ± 15.30 years old. 10 subjects were male and other 10 were female. Most of surgical sites were edentulous area at maxillary central incisor, which had been lost more than 6 months before surgery. Most of participants had good oral hygiene, thick gingival biotype, and medium smile line. All patients were non-smoking, non-alcohol, and have no parafunction habits. Implants'diameter 4.0 mm, and healing abutments' diameter 4.5 mm were mostly used in this study. All implants were 10 mm in length. All cover screws were same height at 2 mm, and same diameter at 3.0 mm. All operations were done in maxilla with operation time within 1 hour 30 mins. All demographic data of patients between 2 groups were not significantly different.

None of patient experienced soft tissue dehiscence and screw exposure after 2 weeks of surgery. All patients underwent mild inflammation and swelling. No one got severe pain or infection. All participants (10-control and 10-acemannan treated group) attended 3 and 6 months in CBCT follow up. There were no dropouts.

Table 1: Clinical data and patient's demographic data.

Variable	Control N=10	Acemannan N=10	Total N=20	P-value
	N (%)			
Gender				
- Male	4 (40)	6 (60)	10 (50)	0.371
- Female	6 (60)	4 (40)	10 (50)	
Site of operation at maxilla				
- Central	8 (80)	7 (70)	15 (75)	0.606
- Lateral	2 (20)	3(30)	5(25)	
Cause				
- Periodontitis	2 (20)	0 (0)	2 (10)	0.164
- Dental caries	3 (30)	6 (60)	9 (45)	
- Trauma	5 (50)	4 (40)	9 (45)	
Duration of losing teeth				
- 2 - 6 months	5 (50)	3 (30)	8 (40)	0.361
- > 6 months	5 (50)	7 (70)	12 (60)	
Oral hygiene				
- Good	9 (90)	7 (70)	16 (80)	0.264
- Fair	1 (10)	3 (30)	4 (20)	
- Poor	-	-	-	
Gingival biotype				
- Thick	7 (70)	8 (80)	15 (75)	0.606
- Thin	3 (30)	2 (20)	5 (25)	
Smile line				
- High	1 (10)	1 (10)	2 (10)	0.890
- Medium	6 (60)	5 (50)	11 (55)	
- Low	3 (30)	4 (40)	7 (35)	
Diameter of implant				
- 3.5 mm.	1 (10)	1 (10)	2 (10)	1.0
- 4.0 mm.	9 (90)	9 (90)	18 (90)	
Diameter of healing abutment				
- 3.3 mm.	1 (10)	0 (0)	1 (5)	0.305
- 4.5 mm.	9 (90)	10 (100)	19 (95)	

Height of healing abutment				
- 4.5 mm.	5 (50)	5 (50)	10 (50)	1.0
- 5.5 mm.	5 (50)	5 (50)	10 (50)	
Operator				
- N.D.	3 (30)	3 (30)	6 (30)	0.867
- N.B.	3 (30)	4 (40)	7 (35)	
- N.C.	4 (40)	3 (30)	7 (35)	
	Mean ± S.D.			
Age (20-78 years)	50.2 ± 19.17	50.8 ± 11.25	50.5 ± 15.3	0.933
Width of bone defect (1.0-4.0 mm.)	2.2 ± 1.4	2.4 ± 1.08	2.3 ± 1.22	0.582
Length of bone defect (3.0-13.0 mm.)	7.1 ± 3.21	7.6 ± 3.23	7.35 ± 3.17	0.734

12.1 Clinical results

The vertical (initial IS-BIC, initial IS-AC) and horizontal (initial HDW) buccal bone after implant placement between 2 groups were not significantly different. Width of keratinized mucosa between 2 groups at pre-operative, post-operative 3 and 6 months were also not different. Width of keratinized mucosa reduced after the operation with average at pre-operative, 3 and, 6 months post-operative 6.1 ± 2.05 mm, 5.7 ± 1.87 mm, and 5.55 ± 1.76 mm, respectively. Average depth of probing after prosthesis fixation was 2.70 ± 0.57 mm with not statistically different between 2 groups as shown in Table2.

Table 2: The clinical baseline of labial bone and soft tissue change.

Variable	Control N=10	Acemannan N=10	Total N=20	P-value
	Mean ± S.D.			
Initial IS-BIC (1.0-10.0 mm.)	3.65 ± 2.11	4.7 ± 2.83	4.18 ± 2.49	0.36
Initial IS-AC (mm.)				
- Mesial (-1.0 to -4.0 mm.)	-2.8 ± 1.03	-2.45 ± 0.89	-2.63 ± 0.96	0.439
- Distal (-1.0 to -4.0 mm.)	-2.4 ± 1.17	-2.25 ± 0.86	-2.33 ± 1.00	0.782

Initial HDW (0-2.0 mm.)	0.95 ± 0.79	0.90 ± 0.88	0.93 ± 0.82	0.875
Keratinized mucosa (mm.)				
- pre-operative (3.0-9.0 mm.)	5.4 ± 2.12	6.8 ± 1.82	6.1 ± 2.05	0.13
- post-op 3 m. (3.0-9.0 mm.)	4.9 ± 1.73	6.5 ± 1.72	5.7 ± 1.87	0.052
- post-op 6 m. (2.5-8.0 mm.)	4.8 ± 1.62	6.3 ±1.64	5.55 ± 1.76	0.054
Difference of keratinized mucosa				
- 3 m. – preop (0 to -3 mm.)	-0.7 ± 1.06	-0.3 ± 0.48	-0.5 ± 0.83	0.298
- 6 m.– preop (0 to -2 mm.)	-0.2 ± 0.32	-0.1 ± 0.42	-0.15 ± 0.37	0.556
- 6 m. – 3 m. (0 to -1 mm.)	-0.6 ± 0.84	-0.5 ± 0.53	-0.55 ± 0.69	0.754
Probing depth after crown fixation (2.0-4.0 mm.)	2.65 ± 0.57	2.75 ± 0.59	2.70 ± 0.57	0.912

12.2 Imaging results

The CBCT data of 2 groups were randomly before measured by double blinded oral and maxillofacial surgery and radiology specialists. However, the images were re-evaluated by the same examiners one month after first evaluation. The interobserver and intraobserver value (Intraclass correlation coefficient: ICC) for image estimation were 0.96 and 0.98, individually.

The change in vertical and horizontal of buccal bone height (ΔVBH and ΔHBBT) between 3 months after surgery and immediately post-surgery in the acemannan-treated group was significantly smaller compared with the control group as report by table3 (ΔVBH: independent t-test, F= -2.538; df=18; $p<0.05$) ($\Delta HBBT_0$: independent t-test, F= -2.177; df=18; $p<0.05$) ($\Delta HBBT_2$: independent t-test, F= -4.024; df=18; $p<0.05$) ($\Delta HBBT_4$: Mann-Whitney U test, U= 14; $p<0.05$) ($\Delta HBBT_6$: Mann-Whitney U test, U= 19.5; $p<0.05$) ($\Delta HBBT_8$: Mann-Whitney U test, U= 24; $p<0.05$). The difference in the dimensional change of buccal bone between the two groups was not significant for both time points at 6 months - immediately post-surgery and 6

months – 3 months. However, the amount of bone resorption in acemannan group was less than controlled group (Table3-4) (Figure17-18).

Table 3: The dimensional change of labial bone in 3 months and 6 months post-operation.

Measurement	Control N=10	Acemannan N=10	P-value
1. 3 months – immediate ($\Delta VFBT_1$, $\Delta HFBT_1$) (mm.)			
Δ_{VFBT}	-0.80 ± 0.46	-0.28 ± 0.46	0.021*
Δ_{HFBT_0}	-0.99 ± 0.71	-0.38 ± 0.52	0.044*
Δ_{HFBT_2}	-0.98 ± 0.57	-0.10 ± 0.39	0.001*
Δ_{HFBT_4}	-0.70 ± 0.50	0.01 ± 0.62	0.005*
Δ_{HFBT_6}	-0.32 ± 0.58	0.14 ± 0.55	0.019*
Δ_{HFBT_8}	-0.37 ± 0.59	0.32 ± 1.05	0.05*
2. 6 months – immediate ($\Delta VFBT_2$, $\Delta HFBT_2$) (mm.)			
Δ_{VFBT}	-0.96 ± 0.64	-0.52 ± 0.58	0.125
Δ_{HFBT_0}	-0.99 ± 0.74	-0.6 ± 0.65	0.229
Δ_{HFBT_2}	-0.93 ± 0.56	-0.55 ± 0.83	0.089
Δ_{HFBT_4}	-0.70 ± 0.61	-0.19 ± 0.73	0.111
Δ_{HFBT_6}	-0.34 ± 0.73	-0.15 ± 0.63	0.553
Δ_{HFBT_8}	-0.21 ± 0.77	0.14 ± 0.64	0.286
3. 6 months – 3 months ($\Delta VFBT_3$, $\Delta HFBT_3$) (mm.)			
Δ_{VFBT}	-0.24 ± 0.28	-0.15 ± 0.36	0.582
Δ_{HFBT_0}	-0.22 ± 0.24	0.01 ± 0.42	0.176
Δ_{HFBT_2}	-0.45 ± 0.59	0.06 ± 0.28	0.30
Δ_{HFBT_4}	-0.20 ± 0.35	0.01 ± 0.37	0.19
Δ_{HFBT_6}	-0.29 ± 0.66	-0.02 ± 0.40	0.143
Δ_{HFBT_8}	-0.21 ± 0.77	0.14 ± 0.63	0.286

*denotes statistically significant difference at 0.05 level

Table 4: The percent dimensional change of labial bone in 3 months and 6 months post-operation.

Measurement	Control N=10	Acemannan N=10	P-value
1. 3 months – immediate ($\Delta VFBT_1$, $\Delta HFBT_1$) (%)			
Δ_{VFBT}	-40.13 ± 17.44	-12.77 ± 18.38	0.003*
Δ_{HFBT_0}	-39.79 ± 21.69	-13.50 ± 17.71	0.010*
Δ_{HFBT_2}	-34.29 ± 16.46	-0.94 ± 16.71	0.001*
Δ_{HFBT_4}	-27.27 ± 14.60	17.63 ± 53.97	0.001*
Δ_{HFBT_6}	-22.08± 9.58	13.38 ± 33.86	0.001*
Δ_{HFBT_8}	-28.35 ± 23.21	30.75 ± 79.74	0.038*
2. 6 months – immediate ($\Delta VFBT_2$, $\Delta HFBT_2$) (mm.)			
Δ_{VFBT}	-45.57 ± 23.65	-19.14 ± 25.77	0.028*
Δ_{HFBT_0}	-38.29 ± 26.96	-22.57 ± 22.91	0.177
Δ_{HFBT_2}	-34.05 ± 20.94	-16.96 ± 23.07	0.100
Δ_{HFBT_4}	-24.18 ± 35.31	7.14 ± 44.08	0.043*
Δ_{HFBT_6}	-22.56 ± 22.35	-0.10 ± 34.45	0.115
Δ_{HFBT_8}	-16.95 ± 35.41	13.99 ± 40.37	0.125
3. 6 months – 3 months ($\Delta VFBT_3$, $\Delta HFBT_3$) (mm.)			
Δ_{VFBT}	-8.70 ± 30.32	-8.10 ± 20.50	0.739
Δ_{HFBT_0}	-11.27 ± 16.31	0.33 ± 35.05	0.250
Δ_{HFBT_2}	-16.60 ± 17.11	0.27 ± 17.84	0.011*
Δ_{HFBT_4}	-7.26 ± 12.75	0.31 ± 39.72	0.289
Δ_{HFBT_6}	-9.32 ± 24.89	0.43 ± 26.75	0.410
Δ_{HFBT_8}	-11.00 ± 114.39	0.65 ± 37.65	0.687

*denotes statistically significant difference at 0.05 level

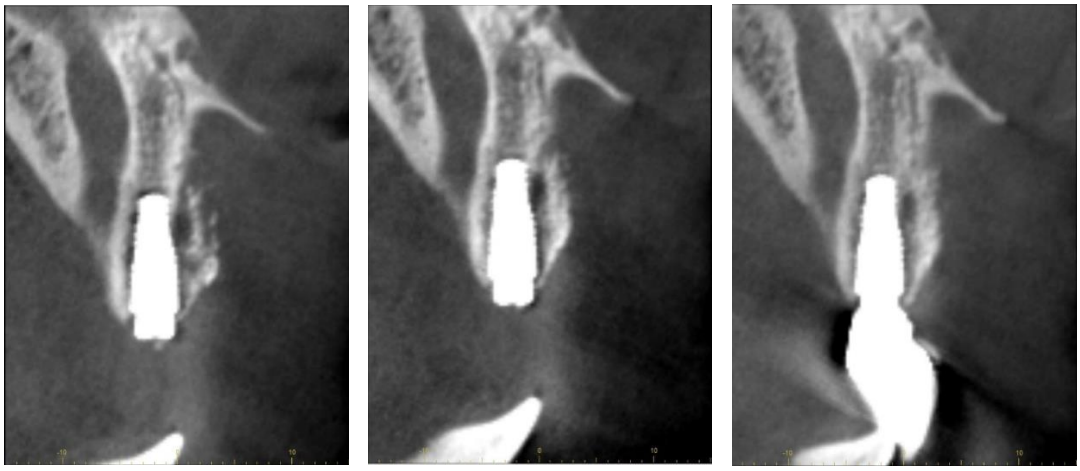


Figure 16: shows radiographic image of acemannan-treated group with implant placement in immediate, 3 months, and 6 months post-operation.

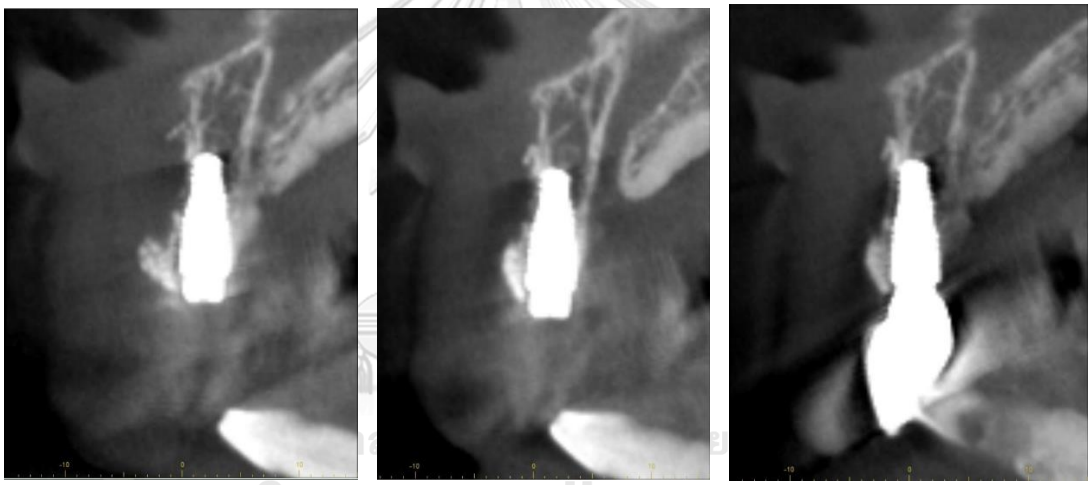


Figure 17: shows radiographic image of control non-acemannan group with implant placement in immediate, 3 months, and 6 months post-operation.

13. Discussion

At present, implant placement with simultaneous guided bone regeneration is a widely utilized procedure due to the anatomic characteristics and limitations of anterior maxilla. Studies have shown that early or delayed implant placement with simultaneous GBR is a predictable treatment modality with good clinical and aesthetic outcomes in the long term[42-44]. Nevertheless, the fact that xenogenic graft has been merely an inactive osteoconductive scaffold for the gradual growth of natural bone, leaves much space for improvement[45]. Due to the wide application of such techniques, enhancing the level of osteoconductivity or even better introducing osteoinductive potential could be of major clinical significance. It is therefore no surprise that significant research effort is focused in adding biological agents to the xenografts, with growth factors[46], platelet rich fibrin, bio-active coatings and more[47, 48].

For demographic data of patient as shown in Table 1, all data were not significant different between acemannan and controlled groups (including age, gender (male-female), site (central-lateral incisor), duration of losing teeth (2-6months, >6months), cause of losing teeth (periodontitis, dental caries, trauma), oral hygiene (good-fair), gingival biotype (thick-thin), smile line (high, medium, low), width and length of bone defect). Study of Shah[49] found a positive correlation between gingival thickness and width of keratinized mucosa. However, this study did not found relation, this probably due to less sample sizes. This study includes of 3 operators (N.D, N.B, N.C.) which had random assigned to do surgery in both acemannan and controlled group with no significant difference. Diameter of implants, diameter and height of healing abutments were also not significant different between 2 groups. These showed that all participants in 2 groups were not different and revealed no bias for sample selection.

In Table 2, clinical baseline of labial bone including initial IS-BIC, initial IS-AC, and initial HDW were not significant different between 2 groups. These meant labial

bone in both acemannan and controlled groups were similar at baseline. Therefore, the different of labial bone in image at 3 months post-operation was the effect of acemannan and xenograft. Nevertheless, IS-BIC, IS-AC, and HDW could not be measured at 3- and 6-months follow-up. Because the following operation did not require flap opening, the measurement could be done in implant placement step only. For the soft tissue outcome, width of keratinized mucosa and probing depth between 2 groups were not significantly different. Keratinized mucosa width was reduction after 3- and 6-months post-operation because of inflammation after flap operation in implant placement procedure. Although width of keratinized mucosa at 6 months post-operation was less than 3 months and pre-operation, acemannan-treated group still found less reduction than controlled-group. Comparing between 6 months post-operation and pre-operation, width of keratinized mucosa reduced about 0.1 and 0.2 mm. in acemannan and controlled groups, respectively. Nevertheless, no research study about correlation between acemannan and width of keratinized mucosa. Regarding to probing depth, Pradeep et al[50] revealed that acemannan enhance greater reduction in probing depth as well as more gain in clinical attachment level in type 2 diabetes and chronic periodontitis patients. This study recorded probing depth only 1 time after prosthesis fixation due to limit of time. For that reason, the effect of acemannan on probing depth could not be concluded in this study.

This research used acemannan with xenograft for implant placement with simultaneous GBR. Edentulous areas were allowed for 2 months of healing after extraction. After 2 months of undisturbed healing, the socket partly fills with new bone formation mainly in the apical areas, while much of the buccal bone is already resorbed. Such dimensional change could be easily assessed by means of dental cone beam computer tomography, as such areas are not superimposed to any other anatomical structures such as maxillary sinus, zygomatic bone, nasal structure, or mental foramen. Consequently, volumetric changes of bone were evaluated

prospectively in both groups, in order to assess the impact of acemannan during the early healing process and short-term maintenance. In the early phases of the healing, volumetric changes are mainly attributed to the shrinking of the augmented area under functional forces and mastication, while at later phases, new bone formation is taking place in the spaces between the graft particles[51]. In the meanwhile, the biodegradation of the Jason membrane in expected to occur within 8 to 12 weeks, protecting the regenerated area from gingival tissue migration during the early stages of healing[52]. As the resorbable collagen membrane offers no support in maintaining space, areas augmented with particulate graft might initially lose volume due to compression of early wound from functional forces, especially in non-self-contained defects.

For the CBCT outcome as shown in Table 3, there was significantly less bone reduction in the augmented areas of the test group at 3 months, which might suggest some positive influence of the acemannan in the early stages of healing. This could be potentially attributed to better stabilization of the blood clot, or possibly a faster maturation of the connective tissue at the early stages. This difference did not reach the level of significance between 3 and 6 months, although for the overall period of observation the experimental group lost significantly less volume than the control. This might imply a more important role for the acemannan in the early phase of healing, which includes inflammatory, reparative, and remodeling stage[53].

The CBCT results of this research confirmed with previous study of Jettanacheawchankit et al[29]. They reported that acemannan stimulated the healing process of extraction socket and accelerated the functions of alkaline phosphatase enzyme and bone morphogenic protein 2 which are the important components for bone formation. This efficacy of acemannan in the present study could be a result of the upregulation of cell proliferation, expression of Runx2, GDF-5, VEGF, BMP-2, alkaline phosphatse, type I collagen, osteopontin, osteocalcin bone sialophosphoprotein, or mineralization[11, 13, 34, 54]. Furthermore, acemannan has an

immunomodulatory function that can minimize the inflammatory phase before bone formation phase[55]. Modulation of inflammatory cell response can enhance bone tissue regeneration[56]. Boonyagul et al[11] reported that the acemannan-treated group had higher bone mineral density and faster bone healing detected by radiographs after placing acemannan sponge in the extraction socket after 4 weeks. It is the same as Chantarawatit et al's study. They revealed a significantly acceleration of new alveolar bone after 60 days of applying acemannan sponge into the defects[13]. Another confirmed research, study of Pachimalla et al[57] revealed that acemannan hydrophilic gel coating on implant surface increased new bone regeneration, proliferation of osteoblast cells, and bone to implant contact by histomorphometric analysis in 4 weeks. For the result from Micro-Computed tomography (Micro-CT), Godoy et al[34] described that a significant increase in bone surface and bone volume of calvarial specimens was detected after added acemannan in defects for 4 weeks. The radiographic outcome of this study was supported by Jansisyanont's study[12]. They reported a greater significantly difference of percent radiographic density of formed bone in the sockets in acemannan-treated group after 3 months post-extraction. However, the results after 3 months post-extraction were unknown due to follow-up period was ended in 3 months. Recently research about acemannan by Le Van et al[58] revealed a significantly greater of the percentage of total bone defect volume reduction at 3 months after adding acemannan sponges with apical surgery of teeth. However, there was not significant different in 6- and 12-months follow-up which was the same with this study. The area of acemannan placing was 3-walls defect which acemannan could not stabilized and and comfortably to resorb. It was the same reason at this study which placing acemannan at defect in anterior maxilla. That was why the result at 6- and 12-months post operation were not significant difference. It showed that acemannan induced rapid early osseous healing of defect in 3 months. Moreover, using acemannan sponge with direct and indirect sinus lift showed significantly enhanced bone formation in 3, and 6 months follow-up in study of Trinh et al[59, 60]. Study of Vu et al[61] revealed that acemannan induced significant

reduction in socket volume at 3-, 6-, and 12- months post-surgery. In this study, dimensional change of labial bone between two groups were similar at 6 months. This result was inconsistent with Trinh et al's study[59] and Vu et al's study[61]. Their surgical sites were maxillary sinus and tooth socket which had walls and space for acemnannan to maintain in the surgical site. Nonetheless, labial bone defect of anterior maxilla does not have enough walls and space for acemannan. Although using with membrane coverage, acemannan maybe leak out and resorb. This expected to be the reason for the outcome at 6 months which revealed greater bone in acemannan group, but not significantly. Less of sample size was also the reason. Large amount of sample size could be affected the difference between 2 groups to be significantly differented.

This observation might be simply reflecting the fact that most of the volumetric changes take place withing the first 3 months, with much slower change after that point. It is well documented that the rate of marginal bone remodeling around implants is changing at different stages after placement, with the fastest bone loss being observed during the first months after placement same as study of De Santis et al[62].

The results of this study should be perceived in the light of the limitations of the study sample. Although the implants were placed in narrow anatomic range (centrals and laterals) the morphology of the defect and the initial volume of the augmented area was not possible to be standardized. Defect morphology (e.g. self-contained – partially contained) as well as the clinical technique (e.g. overcontouring – undercontouring), the amount of graft particles used, tension of closing of the flap, could influence the initial volume reduction observed in the first stages of healing. Calibration of the operators and standardization of the surgical technique was conducted, but nevertheless the defect morphology and anatomic variations might have had an impact in the observed outcomes in a study of that size. Although the 3 operators had been trained by the same specialist members of the same clinic and

trained by the same oral and maxillofacial surgeon, the experience level might have differed. Furthermore, Acemannan particles cannot be placed alone as augmentation material due to its small size that might prone to creeping under mechanical forces. As well as acemannan in sponge form, also could not be used in this study. It was difficult to manipulate and could not be placed at defect site at anterior maxilla. Consequently, as the Acemannan was mixed 50-50 with DBB, its biological impact might have been reduced or modified. Finally, as the study was limited to radiographic measurements, no conclusions could be drawn as to the actual nature of the healing of the regenerated area and the rate of tissue maturation and formation of new bone. Further studies with longer follow up periods, greater sample size, and the addition of histological observations would be required to clarify the observations of this study and clarify the potential of biological agents like Acemannan in GBR procedures.

14. Conclusion

The results of this study revealed that Acemannan is a safe biomaterial for guided bone regeneration with implant placement and could demonstrate a potential favorable impact on imaging outcomes of bone formation in the early stages of healing.

15. Annex

แบบฟอร์มบันทึก Treatment Record

1.ซักประวัติ

1.1 ชื่อ.....นามสกุล.....

1.2 No.....HN.....

1.3 วัน/เดือน/ปี เกิด.....อายุ.....เพศ.....

1.4 เชื้อชาติ.....สัญชาติ.....

1.5 โรคประจำตัว.....

.....

1.6 ยาที่รับประทาน.....

.....

1.7 ประวัติการแพ้ยา/อาหาร.....

.....

1.8 ประวัติการรักษาทางทันตกรรมในอดีต.....

.....

1.9 ประวัติการได้รับรังสีรักษา/ฉายแสง ☐ ไม่เคย ☐ เคย เป็นเวลานาน.....

1.10 ประวัติการสูบบุหรี่ ☐ ไม่สูบ ☐ สูบ จำนวน.....

1.11 ประวัติการดื่มแอลกอฮอล์ ☐ ไม่ดื่ม ☐ ดื่ม ความถี่.....

1.12 Chief complaint.....

1.13 Patient illness.....

1.14 สาเหตุของการสูญเสียฟัน.....

1.15 จำนวนระยะเวลาที่สูญเสียฟัน.....ปี.....เดือน

2.ตรวจร่างกาย

2.1 ก่อนทำการผ่าตัดฝังรากเทียม

2.1.1 ตำแหน่งซี่ฟัน..... ☐ maxilla ☐ mandible

☐ ฟันหน้า ☐ ฟันกรามน้อย

2.1.2 ปริมาณกระดูกที่หายไป

ด้าน buccal ☐ mild (<25%) ด้าน lingual ☐ mild (<25%)

☐ moderate (25-50%) ☐ moderate (25-50%)

☐ severe (>50%) ☐ severe (>50%)

Depth.....Width.....

2.1.3 Parafunction habit ☐ มี ☐ ไม่มี

2.1.4 Oral hygiene ☐ good ☐ fair ☐ poor

2.1.5 Gingival biotype ☐ thick ☐ thin

2.1.6 Smile line ☐ high ☐ medium ☐ low

2.2 ขณะทำการผ่าตัดฝังรากเทียม

2.2.1 รากเทียมที่ใช้ขนาดเส้นผ่านศูนย์กลาง.....ความยาว.....

2.2.2 cover screw ที่ใช้ขนาดเส้นผ่านศูนย์กลาง.....ความสูง.....

2.2.3 ตำแหน่งและขนาดรากเทียมที่ expose(thread).....

2.2.4 ปริมาณและขนาดกระดูกที่ใช้.....

2.2.5 ปริมาณและขนาดเมมเบรนที่ใช้.....

2.2.6 มีส่วนผสมของสารอะซิแมนแนน ☐ มี ☐ ไม่มี

2.2.7 ระยะเวลาที่ใช้ในการผ่าตัด.....

2.2.8 ผู้ผ่าตัด ☐ ณฐพร ดีศรีเจริญเกียรติ

☐ ณัฐชา เบญจพลากร

☐ เนตรนฎา จงเรืองศรี

☐ อื่นๆ

2.3 หลังทำการผ่าตัดฝังรากเทียม

2.3.1 การตรวจทางคลินิก

	Width of KM	Inflammation	IS-AC	IS-BIC	HDW	PD	Recession
Immediate post-op (pre-op)							
Post-op 2 weeks							
Post-op 3 months							
Post-op 6 months							

*IS-AC = ระยะแนว vertical จาก implant surface ไปยัง alveolar crest

IS-BIC = ระยะแนว vertical จาก implant surface ไปยัง first bone to implant contact

HDW = ระยะแนว horizontal จาก implant surface ไปยัง alveolar crest

2.3.2 การตรวจทางภาพรังสี

	VFBT	HFBT				
		0	2	4	6	8
Immediate post-op						
Post-op 3 months						
Post-op 6 months						

*VFBT = vertical facial bone thickness ระยะแนว vertical จาก implant platform ไปยัง จุดสูงสุดของ facial bone

HFBT = horizontal facial bone thickness ระยะแนว horizontal จาก implant platform ไปยัง ขอบ facial bone ที่ระยะต่างๆ

แบบฟอร์มบันทึกข้อมูล

ID	Bone formation																		1 stage intra-operation									stage intra-operatio	
	Radiographic measurement																												
	VFBT			HFBT															implant		cover screw		thread expose	bone add	Acemannan	operation time	operator	healing abutment	
				0			2			4			6			8			diameter	length	diameter	length						diameter	height
	immediate postop	3 m.	6m.																0=3.5 1=4.0	0=8 1=10	0=2	0=0 1=2			0=none 1=add	0= <1h. 1= 1-2h. 2= >2 h.	0=donut 1=nutcha 2=sai	0=3.3 1= 4.5	0=3.5 1=4.5
				immediate postop	3 m.	6m.	immediate postop	3 m.	6m.	immediate postop	3 m.	6m.	immediate postop	3 m.	6m.	immediate postop	3 m.	6m.											
1																													
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ID	History						Soft tissue									Bone formation							
																Clinical measurement							
	Gender	DOB	Age	Missing tooth		Cause	Parafunction habits	OH	Gingival biotype	Smile line	PD	Recession	KM			defect		bone loss		IS-AC		IS-BIC	HDW
	0=male 1=female			1=central 2=lateral 3=canine	0=maxilla 1=mandible	0=periodontitis 1=dental caries 2=trauma 3=other	0=none 1=detect	0=good 1=fair 2=poor	0=thick 1=thin	0=high 1=medium 2=low	6 m.	6 m.	preop	3 m.	6 m.	width	height	buccal 0= <25% 1= 25-50% 2= >50%	lingual 0= <25% 1= 25-50% 2= >50%	immediate postop		immediate postop	immediate postop
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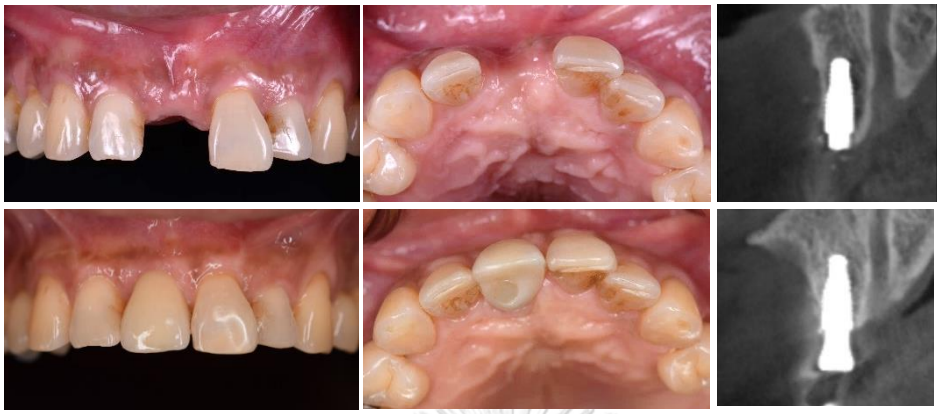
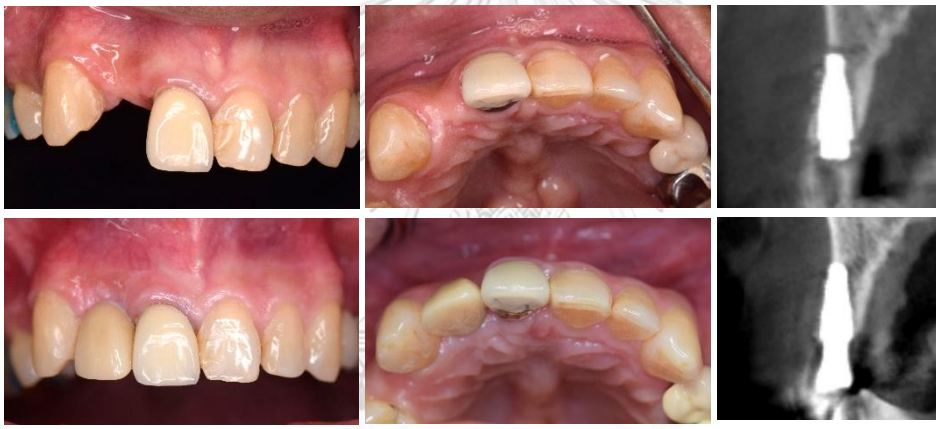
Pictures of acemannan group

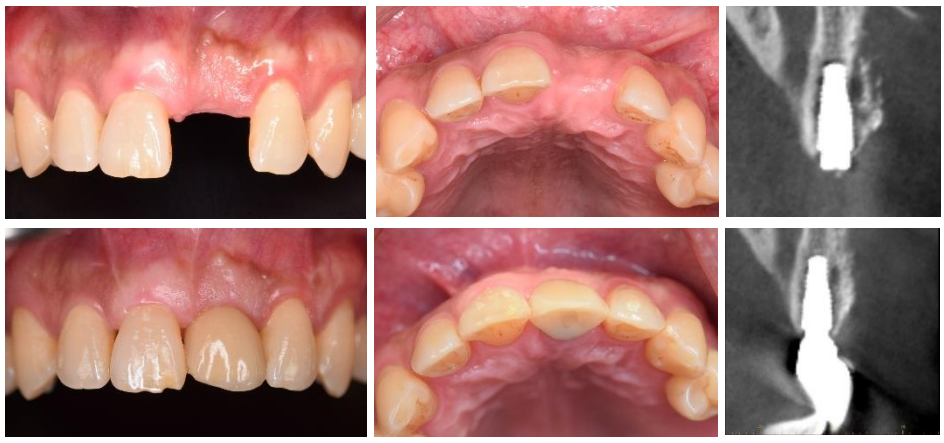
Case #1



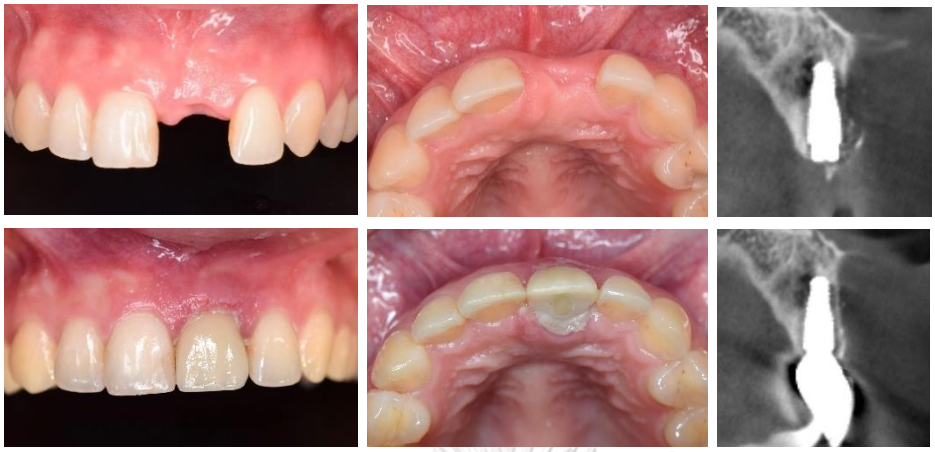
Case #2



case #3



Case #4



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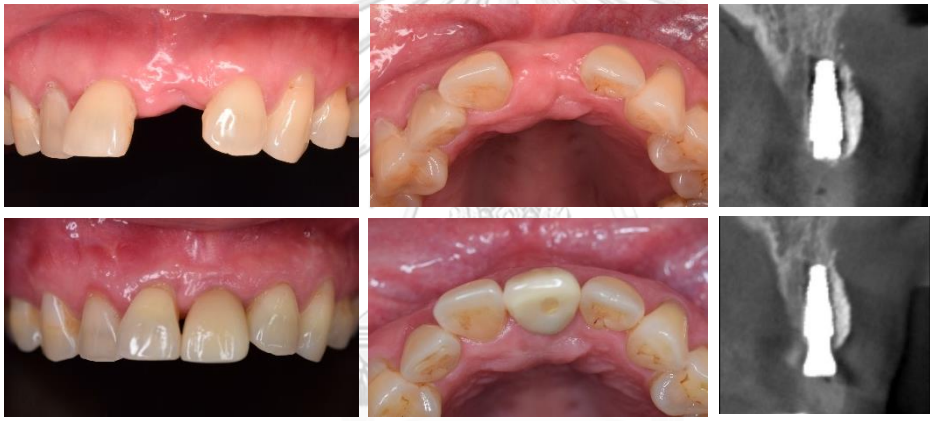
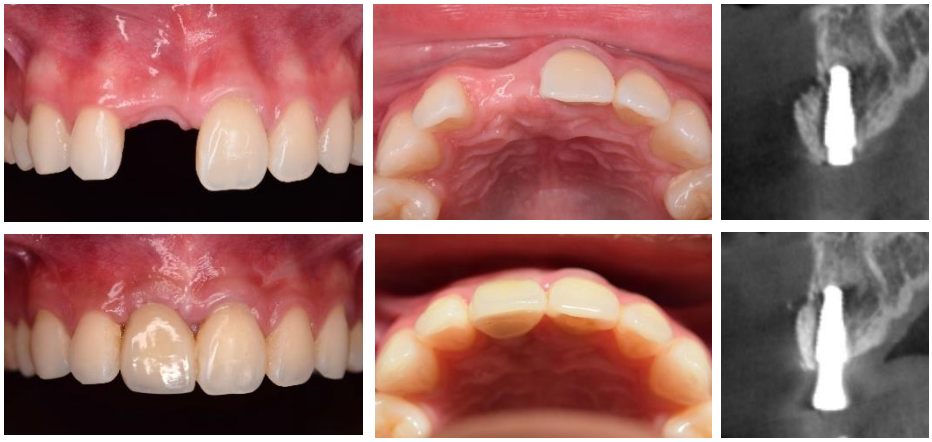
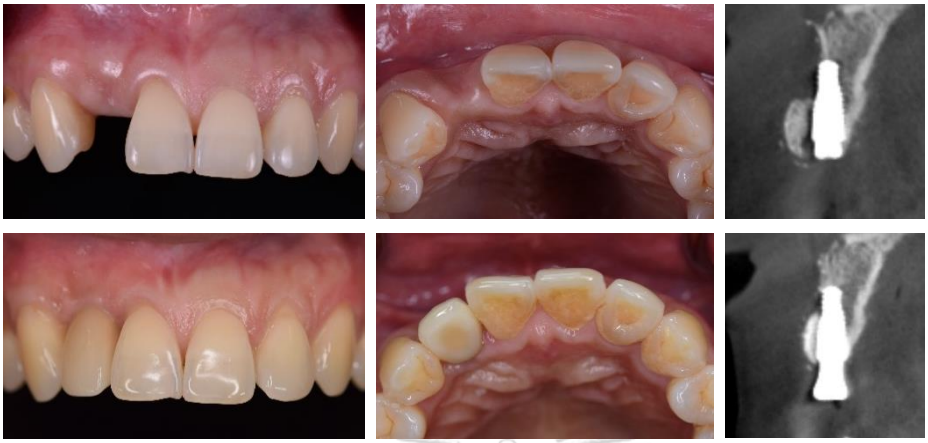


Case #6

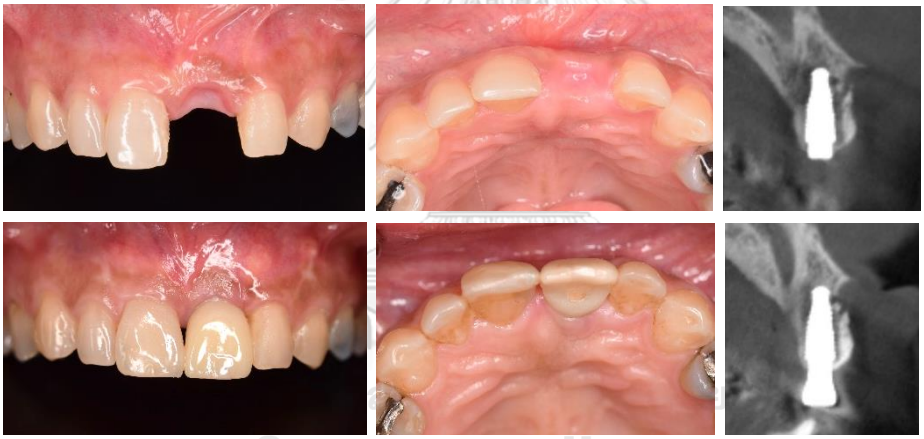


Pictures of controlled group (non-acemannan)

Case #1



case #2



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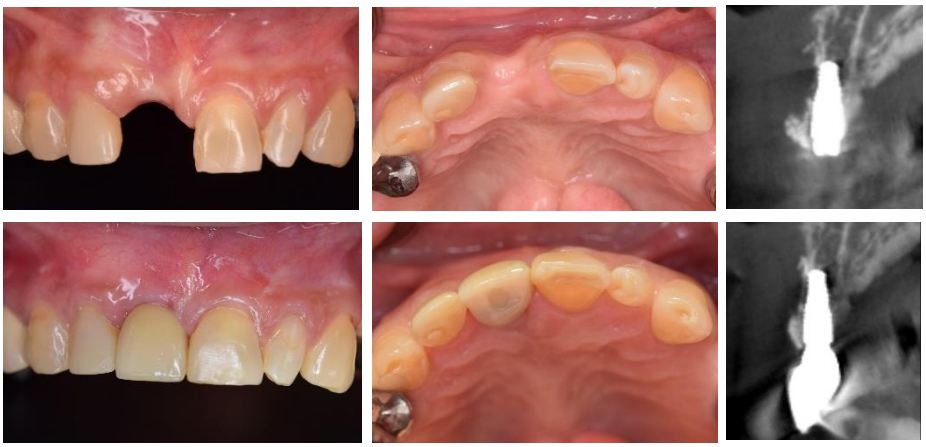

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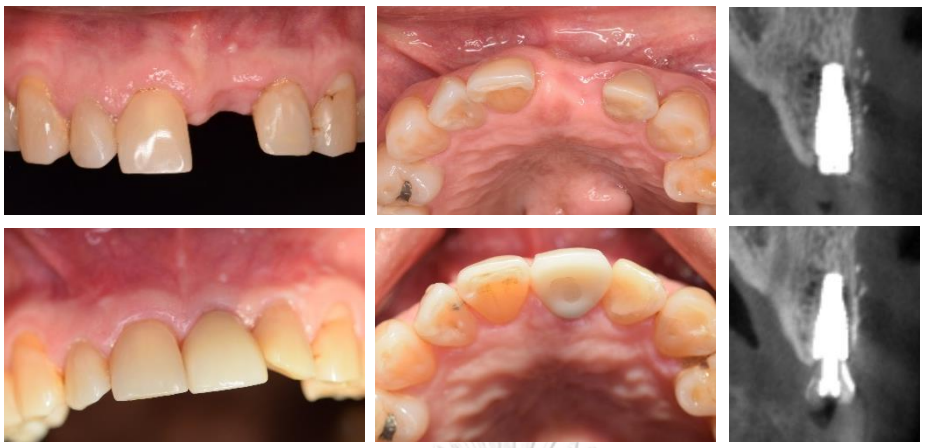
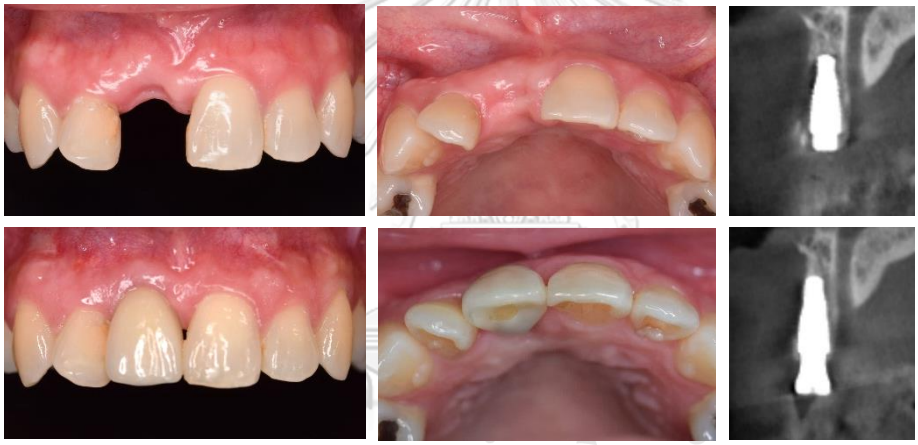
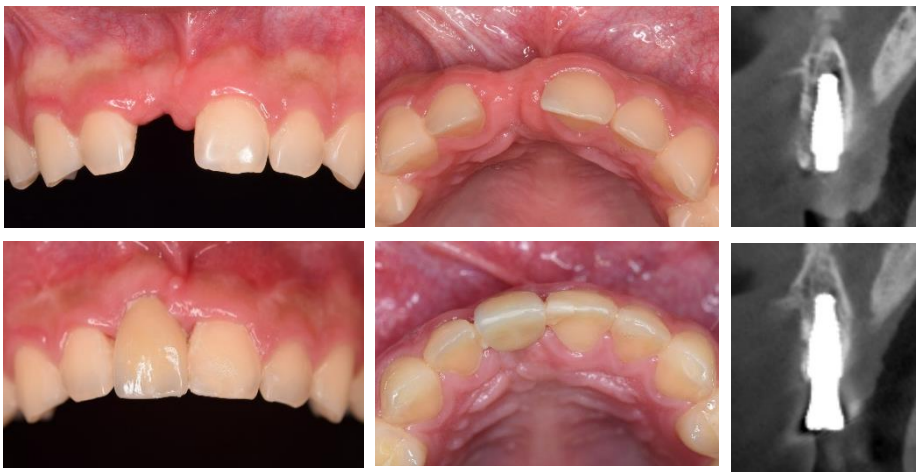


case #5



case #6



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