Comparative study between vitamin B 1-6-12 and vitamin B 12 for neurosensory recovery after bilateral sagittal split ramus osteotomy

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A Thesis Submitted in Partial Fulfillment of the Requirements
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การศึกษาเปรียบเทียบผลของวิตามินบี1-6-12 และวิตามินบี12 ต่อการหายของอาการชาของเส้นประสาทเบ้าฟันล่างหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟัน

น.ส.วรวีร์ ไตรสิงห์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ภาวะแทรกซ้อนสำคัญจากการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟันคือการบาดเจ็บต่อเส้นประสาทเบ้าฟันล่างซึ่งก่อให้เกิดอาการชาที่ริมฝีปากล่างและคาง แม้ว่าอาการชานี้จะไม่ใช่ปัญหารุนแรงต่อชีวิต แต่มีผลต่อคุณภาพชีวิตของผู้ป่วย วิตามินบีเป็นวิธีหนึ่งของการรักษาอาการชาของระบบประสาทส่วนปลายแบบไม่ต้องผ่าตัด แต่การศึกษาเกี่ยวกับวิตามินบีในอาการชาหลังจากศัลยกรรมขากรรไกรล่างเพื่อการจัดฟันยังมีจำกัด การศึกษานี้จึงทำการศึกษาผลของวิตามินบี 1-6-12 และวิตามินบี 12ในรูปแบบรับประทานต่ออาการชาหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟัน การศึกษานี้เป็นการศึกษาแบบสุ่มในผู้ป่วยที่มีอาการชาหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟันจำนวน 75 คน แบ่งผู้ป่วยเป็น 3 กลุ่มๆละ 25 คน คือ กลุ่มที่ได้รับวิตามินบี 1-6-12 กลุ่มที่ได้รับวิตามินบี 12 และกลุ่มควบคุม โดยกลุ่มที่ได้รับวิตามินบีจะได้รับเป็นชนิดเม็ด ทาน 1 เม็ด วันละ 3 ครั้งหลังผ่าตัดเป็นเวลา 6 เดือน และกลุ่มควบคุมจะไม่ได้รับวิตามินหลังการผ่าตัด การวัดอาการชาจะใช้การวัด 4 ชนิด คือ การแยกสองจุดแบบนิ่ง, การแยกสองจุดแบบเคลื่อนไหว การแตะแบบเบา และการแตะด้วยเครื่องมือปลายแหลม แล้วนำมาคิดเป็นคะแนน นำคะแนนที่ได้มาหาค่าสัดส่วนการหายของอาการชา ผลการศึกษาพบว่าทุกกลุ่มมีสัดส่วนการหายของอาการชาในกลุ่มตัวเองสูงขึ้นอย่างมีนัยสำคัญเมื่อเวลาผ่านไป เมื่อเปรียบเทียบระหว่างกลุ่มพบว่ากลุ่มที่ได้รับวิตามินบี 1-6-12 มีสัดส่วนการหายชาสูงสุดอย่างมีนัยสำคัญเมื่อเทียบกับกลุ่มควบคุมและกลุ่มวิตามินบี 12 สรุปได้ว่า วิตามินบี 1-6-12 ในรูปแบบรับประทานทำให้เกิดการหายชาหลังศัลยกรรมขากรรไกรล่างมากกว่าเมื่อเปรียบเทียบกับวิตามินบี 12 ในรูปแบบรับประทานและกลุ่มที่ไม่ได้รับวิตามินบีหลังการผ่าตัด

สาขาวิชา	ศัลยศาสตร์ช่องปากและแม็กซิลโลเฟเชียล	ลายมือชื่อนิสิต .....
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Worawee Trising : Comparative study between vitamin B 1-6-12 and vitamin B 12 for neurosensory recovery after bilateral sagittal split ramus osteotomy. Advisor: Paksinee Kamolratanakul, DDS, PhD

A major complication from Bilateral Sagittal Split Ramus Osteotomy (BSSRO) is inferior alveolar nerve injured that manifest as neurosensory disturbance (NSD) on the lower lip, chin. Although the NSD is not a life-threatening problem but it impacts the patient's daily life. Vitamin B is commonly used to treat peripheral neuropathy but it is only few study for NSD from BSSRO. The aim of this study was to evaluate the effect of oral vitamin B1-6-12 and vitamin B12 on NSD after BSSRO. The study design was as a randomized, single blinded control trial of 75 patients who were NSD from BSSRO (n=25). The first group was vitamin B1-6-12 group that taking 1 tablet 3 times daily. The second group was vitamin B12 group that taking 1 tablet 3 times daily. The third group was the control group without taking vitamin B. Clinical Neurosensory Testing (CNT) was performed with static two-point discrimination, moving two-point discrimination, light touch and pinprick at preoperation, immediate, 1 week, 1 month, 3 months and 6 months and converted to Global Sensitivity Score (GSS). GSS was calculated to recovery proportion and was analysed with Friedman test and post hoc analysis with Wilcoxon signed rank test for intragroup comparison on the passing time and Kruskal Wallis H test and post hoc with Mann Whitney U test were used for intergroup comparison. Results showed significantly increasing recovery improvement in all groups on the passing time (p<0.05). Vitamin B1-6-12 orally were significantly highest recovery proportion when comparing with and control vitamin B12 at 6 months (p=0.038, p=0.033).

Field of Study:	Oral and Maxillofacial Surgery	Student's Signature .....
Academic Year:	2018	Advisor's Signature .....

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Worawee Trising

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

BSSRO	Bilateral Sagittal Split Ramus Osteotomy
CNT	Clinical Neurosensory Testing
CT	Computed Tomography
GSS	Global Sensitivity Score
IAN	Inferior Alveolar Nerve
im. postop.	immediate postoperation
LT	Light Touch
MPD	Moving Two-Point Discrimination
mcg	microgram
mg	milligram
mm.	millimeter
NSD	Neurosensory Disturbance
OIDP	Oral Impact on Daily Performance
pc	after meal
po	per oral
PP	Pinprick
s	second
SD	Standard Deviation
SPD	Static Two-Point Discrimination
SSRO	Sagittal Split Ramus Osteotomy
tid	three times daily
VAS	Visual Analog Scale
VRO	Vertical Ramus Osteotomy
1 wk	1 week

1 mo	1 month
3 mo	3 months
6 mo	6 months

CHATER I
INTRODUCTION

1.1 Background and Rationale

Bilateral Sagittal Split Ramus Osteotomy (BSSRO) is a successful and most common surgical technique that combined with orthodontic treatment to correct the skeletal deformities of mandible. Although BSSRO is useful procedure, a major complication is the neurosensory disturbance (NSD) from inferior alveolar nerve (IAN) injured (1-3). This injury manifest as reduced sensation (hypoesthesia) on the lower lip, chin, buccal gingiva and dentition of the operating side postoperatively (4, 5).

The IAN injury is caused by iatrogenic damage, especially from incorrect splitting techniques or osteotomies. Nerve bruising may also result from excessive nerve manipulation after soft tissue dissection at the medial aspect of the mandibular ramus, nerve laceration, incorrect position of screws during fixation, large amount of mandibular movement and bad splits (6-10). Compression or stretching of nerve causes neurapraxia or axonotmesis (11-13). Moreover, the secondary effect of hypoxia and edema from surgery can damage the nerve which regularly results in a combination of neurapraxia and partial axonotmesis (9, 14). The neurapraxia and axonotmesis are recovery for day or months. Some cases, IAN transection occurs with results in neurotmesis and ranged from 1.3% to 7.0% (15). Neurotmesis is not unlikely spontaneous recovery but requires microneurosurgery (16).

The incidence of temporary NSD from several literatures vary from 20% (17) to 98 % (4). Moreover, the recent study showed immediately NSD after BSSRO was high as 80% (sides) and 91% (patients) subjectively (18).

Many studies reported that a majority of NSD (90%) was transient sensory impairment and spontaneous recovery was found within eight weeks (19-23). If NSD was present at 6 months (24, 25) or 1 year (26, 27) after surgery, it was considered permanent and the incidence was ranged from 0% (5, 28) to 82% (24).

Although the postoperative NSD is not a life-threatening problem but it impacts the quality of life of the patients (29-32) including eating, speaking, cleaning teeth, relaxing or sleeping, emotion, smiling or laughing, studying or working and enjoy contact with other people based on Oral Impact on Daily Performance (OIDP) (33, 34).

Many interventions are used to promote neurosensory recovery for peripheral neuropathy that can be classified into surgical treatment and non-surgical treatment (35). Vitamin B is a non-surgical treatment commonly used to treat peripheral neuropathy from diabetes, alcohol, human immunodeficiency virus infection, and leprosy because of the availability, affordability, generally well-tolerated with only a few reports of mild side effects. Thiamine (vitamin B1), pyridoxine (vitamin B6) and methylcobalamin (vitamin B12) play a role in nerve healing (36).

In Vivo studies, vitamin B1-6-12 or vitamin B12 exhibited beneficial for accelerated nerve regeneration in injury of sciatic nerve (37, 38), spinal cord (39), infraorbital nerve (40), corneal nerve (41) or optic nerve (42).Vitamin B1-6-12 and B12 has been common used for treat the NSD of IAN injury from orthognathic surgery or BSSRO. At present, few studies reported about effect of vitamin B in BSSRO. Vitamin B12 has been use for treat the NSD and the previous study revealed that the intranasal vitamin B12 spray effects on sensory function (43) and retrospective study reported vitamin B12 effected for nerve healing after BSSRO (18). In contrast, one prospective study reported that the combination of hydroxycobalamin (vitamin B12), uridine triphosphate and cystidine monophosphate intramuscular and orally administration did not effect to improve NSD (44). Moreover, there are limited studies using vitamin B12 nasal spray after BSSRO and no prospective clinical report using oral vitamin B1-6-12 or vitamin B12 to promote nerve healing after BSSRO. Thus, the aim of this study is to evaluate the effect of oral vitamin B1-6-12 and vitamin B12 on the recovery of nerve injury from BSSRO.

1.2 Research questions, objectives, hypothesis, Research design, Expected Benefits, Methodology Framework

1.2.1 Research questions

Do oral vitamin B1-6-12 or single vitamin B12 promote neurosensory recovery after Bilateral Sagittal Split Ramus Osteotomy (BSSRO)?

1.2.2 Research objectives

To evaluate the effect of oral vitamin B 1-6-12 or oral vitamin B12 in neurosensory recovery after BSSRO compared to control.

1.2.3 Research Hypothesis

Recovery from neurosensory disturbance after BSSRO is greater in patients receiving vitamin B1-6-12 or B12 compared to that of those who do not receive vitamin B1-6-12 or vitamin B12 after the same surgery.

H_{01}: Recovery proportion of NSD after BSSRO in patients who receiving vitamin B1-6-12 or vitamin B12 or non-vitamin B will not be different.

H_{02}: Recovery period of NSD after BSSRO in patients who receiving oral vitamin B1-6-12 or vitamin B12 or non-vitamin B will not be different.

H_{a1}: Recovery proportion of NSD after BSSRO in patients who receiving vitamin B1-6-12 or vitamin B12 or non-vitamin B will be different.

H_{a2}: Recovery period of NSD after BSSRO in patients who receiving oral vitamin B1-6-12 or vitamin B12 or non-vitamin B will be different.

1.2.4 Research Design

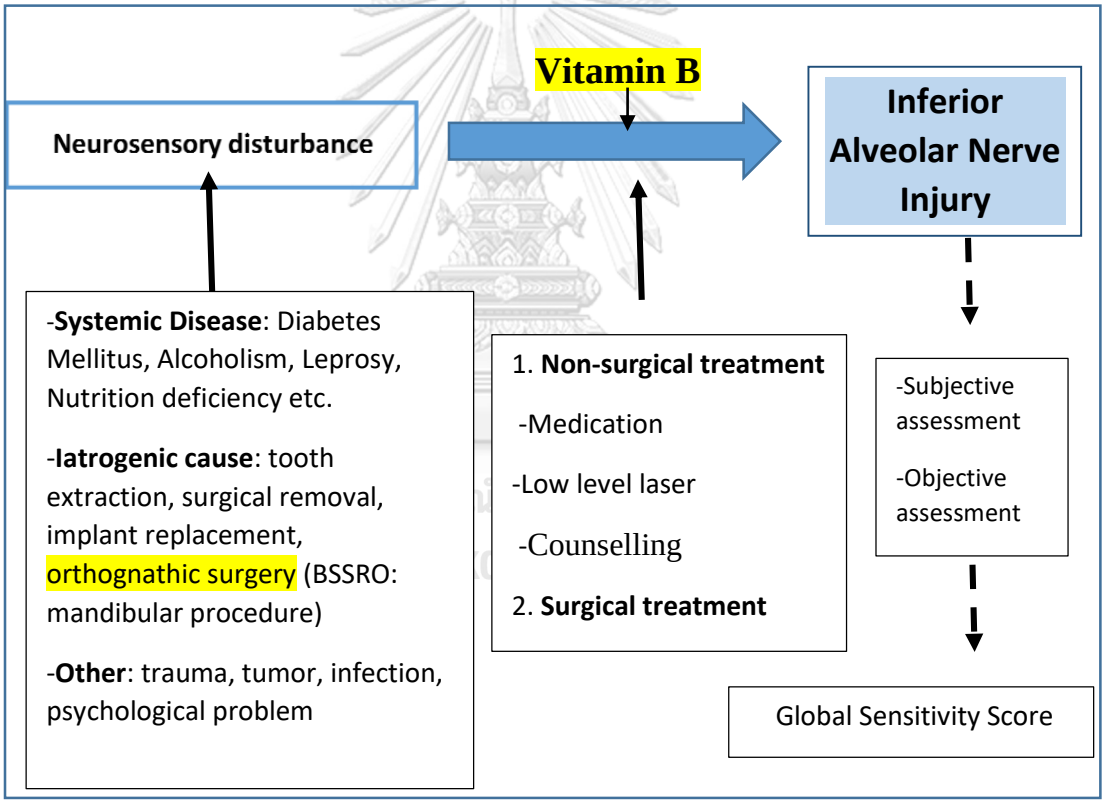
Randomized, single blind controlled clinical trial

1.2.5 Expected Benefits

1. This study will provide information about the efficacy of vitamin B 1-6-12 or vitamin B12 in treating neurosensory disturbance after BSSRO.

2. Vitamin B 1-6-12 or vitamin B12 can be used to treat patients after other oral surgical procedures as the standard of care.

1.2.6 Research Methodology Framework



CHAPTER II
REVIEW OF THE LITERATURES

2.1 Bilateral Sagittal Split Ramus Osteotomy (BSSRO)

In orthognathic surgery of the mandible, Bilateral Sagittal split Ramus Osteotomy or BSSRO is widely used procedure (45). BSSRO was introduced by Trauner and Obwegeser (46) in 1957 and was modified and improved by Dal Pont et al (47) in 1961, by Hunsuck (48) in 1968 and Epker (49) in 1977 to improve stability and reduced complication from surgical procedure. The BSSRO divides the mandible in the angular region of the ramus and body of the mandible. Between a medial horizontal cut on the ramus and a lateral vertical cut in the molar region, the mandible is sagittal split, ideally along the inner surface of the lateral cortex as Figure 1 (45). This osteotomy can be used for mandibular setback, advancement, and rotational movements. The proximal and distal bone fragments can be fixated with plate and screw and devices (45).

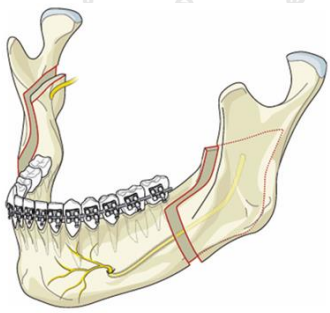


Figure 1 Risk of IAN injury due to osteotomy line in BSSRO procedure

The most incidence of postoperative complications are neurosensory disturbance, respiratory difficulty, neck pain, anterior open bite, and gastrointestinal disease respectively. The incidence of immediately neurosensory disturbance from BSSRO was 73.3% (2). Postoperative paresthesia is usually considered to be caused by mechanical damage of the sensory fibers of the IAN (50). The IAN is probably affected during BSSRO procedure due to line of the osteotomy close proximity to IAN (51). Normally, nerve runs along distal segment proximal segment. When nerve is attached to proximal segment and need direct manipulation of the nerve that cause compression or stretching, sawing and splitting of the mandible, presence of nerve exposure, nerve laceration or cutting, amount and direction of bony movement and fixation of osteotomy fragments, compression of the nerve, surgeon's skills, and indirect damage from edema or hematoma (52-55). Moreover, patient factors such as altered position of anatomical structure, age, sex, and medical status affect the risk of postoperative IAN injury (52). In addition, the incidence of neurosensory disturbance in patients undergoing a BSSRO with a genioplasty was higher than in those undergoing a BSSRO without a genioplasty (56).

2.2 Classification of Neurosensory Disturbance (NSD)

The trigeminal nerve is composed of a functional unit with differing fiber type as described in Table 1 (57). The A-alpha fibers are the largest myelinated fibers with the fastest conduction velocity, their function are position and fine touch in muscle spindle and skeletal muscle efferents. The A-beta fibers mediate proprioception. The A-delta fibers

are the smallest myelinated fibers and carry superficial pain and temperature sensation. The smaller-diameter and slow conduction is unmyelinated C fibers that mediate slow pain and temperature sensation (57).

Fiber	Size (μ)	Conduction Velocity (m/sec)	Function
A alpha (myelin)	12-20	70-120	Position, fine touch
A beta (myelin)	6.0-12	35-170	Proprioception
A delta (thin myelin)	1.0-6.0	2.5-3.5	Superficial (first) pain, temperature
C(unmyelinated)	0.5-1.0	0.7-1.5	Deep (second) pain, temperature

Table 1 Trigeminal nerve fibers

Nerve injuries are classification by Seddon (1943) and Sunderland (1951) as follows:

1. **Neurapraxia (Seddon) or first-degree (Sunderland) injury** is the mildest injury type that is temporary. There is no effect on nerve continuity. The transient nature of this injury is believed to be caused by a temporary disturbance in the conduction pathway that blocks neural transmission but does not damage the axon as described in Figure 2, Figure 3, Figure 4. Symptoms include motor paralysis (for motor nerves), numbness, tingling, and loss of vibration and postural sensation. All of these effects resemble the common effects of local anesthesia. Spontaneous recovery usually occurs within 4 weeks or less time and no surgical intervention is required as described in Table 2 (45, 57).
2. **Axonotmesis (Seddon) or second-, third-, and fourth-degree (Sunderland) injuries** is the complete interruption of the nerve fibers. The difference degree of Sunderland classification is the

degree of axon damage as described in Figure 2, Figure 3, Figure 4. Second-degree injuries are compression or traction injuries that results in ischemia, intrafascicular edema or demyelination. Recovery is slow and may take weeks to months and may not be complete healing. Third-degree injuries is more trauma to nerve and damage extend to perineurium. Recovery is vary and may take months and may not be complete. Fourth-degree injuries is damage to fascicle that extend through the perineurium to epineurium but epineurium is intact as a near-complete transection injury. Spontaneous recovery is unlikely but minimal improvement may occur in 6 to 12 months as described in Table 2 (45, 57)

Nerve Injuries Classifications : Seddon versus Sunderland			
Seddon	**Sunderland**	**Histology**	**Outcomes**
Neurapraxia	First degree	No axonal damage, no demyelination, no neuroma	Loss of sensation, rapid recovery (days to weeks), no microneurosurgery
Axonotmesis	Second, third and fourth degrees	More axonal damage, demyelination, possible neuroma	Loss of sensation, slow incomplete recovery (weeks to months), possible microsurgery
Neurotmesis	Fifth degree	Severe axonal damage, epineurial discontinuity, neuroma formation	Loss of sensation, spontaneous recovery unlikely, microneurosurgery

Table 2 Nerve Injury Classifications : Seddon Versus Sunderland

3. Neurotmesis (Seddon) or fifth-degree (Sunderland) injuries is severe nerve injury type and involves disconnection of a nerve as described in Figure 2 (57), Figure 3 (57), Figure 4.(57) It results from complete transection of the nerve. Functional loss is complete and need surgical procedure for recovery. There is a complete loss of motor and

sensory function. If there is recovery, it is usually incomplete recovery pattern because of scar formation and the loss of mesenchymal guide that properlydirects axonal re-growth as described in Table 2 (45, 57).

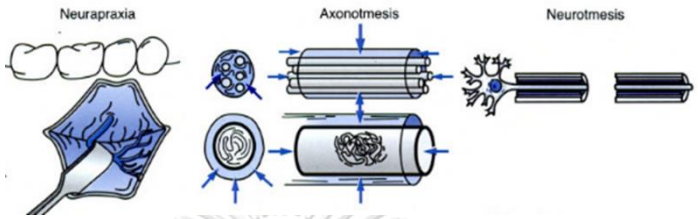


Figure 2 Nerve injury classification: Seddon Classification

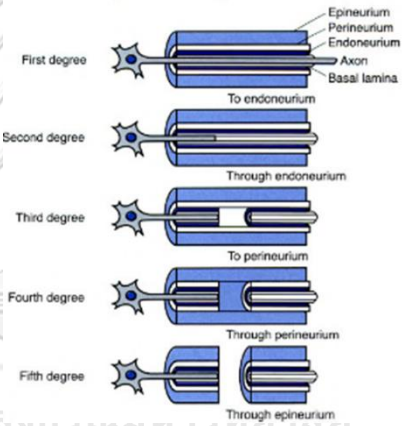


Figure 3 Nerve injury classification : Sunderland

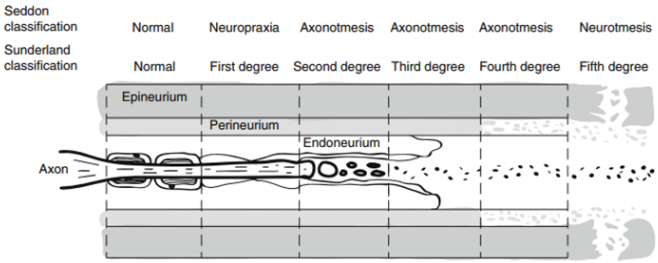


Figure 4 Seddon and Sunderland classification of nerve injury based upon histological neural changes

The types of nerve injury are also described in symptomatic classification as follows:

1. **Paresthesia**: It is an abnormal sensation ,whether stimulate or spontaneous (58). Patient may complain of numbness, tingling or itching or swollen sensation (59).

2. **Anesthesia**: It is complete absence of any stimulus detection and stimulus perception, including mechanoreceptive and nociceptive stimuli. It is usually associated with a severe injury interrupting the integrity of the axons. Sensory recovery is unpredictable and slow (59).

3. **Dysesthesia**: It is an altered sensation of abnormal stimulus detection and stimulus perception that may be perceived as unpleasant and painful (59). It is developed from adjacent nerve fibers may connect, impulse and transmit to wrong way (60, 61).

4. **Hyperalgesia**: Increased pain response by noxious stimuli (58).

5. **Allodynia**: Pain that stimulated by unnoxius stimuli (58).

6. **Hypoesthesia**: Decreased touch and pressure stimuli detection (59).

7. **Hyperesthesia**: Increased touch and pressure stimuli detection (59).

The most common postoperative complication is neurosensory disturbance at the lower lip and chin after the Bilateral Sagittal Split Ramus Osteotomy (BSSRO).

Injuries of inferior alveolar nerve after the BSSRO are usually combination of neurapraxia and partial axonotmesis (62). In some case, incidence of severe nerve injuries (neurotmesis) from BSSRO are rare (63, 64).

2.3 Clinical Neurosensory Testing (CNT)

The Clinical Neurosensory Testing (CNT)
Subjective assessment: Visual Analogue Scale
Objective assessment
Level A: Static two-point discrimination, brush stroke direction
Level B: Contact detection
Level C: Pinprick nociception, thermal discrimination

Table 3 Clinical Neurosensory Testing (CNT)

The Clinical Neurosensory test (CNT) is classified to subjective assessment and objective assessment. Subjective assessment is performed using Visual Analogue Scale (VAS) that score vary from 0-5 as described in Figure 5 (57). The commonly method is used for the evaluation of the neurosensory disturbance was subjective assessment but this method is difficult to standardize because of the difference in interpretation of the deficit between examiner and patient. Patients tend to adapt to a deficit and report a normal sensation, whereas the clinical investigation shows a deficit (65). In contrast, patients may still complain of neurosensory alterations, whereas clinical tests are normal (6).

Right	1 Complete absence of sensation	2 Almost no sensation	3 Reduced sensation	4 Almost normal sensation	5 Fully normal sensation
Left	1 Complete absence of sensation	2 Almost no sensation	3 Reduced sensation	4 Almost normal sensation	5 Fully normal sensation

Figure 5 Visual Analogue Scale (VAS)

The objective assessment of CNT is performed at three levels A, B and C as described in Table 3 (57).

If the results of level A testing are normal, the CNT is terminated and the patient is considered normal; this would correspond to a Sunderland first-degree injury or neurapraxia in Seddon classification. An abnormal result at level A indicates the need to proceed to level B testing. If the results of level B are normal, the patient is considered mildly impaired (Sunderland second-degree injury or axonotmesis in Seddon classification).

If level B results are abnormal, level C testing is performed. If level C results are normal, the patient is considered to have a moderate nerve impairment (Sunderland third-degree injury or axonotmesis in Seddon classification). If level C results are abnormal, the patient is considered severely impaired (Sunderland fourth-degree injury or axonotmesis in Seddon classification).

If the patient's test results are abnormal at level A, B, and C and there is no response to any noxious stimulus at level C, the patient is considered completely impaired (Sunderland fifth-degree injury or neurotmesis in Seddon classification) are described in Figure 6 (57). The recovery of nerve injury varies from the degree of injury described in Table 4 (66). The fourth and the fifth degree are not spontaneous recovery and need microneurosurgery (66).

Degree of Injury	Recovery Pattern	Rate of Recovery	Treatment
First degree	Complete	Fast (days to weeks)	None
Second degree	Complete	Slow (weeks)	None
Third degree	Variable	Slow (weeks to months)	Possible nerve exploration
Fourth degree	None	Unlikely recovery	Microneurosurgery
Fifth degree	None	No recovery	Microneurosurgery

Table 4 Sunderland Grade and Recovery Pattern

Although these five tests of the CNT are considered “objective” test, they are, in reality, “subjective” because they require a “subjective” patient response (57). Few purely objective assessment of nerve function are available that included trigeminal somatosensory evoked potentials and magnetic source imaging (67). However, these tests are not readily available and not use for the routine assessment for patients with nerve injury.

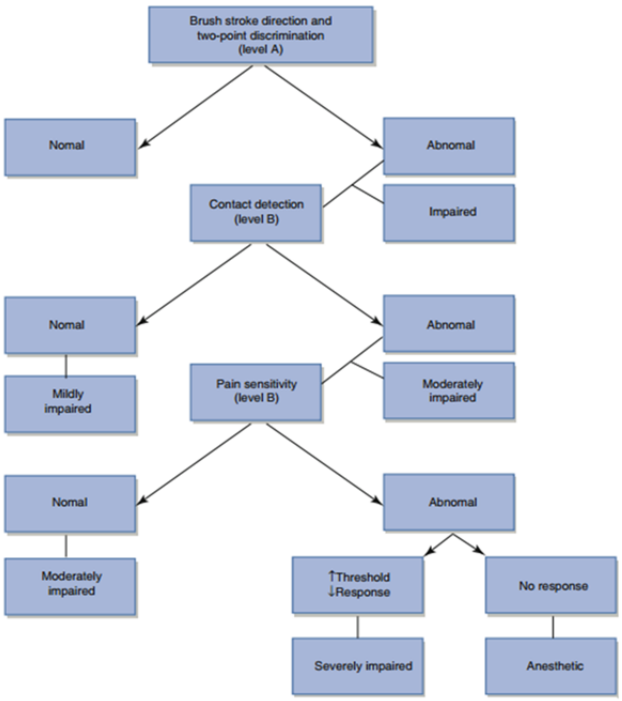


Figure 6 Grading algorithm for evaluating trigeminal nerve injury

2.3.1 Area of clinical neurosensory testing

The lower lip and the mental region are divided into four zones as Figure 7 (55), randomly selected points in each zone to stimulated with neurosensory testing (55).

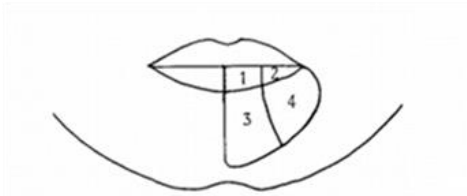


Figure 7 Four sites tested for threshold pressure

2.3.2 Methods of testing

Geha and D'Agostino used the same methods for neurosensory testing that is light touch sensation, pinprick sensation, static two-point discrimination, and moving two-point discrimination (68, 69).

1) Light-Touch Sensation

Light touch sensory is the test that performed to evaluate the function of large axon fiber such as A-alfa myelinic fibers. Generally, two methods are used: a cotton wisp or a Semmes-Weinstein monofilament. The Semmes-Weinstein monofilament is Nylon fiber that can produce static pressure when using with protocol. The Semmes-Weinstein monofilament is placed perpendicular to the skin and pressed until the filament begins to deform. At this point, a known reproducible pressure is applied. Different monofilaments exist that produce different amounts of pressure. This is more reproducible but time-consuming compared with the cotton wisp (24).

Geha performed this test with using the nylon suture in the difference size diameter mounted perpendicularly at the extremities of 10-cm-long stainless steel handles. In preoperative measurement, all patients who normal response can reply positive to 6-0 monofilament caliper. In postoperative measurement, used the same procedure and changed the size of nylon that patient can perceive to the ordinal score as described in Table 5 (68). The scores ranged from 4 to 0 (68).

Monofilament Caliber Eliciting a Positive Response	Corresponding Ordinal Score
6-0	4
5-0	3
4-0	2
3-0	1
Negative response to all	0

Table 5 Scoring for light touch sensation

Patient Response	Light-Touch Sensation Score
The patient does not show any change as regards the preoperative situation and correctly perceives mild stimuli	4
The patient shows a change as regards the preoperative situation but still perceives mild stimuli	3
The patient shows a change as regards the preoperative situation and hardly perceives mild stimuli	2
The patient shows a change as regards the preoperative situation and presents a serious perception loss	1
The patient shows a change in the preoperative situation and does not respond to stimuli	0

Table 6 Score Assigned for Light-Touch Sensation Test According to the patient's response

While D'Agostino performed this test by manually on the lower lip and mental region. The scores ranged between 0 and 4 and they were determined using patient's recalled comparative feelings between preoperative and postoperative sensation as described in Table 6 (69)

Semmes-Weinstein monofilament is nylon fiber that are used to evaluate light touch sensation of labiomental or chin area. The many size of monofilaments and their force are shown in Table 7 (70, 71). The 3-digit code of monofilament correspond with Log_{10} of 10 times the force in milligrams (72). From previous study, patients could detect monofilament size 2.83 to size 4.74 at presurgery and 1 month after BSSO respectively (73). Another study reported that patients could detect monofilament size 3.22 and 4.74 at presurgery and 1 month after surgery (74).

Monofilament	Target Force (g)
1.65	0.0008
2.36	0.02
2.44	0.04
2.83	0.07
3.22	0.16
3.61	0.4
3.84	0.6
4.08	1
4.17	1.4
4.31	2
4.56	4
4.74	6
4.93	8
5.07	10
5.18	15
5.46	26
5.88	60
6.10	100
6.45	180
6.65	300

NOTE. The sizes (represented by a 3-digit code) and the respective target forces (in grams) of the monofilaments are shown.

Table 7 Semmes-Weinstein monofilaments

2) Pinprick sensation

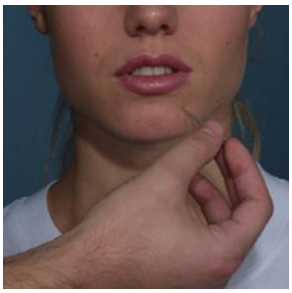


Figure 8 Pinprick sensation

Geha and D'Agostino used the same procedure for pinprick sensation test.

This test evaluates A-delta myelinic A-delta fibers and C fibers, which convey the painful stimuli. The test is performed by gently apply a pointed instrument to the patient's face and the patient had to identify to the sensation as Fig 8(69). For this test, only positive response (sharp sensation) and negative responses (dull sensation) to painful stimulation are registered as 1 and 0, respectively (28, 68, 75).

3) Static Two-Point Discrimination or Weber Test

Static Two-Point Discrimination (SPD) or Weber test is the test that performed to evaluate slowly adaptive A-alfa myelinic fibers. This test is performed with a instrument with 2 tool spikes open at various distances on the regions of interest on the patient's face as Fig 9 (69). The patients are instructed to tell "one" if they feel the sensation at a single point and "two" if they feel the sensation at two points separated by a small distance.

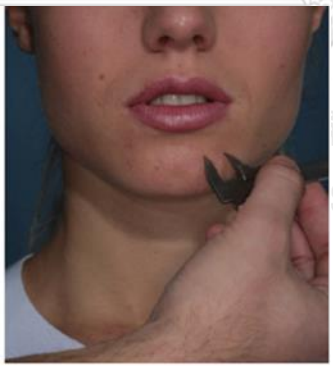


Figure 9 Static Two-Point Discrimination and Moving Two-Point Discrimination

The distance between the two points is measured in millimeters and the device is placed at intervals ranging from 5 to 20 mm. The smallest distance between 2 spikes in millimeters that patients can differentiate at two point will be interpreted to the score later. The

distance that most patients can distinguish the 2 separated points on normal lower lip and chin is <5 mm. and abnormal is >20 mm. (76, 77).

D'Agostino used SPD test on the face (28, 68, 78) with scores range from 0 to 5. The ordinal score was interpreted the distance of 2 spikes from only postoperative measurement and assigned score as described in Table 8 (69).

Difference between Perioperative and Postoperative Values	**Corresponding Ordinal Score**
No difference, same value as preoperatively	5
1-2 mm.	4
2-3 mm.	3
3-4 mm.	2
5-6 mm.	1
≥ 6 mm.	0

Table 8 Scores Assigned for the Static Two-Point Discrimination and Moving Two-Point Discrimination Tests According to the Extinction Distance of the Double Stimulation

Geha used this test and compared the distance of preoperative and postoperative distance. The difference distance was interpreted to the ordinal score range from 0-5 as described in Table 9 (68). Due to personal threshold, Geha design the measurement that compare the preoperative and postoperative distance in each patient (68).

Extinction Distance of the Double Stimulation	**Score Assigned**
≤5 mm	5
5–7 mm	4
7–9 mm	3
9–10 mm	2
10–15 mm	1
≥15 mm	0

Table 9 Scoring for the Static Two-Point Discrimination and Moving Two-Point Discrimination Tests determined by the difference of the distance preoperatively and postoperatively

4) Moving Two-point Discrimination (MPD) or Dellon Test

Moving Two-Point Discrimination (MPD) or Dellon Test is the test that performed to evaluate the rapidly adaptive fiber-receptor mechanism of the A-alfa fibers. It is performed as for the static two-point discrimination test, with the caliper tips in vary distance of 2 spikes and being moved between 1 and 2 cm along the areas to be tested as Figure 9. The smallest distances that patients can distinguish is interpreted to the score. The scores are recorded with the same criteria used for the static 2-point discrimination test as described in Table 8 and Table 9 (68, 69).

2.3.3 Global Sensitivity Score

Geha and D'Agostino used the same Global Sensitivity Score (GSS) (68, 69). A score of global sensitivity is calculated summing from the light touch, pinprick, static two-point discrimination and moving two-point discrimination. The maximum score of light touch, pinprick, static two-point discrimination and moving GSS is 0-15. According to the score obtained, separately each patient's side is classified as follows and described in Table 10: normal, subnormal, intermediate, and reduced sensitivity (68, 69).

Global Sensitivity Score on the Tested Side	Classification of the Sensitive Functionality of IAN
≥12	Normal
9–12	Subnormal
6–9	Intermediate
≤6	Reduced

Table 10 Classification of the Sensitivity of the Inferior Alveolar Nerve According to the Global Sensitivity Score

2.4 Treatments of neurosensory disturbance

The peripheral neuropathy has been used to cover any disorder of the peripheral nervous system which may affect the sensory, motor or autonomic functions. The common causes are diabetes, alcohol, human immunodeficiency virus infection, and, in some parts of the world, leprosy (36). The treatments those have indirect effect on nerve healing and can categorized as follow:

4.1 Non-surgical treatment

Many systemic Table 11 (57) and topical medication Table 12 are available (57).

1) Medical

Systemic Pharmacologic Agents
Local anesthetics
Corticosteroids
Nonsteroidal anti-inflammatory agents
Antidepressants
Narcotic analgesics
Anticonvulsants
Muscle relaxants
Benzodiazepines
Antisympathetic agents

Table 11 Systemic Pharmacologic Agents

Topical Medications Category	Example
Topical anesthetics	5% viscous lidocaine gel; 20% benzocaine gel; 2.5% lidocaine with 2.5% prilocaine
Neuropeptides	Capsaicin cream (0.025% or 0.075%)
Nonsteroidal anti-inflammatory drugs	Ketoprofen 10-20% PLO base; diclofenac 10-20% PLO base
Sympathomimetics	Clonidine 0.01% PLO base or patch
N-methyl-D-aspartate blocking agents	Ketamine 0.5% PLO base
Anticonvulsants	Carbamazepine 2% PLO base
Tricyclic antidepressants	Amitriptyline 2% PLO base
Antispasmodics	Baclofen 2% PLO base

Table 12 Topical Medications

2)Laser : low-level (soft) laser (gallium-aluminium-arsenide, wave length of approximately 820 nm.) treatment has been used to improve the sensory impairment (79, 80).

3) Psychological : counselling, acupuncture, cognitive behavioural therapy, relaxation therapy, behaviour modification, electromyographic biofeedback, hypnosis, re-education (58).

4.2 Surgical treatment

The surgical treatment for nerve injury includes exposure, external neurolysis, internal neurolysis, nerve stump preparation, Approximation, coaptation, neurorrhaphy, nerve grafting, neuroma excision, entubulation technique (57, 58). The indications for referral include to lists in Table 13 (57).

Microneurosurgeon Referral Indications
Observed nerve transection
Complete postoperative anesthesia
Persistent paresthesia (lack of improvement in symptoms) at 4 week
Presence or development of dysesthesia

Table 13 Microneurosurgeon Referral Indications

2.5 Vitamin B

Vitamin B is a frequently given supplementation for treating peripheral neuropathy because of the availability, affordability, generally well-tolerated with only a few reports of mild side effects but lacking of strong evidence in the literatures and unclear mechanism on the efficacy of vitamin B (36). The vitamin B is a group of water soluble compounds. The vitamin B complex includes thiamine (vitamin B1), riboflavin

(vitamin B2), nicotinic acid (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), biotin (vitamin B7), folic acid (vitamin B9), cyanocobalamin (vitamin B12), para-aminobenzoic acid, inositol, and choline (81).

Thiamine is converted to thiamine pyrophosphate that appears to play a role in the nerve transmission. Thiamine are absorbed mainly in jejunum and ileum. Distribution of thiamine is transported in plasma bound to albumin and stored in heart, liver muscle, kidneys and brain. The stored of thiamine is only small amounts and turnover is high so intake thiamine is necessary. Elimination occurs mainly in the urine and crosses the placenta and excreted in breast milk. Bioavailability of thiamine may be reduced by alcohol. It is unstable above pH 7 and destroyed by heat and by processing food at alkaline pH values, high temperature and in the presence of oxygen or other oxidants. The antagonists of thiamine is coffee, tea, raw fish, betel nuts and some vegetables (82). Thiamine deficiency is known as beriberi that characterized by pain (neuritis) and paralysis of legs and arms, cardiovascular changes and edema. Good food sources of thiamine are yeast, pork, whole or enriched grains (e.g. cereals, flour, bread) and legumes (83).

Pyridoxine, pyridoxamine, and pyridoxal are converted to pyridoxal phosphate that is involved in the metabolic transformations of amino acids and in the metabolism of sulfur-containing and hydroxyl-amino acids. Pyridoxal phosphate is required for the synthesis of sphingolipids for myelin formation as well (36). Absorption of vitamin B6 occurs mainly in jejunum. Vitamin B6 is stored in liver, muscle and brain. It is transported in plasma and in erythrocytes. Pyridoxal phosphate

is eliminated in urine. It appears in breast milk. Bioavailability is affected by food processing and storage. It is sensitive to light, acid or neutral solution. Vitamin B6 deficiency does not produce a characteristic syndrome. It may produce dermatitis, cheilosis, glossitis and angular stomatitis. Moreover, it may produce weakness, irritability, depression, dizziness, peripheral neuropathy and seizures in advanced deficiency (82). Good food for vitamin B6 are grains, enriched cereals, liver and kidney and other meats (83).

Cobalamin is converted to methylcobalamin and 5-deoxyadenosylcobalamin which are vital in growth and replication (36). Absorption of vitamin B12 occurs almost in ileum. It is stored mainly in liver. In blood, it bound to specific plasma proteins (transcobalamins). Vitamin B12 is eliminated by urinary, biliary and faecal routes. It appears in breast milk. Deficiency of vitamin B12 leads to macrocytic, megaloblastic anemia. Symptoms are neurological manifestations (due to demyelination of spinal cord, brain, optic nerve and peripheral nerve) and less specific symptoms such as weakness, sore tongue, constipation and postural hypotension (82). Good sources for vitamin B12 are beef liver, lean meat, clams, oysters, herring and crab (83).

The latest reported that tissue level of vitamin B1-6-12 and vitamin B12 vary with progression of crushed nerve in sciatic nerve of rats, and supplementation of these vitamins in the acute period may be helpful for stimulation of nerve regeneration (37). Moreover, the ultrahigh doses of vitamin B12 is essential for the production of neurotrophic factors that promotes nerve degeneration and promotes nerve regeneration in the damaged sciatic nerve of rats (38, 84). In oral surgery, vitamin B1-6-12 and vitamin B12 has been used in clinic for neurosensory treatment but

mechanism of action was incomplete and low evidences support. Many recent studies are not compare the result of vitamin B1-6-12 and vitamin B12 in nerve healing from this injury.

The required daily intakes of vitamin B for a normal adult are as follows; thiamine 1.0 to 1.5 mg, pyridoxine 1.4 to 2.0 mg (85), cobalamin 1.8 to 2.4 mcg (86). Higher doses of vitamin B are recommended for the treatment of the peripheral neuropathy deficiency such as: thiamine 40 mg oral per day for thiamine deficiency, pyridoxine 50 to 100 mg oral per day for peripheral neuropathy induced by isoniazid (87), cobalamin 1000 mcg oral per day influencing the haematological and/or neurological vitamin B12 deficiency symptoms (86). However, no study report recommended dose of vitamin B medication for neurosensory disturbance treatment in oral surgery.

CHAPTER III
MATERIALS AND METHODS

3.1 Inclusion and exclusion criteria

This study was designed as randomized, single blinded trial in total of 75 patients. Inclusion criteria and exclusion criteria were described in Table 14.

Inclusion Criteria	Exclusion Criteria
• BSSRO procedure with or without maxillary procedure (without genioplasty) and have reduced sensation after surgery (GSS 0-12) • Aged between 18-45 years • Healthy patient, no medical problems • No numbness or unusual feeling on the face before surgery • No psychological problems • No infection problems • No sensitivity to vitamin B	• Perioperative complications such as bad split, nerve exposed, partial or complete nerve dissection, excessive bleeding or unfavorable bone fracture • Postoperative complications such as postoperative infection, the operation that need second operation (for example: broken bur, failure device) • Patient with postoperative dysesthesia that need microneurosurgery • Patient who receive other medication that influence nerve healing • Patient lost follow-up in 6 months after surgery • Non co-operative patients

Table 14 Inclusion and Exclusion Criteria

The operation were conducted at the Department of Oral and Maxillofacial Surgery, Chulalongkorn University. This study was

approved by the ethics committee of the Faculty of Dentistry, Chulalongkorn University.

The patients who met an inclusion criteria in November 2015 to March 2019 were enrolled to the study were prepared for treatment plan by using clinical examination, radiographic and computerized tomography. All of patients were examined to record CNT baseline data before BSSRO operation. The 90 patients who has GSS lower than 12 at immediate postoperative were included in this study and were divided into 3 groups randomly with block randomization by co-researcher. Three groups of this study were vitamin B1-6-12 group, vitamin B12 group and control group.

3.2 Operation

All groups of patients received the standard protocol of BSSRO at one center. In perioperative period, the antibiotic was prescribed as 2 mu of Penicillin G Sodium intravenously and in the case of penicillin allergy, 600mg of clindamycin was prescribed intravenously. Steroids were prescribed with 8 mg of dexamethasone intravenous administration preoperatively. After BSSRO, patient who had GSS score 0-12 were included and randomly divided to 3 groups. The first group was taking vitamin B 1-6-12 (SAMBEE® tablet that consists of 100 mg of vitamin B1 (thiamine), 5 mg of vitamin B6 (pyridoxine) and 65 mcg of vitamin B12 (cyanocobalamin) after surgery. The second group was taking vitamin B12 (Methylcobal®: 500 mcg methylcobalamin tablet) after surgery. The third group was the control group without taking vitamin B.

	Vitamin B1-6-12 group	Vitamin B12 group	Control group
Perioperative period			
1. Antibiotic			
- PGs 2mu IV or Clindamycin 600mg IV if allergy to penicillin	✓	✓	✓
2. Steroid - Dexamethasone 8mg IV	✓	✓	✓
Postoperative period			
1. Antibiotics			
- PGs 2mu IV q4h or Clindamycin 600mg IV q8h if allergy to penicillin:	✓	✓	✓
2. Analgesic drugs			
- morphine (0.1 mg/kg of morphine, q4h for severe pain	✓	✓	✓
- Ibuprofen syrup (100mg/5ml po 20ml q8h for pain)	✓	✓	✓
- acetaminophen syrup (120mg/5ml po 20ml q6h for pain and fever)	✓	✓	✓
3. Steroid			
- Dexamethasone 8 mg IV q12h (first postop day)	✓	✓	✓
- Dexamethasone 4 mg IV q12h (second postop day)	✓	✓	✓
- Dexamethasone 2 mg IV q12h (third postop day)	✓	✓	✓
4. Vitamin B			
- Vitamin B1-6-12 (SAMBEE®) 1 tab po tid pc	✓	-	-
- Vitamin B12 (500 mcg of methylcobal®) 1 tab po tid pc	-	✓	-
Home medication			
- Vitamin B1-6-12 (SAMBEE®)1 tab po tid pc	✓	-	-
- Vitamin B12 (500 mcg of methylcobal®) 1 tab po tid pc	-	✓	-

Table 15 Drug and vitamin B administration

In operation, bone splitting was performed with thin spatulas and osteotomes. After proximal and distal part of mandibular bone split separately, the inferior alveolar nerve bundle was identified. After the mandible was placed to a new position and fixed as described in standard procedure, the drain was placed each side of operation in order to reduce the hematoma. The incision was sutured with resorbable material.

Finally, after the position of the mandibles and occlusion were corrected, maxilla-mandibular fixation with wiring or elastic traction was performed. In hospitalization period, antibiotics (2 million units of Penicillin G Sodium intravenously for every 4 hours and in the case of penicillin allergy, 600 mg of clindamycin intravenously were prescribed for every 8 hours), analgesic drug (0.1 mg/kg of morphine, every 4 hours for severe pain) and or Ibuprofen syrup (100 mg/5ml po 20 ml every 8 hour for pain) and or acetaminophen syrup (120 mg/5ml po 20 ml every 6 hour for pain or fever) were prescribed in all groups. Dexamethasone were prescribed with dexamethasone intravenously (8 mg every 12 hour in the first postoperative day, 4 mg every 12 hour in the second postoperative day and 2 mg every 12 hour in the third postoperative day) as described in Table 15. After Hospitalization, the vitamin B 1-6-12 group and vitamin B 12 group were prescribed three times daily and continued prescription for 6 months after surgery or until sensation was completely recovered as described in Table 15.

3.3 Measurement of Clinical Neurosensory Test (CNT)

After operation, patients were examined with immediate Clinical Neurosensory Test (CNT) and converted to Global Sensitivity Score (GSS) that was based on the study of Geha and D'agostino (68, 69). The area of testing with GSS range from 0 to 12 were defined as neurosensory

disturbance and included for study. The CNT consisted of static two-point discrimination, moving two-point discrimination, light touch sensation, pinprick sensation (68, 69). The area of lower lip and chin was divided to 4 areas per side as Figure 10 (modified from Yoshida T (55)) and were tested. Each of the four facial zones per side were tested three times. The precision was confirmed if the patients response similar from two out of three (28).

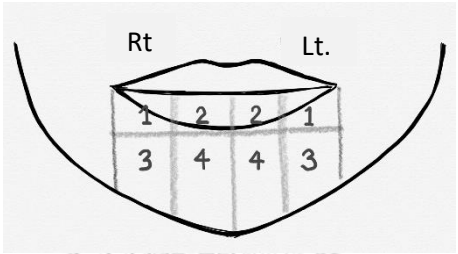


Figure 10 Area of Testing

During the testing, the patients were in a silent room, closed their eyes, devoided of any acoustic or visual disturbance, with relaxed patients, in seated position and separated their lips comfortably.

The static two-point discrimination was performed with the tool spikes of a caliper as Figure 11 that open at various distances on the regions of interest on the patient's face as Figure 12. The distances between 2 spikes began with a minimum distance of 3 mm. The points were gradually separated until the patients perceived them as separate as described in Table 16 (modified from D'Agostino A (69)).

Figure 11 Caliper with 2 spikes for Static Two-Point discrimination and Moving Two-Point Discrimination test

Figure 12 Static Two-Point Discrimination (SPD)

The moving two-point discrimination was performed the distance between the spikes as the static two-point discrimination and moving the caliper for 1–2 cm.in distance as along Figure 13 to Figure 14. The distance in millimeters between the two spikes that the patient can distinguish without confounding the latter with a single spike in preoperative was the baseline data in each patient as Table 16 (modified from D'Agostino A (69)).

Extinction Distance of the Double Stimulation
3 mm.
5 mm.
7 mm.
9 mm.
15 mm.
>15 mm.

Table 16 The distance (mm.) for the Static Two-Point Discrimination and Moving Two-point Discrimination Tests According to the Extinction Distance of the Double Stimulation

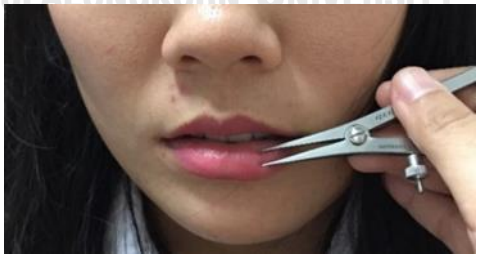


Figure 13 Moving Two-Point Discrimination -1

Figure 14 Moving Two-Point Discrimination -2

In postoperative measurement, static two-point discrimination and moving two- point discrimination were performed similarly to preoperative measurement. The distance between postoperative at the different time point were compared with preoperative measurement in each zone and change to corresponding ordinal scores. These scores were used to eliminate threshold differences between patients, giving a maximal score of 5 per each zone according to the loss in millimeters compared with the patient's preoperative results in 2-point discrimination as Table 17 (modified from Geha HJ (68)).

Difference between preoperative and postoperative value	**Corresponding Ordinal Score**
No difference ,same value as preoperative	5
1-2 mm.	4
3 mm.	3
4 mm.	2
5-6 mm.	1
> 6mm.	0

Table 17 Scoring for static two-point discrimination and moving two-point discrimination

In light touch sensation, the lower lip and the mental skin were touched vertically with a neuropathy monofilament (Amaryl®: monofilament) size 5.07 monofilament as Figure 15 and slowly the force were increased until the monofilament bend to "C" shape as Figure 16 that could produce about 10 gram of force (70, 71). The time needed to bend the monofilament was approximately 1.5 s and maintained this force for 1.5 s (58). Preoperative measurement was tested to check normal patient perception for individual.

Figure 15 Monofilament equipment: Amaryl®

Figure 16 Light touch sensation

Patient response	Light-Touch Sensation score
The patient does not show any change as preoperative situation	4
The patient shows a change as preoperative situation but still perceives mild stimuli	3
The patient shows a change as preoperative situation and hardly perceives mild stimuli	2
The patient shows a change as preoperative situation and presents a serious perception loss	1
The patient shows a change in the preoperative situation and not respond to stimuli	0

Table 18 Scores Assigned for Light-Touch Sensation test According to the Patients' Response

Postoperative measurement were performed with the same method and the patients were asked to grade sensation. The grade of sensation were compared with preoperative measurement on each area as described in Table 18 (modified from D'Agostino A (69)).

The pinprick sensation was performed by touching the patient's face with a spike of caliper as Figure 17. The responses to painful were only positive or negative stimulation if dull sensation and were registered as 1 and 0 respectively on each area (28, 68).

Figure 17 Pinprick Sensation

All neurosensory tests were performed by two-examiner that were blinded. We calibrated the inter-examiner calibration and Kappa value were 0.455, 0.333, 0.85, 0.5 from SPD, MPD, light touch and pinprick respectively. All postoperative CNT ran immediately after surgery to include patients and 1 week, 1 month, 3 months and 6 months. The neurosensory disturbance were classified with Global Sensitivity Score (GSS) (modified from Geha HJ and D'Agostino (68, 69)). GSS ranged from 0-15 as described in Table 19. If GSS at immediate postoperation is 13-15, it was indicated that not neurosensory disturbance and this area was not included to this study. If GSS is 0-12, those areas were indicated for neurosensory disturbance and included to this study.

Global Sensitivity Score on the test area	Classification of the Sensitive Functionality of IAN
13-15	Normal
9-12	Subnormal
6-8	Intermediate
0-5	Reduced

Table 19 Classification of the Sensitivity of the Inferior Alveolar Nerve According to the Global Sensitivity Score

STATISTICAL ANALYSIS

4.1 Sample size

Based on “Non-invasive therapy for altered facial sensation following orthognathic surgery: an exploratory randomized clinical trial of intranasal vitamin B12 spray” (14) study, if we assume the contact detection after 6 months in vitamin B group to be 0.643 (SD=0.260) and the same in the control group to be 0.398 (SD=0.262), to have 80% power and 5% Type I Error probability, we need 20 subjects per group. Total sample size is approximately 60 subjects totally. Sample size calculation was from G*power software version 3.1.9.2. (University of Kiel, Germany). To compensate drop-out about 20%, we need 75 subjects totally.

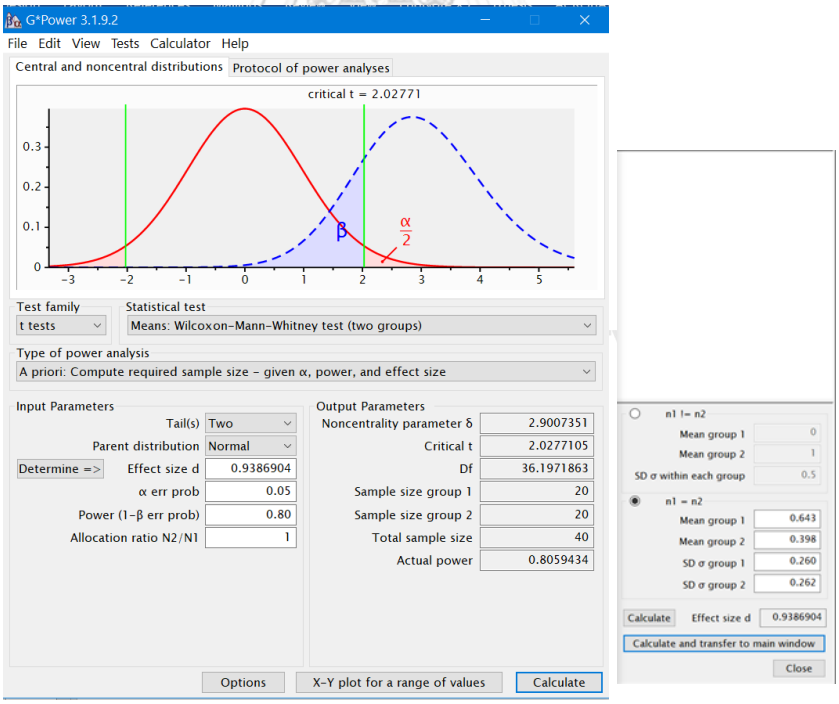


*Figure 18 Sample size calculation from G*power*

4.2 Data analysis

The statistical analysis in this study, we used Chi-square for comparing the difference of sex, type of operation, direction of mandible movement, operation time, estimated blood loss among 3 groups.

Data distribution of age of patients and amount of NSD area were tested with Kolmogorov Smirnov test. One-way ANOVA were used in case of normal distribution and Kruskal Wallis H test was used in case of abnormal distribution.

The GSS data and recovery proportion data were also tested distribution with Kolmogorov Smirnov test.

The GSS were converted to recovery proportion by calculating from GSS at follow up period comparing with GSS at immediate postoperative that showed as this equation. To avoid the mathematical error, we plus 1 to GSS at follow up time and GSS at immediate postoperation before calculating recovery proportion. We analyzed the

$$\text{Recovery proportion} = \frac{(\text{GSS at follow up}+1) - (\text{GSS at immediate}+1)}{(\text{GSS at immediate}+1)}$$

recovery proportion at 1 week, 1 month, 3 months and 6 months.

Recovery proportion were used IBM SPSS Statistic Program version 22 for analyzing data. We compared recovery proportion in 2 point:

1. **Intragroup comparison of recovery proportion on the passing time**

We would use ANOVA, if the data was normal distribution. We would use Friedman test and post hoc with Wilcoxon signed rank test.in case the data was not normal distribution,

2. **Among 3 groups comparison** at same follow up time If data was normal distribution, we would use ANOVA and post hoc with Turkey. We used Kruskal Wallis H test and post hoc with Mann-Whitney U test, when distribution was not normal

4.3 Scope of the study

This study is emphasis on treatment of neurosensory disturbance of inferior alveolar nerve after bilateral sagittal split osteotomy with vitamin B 1-6-12 or vitamin B12. The outcome was evaluated using objective assessment of neurosensory disturbances.

4.4 Instruments/materials

-Dental computerized tomography (dental CT)

-Caliper and kit set for neurosensory testing

-Neuropathy monofilament (Amaryl®)

-Vitamin B 1-6-12 tablets (SAMBEE®)

-Vitamin B12 tablets (500 mcg Methylcobalamin: Methycobal®)

4.5 Place

Department of Oral and Maxillofacial surgery, Faculty of Dentistry, Chulalongkorn University

4.6 Ethical considerations

This study was submitted to the Ethics Committee, Faculty of Dentistry, Chulalongkorn University (HREC-DCU 2017-072)

All clinical procedures used the standard procedures. At present, no standard treatment has been used to treat NSD from oral and maxillofacial surgery. Vitamin B supplementation, an intervention, is approved for administration and widely used for treatment of peripheral neuropathy and has very few side effects.

4.7 Budget

-computerized tomography	67,500	baht
-vitamin B and other medication	50,000	baht
-Document and equipment cost	3,000	baht
-Publication fee	5,000	baht
Total	125,500	baht

CHAPTER IV
RESULTS

This study included totally 90 patients who underwent bilateral sagittal split ramus osteotomy (BSSRO) and were randomly divided to 3 groups. Because of exclusion criteria, we used definitely 75 patients to analyze data and were divided to 25 patients for each group (n=25). The demographic data were described in Table 20. The 75 patients were 30 males and 45 females and gender among 3 groups were no difference (p=0.513). The age of patients were range from 19-41 years and data were not normal distribution (p<0.001). The median ± interquartile range of age were 25.00±9.00. The age of patients among 3 groups showed not difference among 3 groups (p=0.972).

The BSSRO in this study consisted of 53 patients with only BSSRO of mandible and 22 patients with BSSRO and maxillary surgery. The direction of BSSRO were setback, advancement, rotation and setback with rotation. The direction of mandible movement were 56 setback direction, 2 advancement, 5 rotation and 12 setback with rotation. The type of surgery (1 jaw or 2 jaws) and direction of BSSRO were not different among 3 groups (p=0.773, 0.442 respectively).

The estimated blood loss from the surgery were 31 cases that less than 300 ml and 41 cases that estimated blood loss was more than 300 ml. We did not found different among 3 group about blood loss (p=0.094).

The operation time which not more than 180 minutes were 33 cases and more than 180 minutes were 42 cases. The data showed no different of operated time among three group (p=0.850).

The 75 patients were immediately postoperative neurosensory disturbance area (GSS 0-12) and the lip and chin area that included to this study were 426 areas that were vitamin B1-6-12 group = 128 NSD areas from total 200 areas, vitamin B12 group = 159 NSD areas from total 200 areas, control group = 139 NSD areas from total 200 areas (p=0.368).

The data of GSS were not normal distribution *(p<0.001)* and showed as median ± interquartile range from each group at follow up time and were described in Table 21.

	Total	**Vit B1-6-12**	**Vit B12**	**Control**
Gender				
Male	30	10	12	8
Female	45	15	13	17
Aged				
Median ± interquartile rank	25.00±9.00	24.00±9.50	24.00±12.00	25.00±5.50
Range	19-41	20-38	19-41	19-34
Type of operation				
BSSRO	53	19	17	17
Maxillary surgery+BSSRO	22	6	8	8
Direction of mandible movement	56	18	19	19
Setback	2	1	1	0
Advancement	5	0	3	2
Rotation	12	6	2	4
Setback and Rotation				
Operation time				
≤180 mins.	33	12	11	10
>180 mins.	42	13	14	15
Estimated Blood Lost				
≤300 ml	31	6	12	13
>300 ml	44	19	13	12
Amount of NSD area at immediate postoperation (area units)	426/600	128/200	159/200	139/200

Table 20 Demographic data

	GSS (Median ± Interquartile Range)		
	B1-6-12	**B12**	**Control**
Im.postop.	2.00±7	3.50±8	2.00±9
1 wk	5.00±10	6.00±11	7.00±11
1 mo	9.00±10	10.00±8	10.00±12
3 mo	10.00±8	13.00±2	12.00±7
6 mo	12.00±5	13.00±3	13.00±5

Table 21 Global Sensitivity Score among 3 groups at difference follow up time (Im postop., 1 wk, 3 mo and 6 mo were immediate postoperation, 1 week, 3 months and 6 months after surgery retrospectively)

GSS at immediate postoperation of 3 groups were significantly different (p=0.068). We converted GSS to recovery proportion from each area.

The recovery proportion data was not normal distribution so we used non parametric analysis. The recovery proportion among 3 groups were showed as median and interquartile value at the follow up time and were described in Table 22 and Figure 19.

	Recovery proportion (Median ± Interquartile Range)		
	B1-6-12	**B12**	**Control**
Im.postop	0.000	0.000	0.000
1 wk	0.5000±2.00	0.1538±1.00	0.1818±1.14
1 mo	0.7500±3.17	0.6000±2.91	0.4222±3.67
3 mo	1.2857±4.92	0.7889±5.23	1.0000±3.35
6 mo	4.5000±7.00*	2.0000±5.22	2.000±6.58

*Table 22 Recovery proportion among three groups at follow up time by using Kruskal Wallis H test and post hoc analysis with Mann Whitney U test(*p<0.05)*

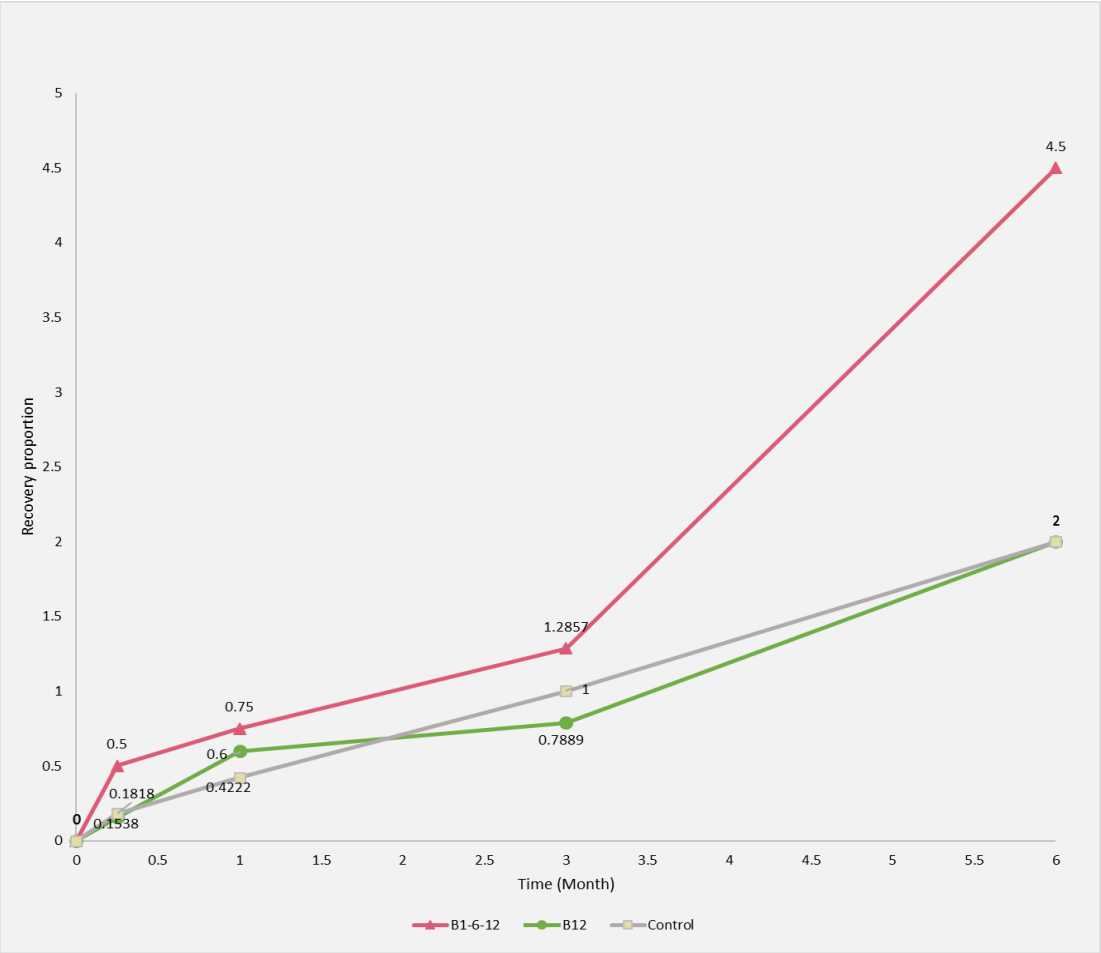


*Figure 19 Recovery proportion of 3 groups at the follow up time (*p<0.05 by using Kruskal Wallis H test)*

Recovery proportion of vitamin B1-6-12 group gradually increased from immediate postoperation and dramatically increased from 3 months to 6 months. The vitamin B12 gradually improved sensation from immediate postoperation to 6 months. The recovery proportion of control group began from immediate after surgery and gradually increased to 6 months that similar pattern as vitamin B12. At 1 month, vitamin B12 was higher recovery proportion than control group but no significantly. Conversely, the recovery proportion of control group was higher than vitamin B12 group but not significantly difference at 3 months. The comparison of intragroup recovery proportion was liable to significantly

higher on the passing time of all groups (p<0.05) except recovery proportion of vitamin B12 group from 3 months to 6 months (p=0.913) that are described in Figure 19.

The comparison among 3 groups of recovery proportion at immediate postoperative time were not different (p=1.00). The difference of recovery proportion occurred at 6 months. The recovery proportion of vitamin B1-6-12 group was significantly higher than control and vitamin B12 at 6 months (p=0.038 and 0.033 respectively) that were described in Table 22 and Figure 19. Vitamin B12 were not difference of recovery proportion when comparing with control group at all the follow up time.

Side effect from this study were 2 patients, were the acne on their face at 6 months and at 3 months after surgery respectively. It did not allergy type from vitamin B but patients discontinued vitamin B since the acne occurred. The other patients were no any side effect from vitamin B.

CHAPTER V
DISCUSSIONS

Neurosensory Disturbance (NSD) from Inferior Alveolar Nerve (IAN) injury from BSSRO had no standard for treatment. Previous studies about efficacy of vitamin B was only few reports and limitation in study design as described in Table 23.

	Phillip C 2012	**Lee CH 2016**	**Vieira CL 2016**	**This study**
Study design (Group)	RCT (2 groups)	Retrospective (2 groups)	RCT (2 groups)	RCT (3 groups)
Randomization	Yes	No	Yes	Yes
Total sample size	35 patients	596 patients	12 patients	75 patients
Vitamin B	B12	B12	B12+UTP+CMP	B1-6-12, B12
Route	Nasal spray 500mcg/spray Once a week	IV 20 mcg/day	IM 3 day and oral 1 cap tid pc B12 2 mg/cap	Oral B1-6-12 or B12 1 tab tid pc
Dosage	B12:500 mcg/week	B12:20 mcg/day	B12:6 mg/day	·**B1-6-12** (B1:300mg+B6:15 mg+B12:195 mg) /day ·**B12** : 1,500 mcg/day
Duration	2 wk before to 6 mo after BSSRO	After BSSRO to 1 wk	After BSSRO to 2 mo	After BSSRO to 6 mo
Control	YES	No	Yes	Yes
Placebo	No	No	Yes	No
Measurement	Contact+Thermal	Subjective	VAS+LT	SPD+MPD+LT+PP
Result to NSD	B12 improve	B12 improve	B12 not improve	B1-6-12 improve B12 not improve

Table 23 Comparing this study to previous study

The prospective study of Phillips C et al, 2012 reported vitamin B12 intranasal spray for 2 weeks before and until 6 months after surgery promoted improvement of NSD after BSSRO. However, it was few sample size and no result from vitamin B1-6-12 and vitamin B12 orally administration in this previous study (43). Lee CH et al, 2016 reported the retrospective study of BSSRO and it was only the data of vitamin B12 intravenously for 1 week after surgery and result showed improvement of NSD (18). Moreover, Vieira CL et al, 2016 reported intramuscular and oral administration of combination vitamin B12 with uridine triphosphate (UTP) and cystidine monophosphate (CMP) did not improve NSD and small sample size in study (44). In this study, we evaluated the efficacy of orally vitamin B1-6-12, vitamin B12 and control group after surgery for 6 months that oral form has been widely and easy to use for NSD in oral surgery. Due to no standard dosage of nerve injury treatment in oral surgery, therefore the dosage of vitamin B in this study were based on medically peripheral neuropathy treatment. Moreover, we used large sample size and used randomization in this study to evaluate the data. The serum level of vitamin B were not studied from this study and many previous studies. Only study of Phillips C 2012 reported that at 6 months, vitamin B12 serum level was significantly higher from control group (43). Moreover, serum level of vitamin B12 were reported higher to therapeutic dose at 4 weeks and 6 weeks after oral (>1000 mcg/day) and intranasal administration respectively (88).

The Clinical Neurosensory Disturbance (CNT) consists of subjective and objective test and no standard test for diagnosis (89). Subjective test is low specificity, lack of reproducibility and trend to false positive result, so using objective test can increase accuracy of

assessment (89). In this study, we used objective assessment and quality control with preoperative and postoperative measurement including calibrating inter-examiner measurement. However, it is not purely objective CNT, but it is relatively objective assessment of NSD because all tests requiring patient responses and patient's cooperation. The purely objective assessment consists of sensory nerve action potential, sensory nerve conduction velocity, mental nerve blink reflex, modified somatosensory evoked potentials, electromyographic recordings of masseter reflex (90) that are difficult to use. Some authors advised the objective assessment was better evaluation of NSD from BSSRO (6, 28). In clinical setting for diagnosis and follow up of NSD, CNT commonly be used and based on stimulated through cutaneous contact (24) that were static two point discrimination , moving two point discrimination, light touch and pinprick in this study.

Injury of nerve fibers are categorized histopathologically as neurapraxia, axonotmesis or neurotmesis which depend on the level of injury (38, 50). Clinical symptoms of NSD are various combinations of nerve injuries that variation of sensory function (89). It is difficult to evaluate the level of nerve injury from clinical symptom such as demyelination from compression (neurapraxia), Wallerian degeneration at distal to tubes of intact cell (axonotmesis) or Wallerian degeneration at proximal or distal of the tubes of various Schwann cells (neurotmesis) (91). Exposure of IAN at operation may be effect to nerve sheath or nerve transection that cannot use only non-surgery treatment, but it need microneurosurgery (57, 92) hence we excluded from the study. In this study, we evaluated NSD from BSSRO with no nerve exposed and no nerve transection during the operation. Although nerve was absence of

any visible damage at operation but other mechanisms including hematoma, edema, stretching or compression can effect to nerve injury. From the study of Kabasawa Y 2006 believed that most nerve injury caused by compression were myelinated A-delta and A-beta fibers more than C fibers (93). We implied the level of BSSRO in this study was range from neurapraxia and axonotmesis.

Although we used the standard procedure at one center, control many factors for similarity with no difference of demographic data among 3 groups and used randomized controlled trial to avoid nerve injury variation. We expected the similarity of injury level at immediate postoperation from 3 groups. However, nerve injury still showed variation among 3 groups so we used recovery proportion for analyzing the healing of nerve injury.

In this study, the recovery proportion of all groups increased from immediate postoperation and continued improvement to 6 months significantly. Similar to the previous literatures, they reported that almost injuries improved within 3-6 months and the highest improvement occurred after first 3 months (44, 94, 95). Besides NSD was generally reversible and spontaneous recovery occurred by 6 months after surgery (74, 96, 97) and the previous study of long-term follow-up showed largely normalized sensation about after 1 year after BSSRO (98). A previous systematic review, purely objective assessment showed NSD reduced for 1 year of follow-up (90). The 1 year follow up is required in further study to improve the long term of efficacy of vitamin B on nerve recovery.

Among 3 groups, the recovery proportion of vitamin B1-6-12 tend to highest all the time and significantly highest at 6 months. The recovery proportion of vitamin B12 group had no difference from control group. This result can be implied that nerve healing requires not only vitamin B 12 mechanism, but also from vitamin B1 and B6 mechanism. Vitamin B1 plays a role in the nerve transmission, vitamin B6 is important for synthesis of sphingolipids for myelin formation and vitamin B12 is vital in growth, cell replication, nucleoproteins or myelin synthesis (36) and anti-apoptotic and anti-necrotic effect on neurons (99). The requirement of vitamin B12 increase after injury of nerve (91). Consistent to in vivo studies, vitamin B12 promotes functional and morphological recovery after peripheral nerve damage in rat (100-102). The combination of vitamin B1, B6 and B12 administration promote peripheral axon and myelin sheath regeneration (103). At present, many studies reported the nerve injury mechanisms of vitamin B but were unclear.

When comparing oral vitamin B1-6-12 and oral vitamin B12, we can conclude that vitamin B1-6-12 has higher effect to recovery proportion. Nevertheless, previous study reported bioavailability of vitamin B12 from intravenous route, nasal spray and oral route were 100%, 2% and 1% respectively (104). It cannot be concluded the same results if intravenously vitamin B that give 100% bioavailability or nasal spray of vitamin B that give 2% bioavailability so further study was suggested. Moreover, further study can aim to comparing vitamin B1-6-12 and B12 in the same route administration of vitamin B that higher bioavailability than oral route.

One of the limitation of this study was a placebo. Therefore, randomization single-blinded study possibly affects subject result that

grading by patient personally. Moreover, the patient's compliance and daily dietary may influent to the data analysis of this study. In further study, placebo should be used, patient's compliance and daily dietary should be monitored.

Side effect from this study were 2 patients with acne at face. The previous of case report showed acneiform eruption in patients with oral or IM vitamin B12 at 1 week to 5 months. It was characterized by papules and pustules at face, neck, shoulder, chest and upper portion of the back. Acneiform were spontaneously remission 3-6 week after discontinuation of vitamin B12 (105). Moreover, the previous study reported vitamin B12 modulates transcriptional activities of skin bacteria in acne pathogenesis (106).

BSSRO is represent inferior alveolar nerve injury from oral surgery that possibly different from medically nerve injury. Recovery proportion of administration of vitamin B1-6-12 orally after BSSRO significantly highest among 3 group at 6 months. Moreover, vitamin B1-6-12 were available, not expensive and less side effect (36). We can imply this result to use oral vitamin B1-6-12 to treat nerve injury from other oral surgery such as third molar removal, dental implant placement, local anesthesia injection, trauma or tumor that can improve quality of patient's life (107).

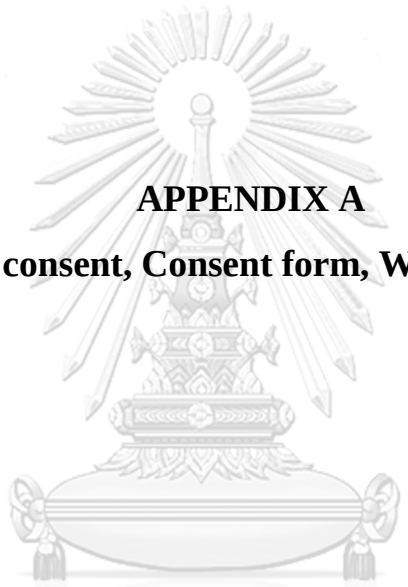
CHAPTER VI
CONCLUSION

Based on this result, vitamin B1-6-12 orally administration after BSSRO influent nerve injury improvement when comparing with control and vitamin B12 at 6 months. We advised using long term of oral vitamin B1-6-12 supplementation at least 6 months after BSSRO for benefit to improve NSD.

APPENDIX

APPENDIX A

Informed consent, Consent form, Withdrawal form



เอกสารข้อมูลคำอธิบายสำหรับอาสาสมัครที่เข้าร่วมในการวิจัย

(Patient/Participant Information Sheet)

1. ชื่อโครงการ (ไทย) การศึกษาเปรียบเทียบผลของวิตามินบี1-6-12และวิตามินบี12ต่อการหายของอาการชาของเส้นประสาทเบ้าฟันล่างหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟัน
   ชื่อโครงการ (อังกฤษ) Comparative study between vitamin B1-6-12 and vitamin B12 for neurosensory recovery after bilateral sagittal split ramus osteotomy
2. ชื่อผู้วิจัยหลัก ทญ.วรวีร์ ไตรสิงห์
   สถาบันที่สังกัด ภาควิชาศัลยศาสตร์ คณะทันตแพทยศาสตร์
   แหล่งทุนวิจัย ทุนรัชดาภิเษกสมโภช ประจำปีงบประมาณ 2558
3. วัตถุประสงค์ของโครงการ เพื่อทดสอบประสิทธิภาพของวิตามินบี1-6-12 และวิตามินบี12ในการรักษาอาการชาในคนไข้ที่ผ่าตัดขากรรไกรร่วมเพื่อการจัดฟัน
4. สถานที่ดำเนินการวิจัย ภาควิชาศัลยศาสตร์ คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
5. วิธีการที่เกี่ยวข้องกับการวิจัย

   อาสาสมัครที่มีข้อบ่งชี้ในการจัดฟันร่วมกับการผ่าตัดขากรรไกรล่างจะได้รับการทดสอบอาการชาที่ริมฝีปากและคางก่อนผ่าตัดขากรรไกรเพื่อเป็นข้อมูลพื้นฐานในผู้ป่วยแต่ละราย หลังการผ่าตัดจะมีการตรวจอาการชาอีกครั้ง หากอาสาสมัครมีอาการชาที่ริมฝีปากและคางหลังผ่าตัดจะได้รับการแบ่งเป็นสามกลุ่มแบบสุ่ม โดยกลุ่มแรกจะได้รับวิตามินบี 1-6-12 หลังผ่าตัดครั้งละ 1เม็ด วันละ 3ครั้ง โดย วิตามิน 1 เม็ดประกอบด้วย วิตามินบี 1 ปริมาณ 100 มิลลิกรัม , วิตามิน บี 6 ปริมาณ 5 มิลลิกรัม และ วิตามิน บี 12 ปริมาณ 65 ไมโครกรัม (ซึ่งเป็นปริมาณวิตามินที่มีรายงานใช้ในการรักษาอาการชาของเส้นประสาทจากสาเหตุอื่นๆทั่วไป) กลุ่มที่สองจะได้รับวิตามินบี 12 หลังผ่าตัด ครั้งละ 1 เม็ด วันละ 3 ครั้ง โดยวิตามิน 1 เม็ดประกอบด้วยวิตามินบี 12 ปริมาณ 500 ไมโครกรัม (ซึ่งเป็นปริมาณวิตามินที่มีรายงานใช้ในการรักษาอาการชาของเส้นประสาทจากสาเหตุอื่นๆทั่วไป) และกลุ่มที่สามจะไม่ได้รับวิตามินบีหลังการผ่าตัดโดยตัวยาอื่นๆ เช่น ยาฆ่าเชื้อ ยาแก้ปวด ยาต้านการอักเสบ จะได้รับเหมือนกันทั้งสามกลุ่มตามมาตรฐานการผ่าตัดขากรรไกรทั่วไป

ในการตรวจติดตามผลการรักษาจะมีการทดสอบอาการชาที่ริมฝีปากล่างและคางที่ 1 สัปดาห์, 1 เดือน, 3 เดือน, 6 เดือนหลังการผ่าตัด นอกจากนี้ผู้ป่วยจะได้รับการประเมินอาการดูแลผลแทรกซ้อนการผ่าตัด การจ่ายยาบรรเทาอาการต่างๆถ้าจำเป็น การถ่ายภาพรังสีประเมินตำแหน่งขากรรไกรและโลหะดามขากรรไกร ตามมาตรฐานทั้งสามกลุ่ม

อาสาสมัครกลุ่มที่ได้รับวิตามินบี จะได้รับยาต่อเนื่องเป็นเวลาอย่างน้อย 6 เดือน (หรือจนกว่าจะหายจากอาการชาก่อนเวลา 6 เดือน) โดยเมื่อครบ 6 เดือน อาสาสมัครจะไม่ได้รับวิตามินบีเพิ่มเติมแล้ว แต่อาสาสมัครทั้งสามกลุ่มจะยังได้รับการนัดเพื่อติดตามผลการรักษาต่อเมื่อครบ 1ปี และนัดผ่าตัดเพื่อเอาโลหะดามกระดูกออก

เมื่อการจัดฟันเสร็จสิ้นสมบูรณ์ มีนัดติดตามผลต่อที่ห้องตรวจผู้ป่วยนอกทุกๆปี ตามมาตรฐานการรักษา

6. เหตุผลที่เชิญเข้าร่วมเป็นอาสาสมัครในโครงการ

เนื่องจากท่านเป็นผู้ป่วยที่จัดฟันร่วมกับการผ่าตัดขากรรไกรล่างและมีอาการชาที่ริมฝีปากและคางหลังผ่าตัด

7. ความรับผิดชอบของอาสาสมัคร ขอให้ท่านปฏิบัติตามที่ผู้วิจัยแนะนำ โดยรับประทานยาที่ทันตแพทย์สั่งจ่ายและกลับมาติดตามผลการรักษาตามกำหนด ในระยะเวลา1 สัปดาห์, 1 เดือน , 3 เดือน, 6 เดือนหลังการผ่าตัด รวมระยะเวลาที่อาสาสมัครจะอยู่ในโครงการทั้งสิ้น 6 เดือนหลังการผ่าตัด หลังจาก 6 เดือน อาสาสมัครยังจะได้รับการนัดเพื่อติดตามผลการรักษาตามมาตรฐานปกติต่อไปทุกปี

8. ประโยชน์ของการวิจัยที่อาสาสมัครและ/หรือผู้อื่นที่อาจได้รับ

ท่านจะไม่ได้รับประโยชน์โดยตรงในการร่วมการวิจัยครั้งนี้ แต่ผลการวิจัยที่ได้จะพัฒนาการรักษาอาการชาซึ่งเป็นผลแทรกซ้อนที่พบได้มากหลังการผ่าตัดขากรรไกร

อย่างไรก็ตามอาสาสมัครที่เข้าร่วมโครงการจะได้รับการสนับสนุนค่าใช้จ่ายเรื่องค่าถ่ายภาพรังสีและค่ายา

9. ความเสี่ยงหรือความไม่สะดวกที่อาจจะเกิดขึ้นแก่อาสาสมัครและในบางกรณีแก่ทารกในครรภ์หรือทารกที่ดื่มนมมารดา

ผู้ป่วยสุขภาพดีที่พร้อมต่อการผ่าตัดขากรรไกรภายใต้การดมยาสลบที่ได้รับเลือกเข้าโครงการจะไม่มีความเสี่ยงที่นอกเหนือจากความเสี่ยงต่อผลแทรกซ้อนจากการผ่าตัดโดยมาตรฐาน

วิตามินบี 1-6-12 หรือวิตามินบี12 ในปริมาณที่ใช้ในการรักษา แม้ว่ายังไม่มีรายงานวิจัยเรื่องการให้วิตามินบีในการรักษาอาการชาในคนไข้ผ่าตัดขากรรไกร แต่ได้มีการให้ในการรักษาอาการชาจากโรคทางระบบอื่นๆ เช่น อาการชาในผู้ป่วยเบาหวานหรือในผู้ป่วยที่มีอาการชาจากพิษสุราเรื้อรังแล้ว พบว่าการให้วิตามินบีในระยะเวลา 6 เดือนนั้น ยังไม่มีรายงานผลแทรกซ้อนหรืออาการแพ้ที่รุนแรงและมีน้อยรายที่เกิดผลแทรกซ้อนจากการรับประทานวิตามินบี 1-6-12 หรือ วิตามินบี 12 เช่นอาการคลื่นไส้ หรืออาการมวนท้อง เป็นต้น ทั้งนี้ อาสาสมัครสามารถอ่านข้อมูลเพิ่มเติมได้ที่ The Cochrane Collaboration 2008

10. ค่าใช้จ่ายที่อาสาสมัครจะต้องจ่าย หรืออาจจะต้องจ่าย

อาสาสมัครจะต้องจ่ายค่าผ่าตัดตามมาตรฐานการผ่าตัดขากรรไกรแต่ จะได้รับการจ่ายชดเชยในส่วนของค่าถ่ายภาพรังสีก่อนและหลังการผ่าตัด รวมถึงยาที่ใช้ในการรักษาทั้งหมด

11. การชดเชยใดๆและการรักษาที่จะจัดให้แก่อาสาสมัครในกรณีที่ได้รับอันตรายซึ่งเกี่ยวข้องกับการวิจัย

หากท่านได้รับอันตรายจากการทำวิจัยผู้วิจัยจะดำเนินการให้ท่านได้รับการรักษาโดยผู้วิจัยจะเป็นผู้รับผิดชอบค่าใช้จ่ายของการรักษา

12. การจ่ายค่าเดินทางค่าเสียเวลาแก่อาสาสมัครที่เข้าร่วมในการวิจัย

ไม่มี

13. เหตุการณ์ที่อาจจะเกิดขึ้นหรือเหตุผลซึ่งผู้วิจัยจะต้องยกเลิกการเข้าร่วมในโครงการวิจัยของอาสาสมัคร

- มีผลแทรกซ้อนจากการผ่าตัดหรือการดมยาที่มีความเสี่ยงถึงชีวิต หรือมีความเสี่ยงต่อการเสียเลือดมาก
- การแตกหักของกระดูกที่ไม่เป็นไปตามแผนการรักษา

14. มีการเก็บชิ้นตัวอย่างที่ได้มาจากอาสาสมัครเอาไว้ใช้ในโครงการวิจัยในอนาคตหรือไม่ เก็บจำนวนเท่าไหร่ อย่างไร และที่ไหน

ไม่มี

15. การกำกับดูแลและควบคุมการดำเนินโครงการ

ผู้กำกับดูแลการวิจัย ผู้ตรวจสอบคณะกรรมการพิจารณาจริยธรรม และคณะกรรมการที่เกี่ยวข้องสามารถเข้าไปตรวจสอบการดำเนินโครงการ รวมทั้ง ตรวจสอบบันทึกข้อมูลของอาสาสมัคร เพื่อเป็นการยืนยันถึงขั้นตอนในการวิจัยทางคลินิกและข้อมูลอื่นๆโดยไม่ล่วงละเมิดเอกสิทธิ์ในการปิดบังข้อมูลของอาสาสมัคร ตามกรอบที่กฎหมายและกฎระเบียบได้อนุญาตไว้ นอกจากนี้ โดยการลงนามให้ความยินยอม อาสาสมัครหรือผู้แทนตามกฎหมายจะมีสิทธิตรวจสอบและมีสิทธิที่จะได้รับข้อมูลด้วยเช่นกัน

16. จริยธรรมการวิจัย

การดำเนินการโครงการวิจัยนี้ ผู้วิจัยคำนึงถึงหลักจริยธรรมการวิจัย ดังนี้

1. หลักความเคารพในบุคคล (Respect for person) โดยการให้ข้อมูลจนอาสาสมัครเข้าใจเป็นอย่างดี

และตัดสินใจอย่างอิสระในการให้ความยินยอมเข้าร่วมในการวิจัย รวมทั้งการเก็บรักษาความลับของ

อาสาสมัคร

2. หลักการให้ประโยชน์ไม่ก่อให้เกิดอันตราย (Beneficence/Non-Maleficence) ซึ่งได้ระบุในข้อ 8 และ 9 ว่าจะมีประโยชน์หรือความเสี่ยงกับอาสาสมัครหรือไม่

3. หลักความยุติธรรม (Justice) คือเกณฑ์คัดเข้าและคัดออกชัดเจน มีการกระจายความเสี่ยงและผลประโยชน์อย่างเท่าเทียมกัน โดยวิธีสุ่มเข้ากลุ่มศึกษา

17. ข้อมูลที่อาจนำไปสู่การเปิดเผยตัวของอาสาสมัครจะได้รับการปกปิด ยกเว้นว่าได้รับคำยินยอมไว้โดยกฎระเบียบและกฎหมายที่เกี่ยวข้องเท่านั้น จึงจะเปิดเผยข้อมูลแก่สาธารณชนได้ ในกรณีที่ผลการวิจัยได้รับการตีพิมพ์ ชื่อและที่อยู่ของอาสาสมัครจะต้องได้รับการปกปิดอยู่เสมอ และอาสาสมัครหรือผู้แทนตามกฎหมายจะได้รับแจ้งโดยทันท่วงที ในกรณีที่มีข้อมูลใหม่ซึ่งอาจใช้ประกอบการตัดสินใจของอาสาสมัครว่าจะยังคงเข้าร่วมในโครงการวิจัยต่อไปได้หรือไม่

18. หากท่านมีข้อสงสัยต้องการสอบถามเกี่ยวกับสิทธิของท่านหรือผู้วิจัยไม่ปฏิบัติตามที่เขียนไว้ในเอกสารข้อมูล

คำอธิบายสำหรับผู้เข้าร่วมในการวิจัย ท่านสามารถติดต่อหรือร้องเรียนได้ที่ ฝ่ายวิจัย คณะทันตแพทยศาสตร์

จุฬาลงกรณ์มหาวิทยาลัย ตึกสมเด็จย่า 93 ชั้น 10 หรือที่หมายเลขโทรศัพท์ 02-218-8866 ในเวลาทำการ

19. หากท่านต้องการยกเลิกการเข้าร่วมเป็นอาสาสมัครในโครงการนี้ ให้ท่านกรอกและส่งเอกสารขอยกเลิกมาที่

ทญ.วรวีร์ ไตรสิงห์ ภาควิชาศัลยศาสตร์ คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย 34 ถนน อังรีดูนังค์

ปทุมวัน กทม. 10330

20. อาสาสมัครสามารถติดต่อผู้วิจัยได้**ตลอด 24 ชั่วโมง** ที่ :

ทญ.วรวีร์ ไตรสิงห์ 08-6557-4096

.....

(.....)

ผู้วิจัยหลัก

วันที่...../...../.....

เอกสารยินยอมเข้าร่วมการวิจัย (Consent Form)

การวิจัยเรื่อง การศึกษาเปรียบเทียบผลของวิตามินบี1-6-12และวิตามินบี12ต่อการหายของอาการชาของเส้นประสาทเบ้าฟันล่างหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟัน

ข้าพเจ้า (นาย/ นาง/ นางสาว/ เด็กชาย/เด็กหญิง)

อยู่บ้านเลขที่.....ถนน.....

ตำบล/แขวง..... อำเภอ/เขต.....

จังหวัด..... รหัสไปรษณีย์.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้

1. ข้าพเจ้าได้รับทราบรายละเอียดข้อมูลคำอธิบายสำหรับอาสาสมัครที่เข้าร่วมในการวิจัย รวมทั้งได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการทำวิจัย อันตรายหรืออาการที่อาจเกิดขึ้นจากการทำวิจัยหรือจากยาที่ใช้รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียดและมีความเข้าใจดีแล้ว

2. ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

3. ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆทีเกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น และผู้วิจัยรับรองว่าหากเกิดอันตรายใดๆ จากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า

4. ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้และการบอกเลิกการเข้าร่วมการวิจัยนี้จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ข้าพเจ้าจึงสมัครใจเข้าร่วมโครงการวิจัยนี้ตามที่ระบุในเอกสารข้อมูลคำอธิบายสำหรับอาสาสมัครและได้ลง นามในใบยินยอมนี้ด้วยความเต็มใจ และได้รับสำเนาเอกสารใบยินยอมที่ข้าพเจ้าลงนามและลงวันที่ และเอกสารยกเลิกการเข้าร่วมวิจัย อย่างละ 1 ฉบับ เป็นที่เรียบร้อยแล้ว ในกรณีที่อาสาสมัครยังไม่บรรลุนิติภาวะจะต้องได้รับการยินยอมจากผู้ปกครองด้วย

ลงนาม..... (อาสาสมัคร) (.....) วันที่...../...../.....	ลงนาม..... (ผู้ปกครอง) (.....) วันที่...../...../.....
ลงนาม..... (ผู้วิจัยหลัก) (.....) วันที่...../...../.....	ลงนาม..... (พยาน) (.....) วันที่...../...../.....

ข้าพเจ้าไม่สามารถอ่านหนังสือได้ แต่ผู้วิจัยได้อ่านข้อความในใบยินยอมนี้ให้แก่ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนาม หรือประทับลายนิ้วหัวแม่มือขวาของข้าพเจ้าในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม..... (อาสาสมัคร) (.....) วันที่...../...../.....	ลงนาม..... (ผู้ปกครอง) (.....) วันที่...../...../.....
ลงนาม..... (ผู้วิจัยหลัก) (.....) วันที่...../...../.....	ลงนาม.....(พยาน) (.....) วันที่...../...../.....

เอกสารยกเลิกการเข้าร่วมวิจัย (Withdrawal Form)

การวิจัยเรื่อง การศึกษาเปรียบเทียบผลของวิตามินบี1-6-12ต่อการหายของอาการชาของเส้นประสาทเบ้าฟันล่างหลังการศัลยกรรมขากรรไกรล่างเพื่อการจัดฟัน

ข้าพเจ้า (นาย/ นาง/ นางสาว/ เด็กชาย/ เด็กหญิง).....

อยู่บ้านเลขที่.....ถนน.....ตำบล/แขวง.....

อำเภอ/เขต.....จังหวัด.....รหัสไปรษณีย์.....

ขอยกเลิกการเข้าร่วมโครงการวิจัยนี้ โดยมีเหตุผลในการยกเลิกการเข้าร่วมวิจัยคือ

- ❑ ย้ายภูมิลำเนา
- ❑ ไม่สะดวกในการเดินทาง
- ❑ เหตุผลอื่น.....

ลงนาม.....

ผู้ยกเลิก

(.....)

วันที่.....เดือน.....พ.ศ. .....

ลงนาม.....

พยาน

(.....)

วันที่.....เดือน.....พ.ศ. .....

ลงนาม.....

ผู้วิจัยหลัก

(.....)

วันที่.....เดือน.....พ.ศ. .....

ที่อยู่สำหรับส่งเอกสาร

ทญ.วรวีร์ ไตรสิงห์

ภาควิชาศัลยศาสตร์ คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย 34 ถนน อังรีดูนังค์ ปทุมวัน กทม. 10330

APPENDIX B

Data output

At immediate postoperation, neurosensory disturbance (GSS range 0-12) from vitamin B1-6-12 group, vitamin B12 group and control group can be separated to reduced (GSS:0-5), intermediate (GSS: 6-8) and subnormal (GSS: 9-12) that were described in Figure 1 and Figure 2. On the passing time, all group improved NSD as showed in Figure 3, 4, 5 and 6 respectively).

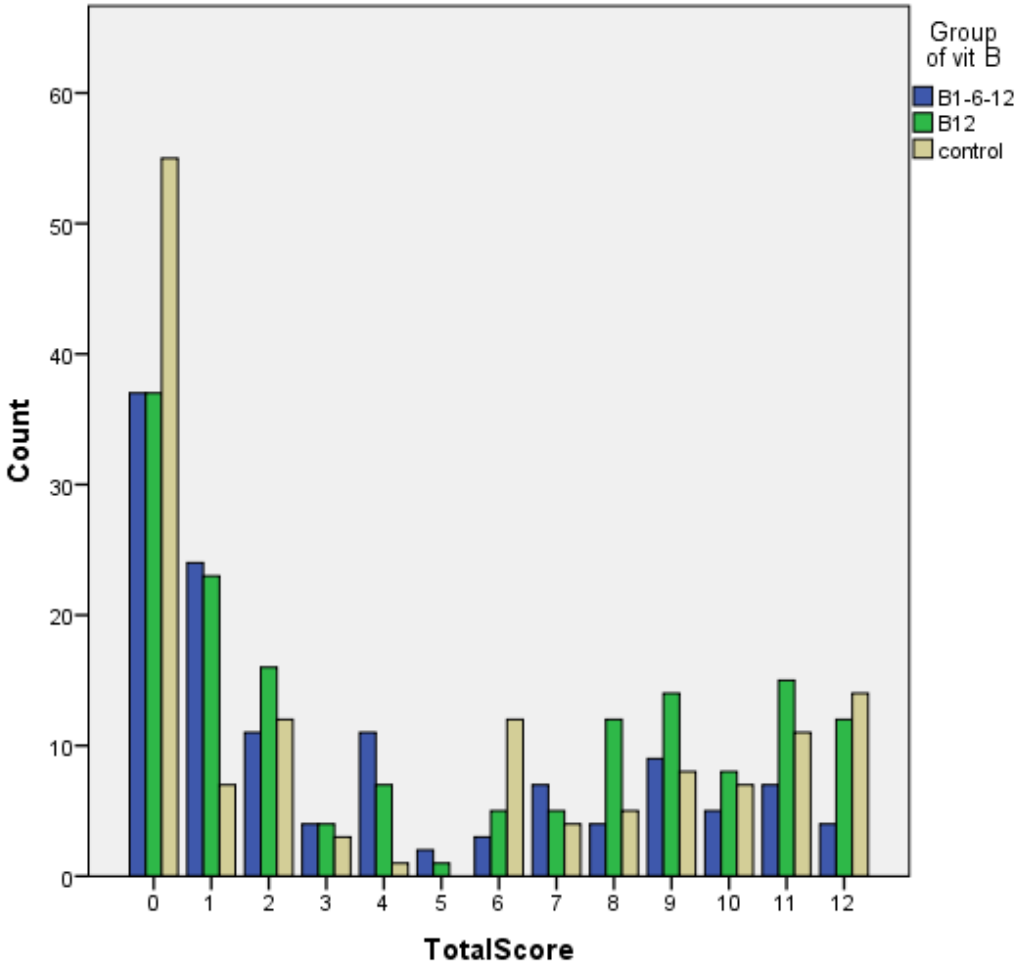


Figure 1 Counting of neurosensory disturbance area of 3 group at immediate postoperation that included to this study

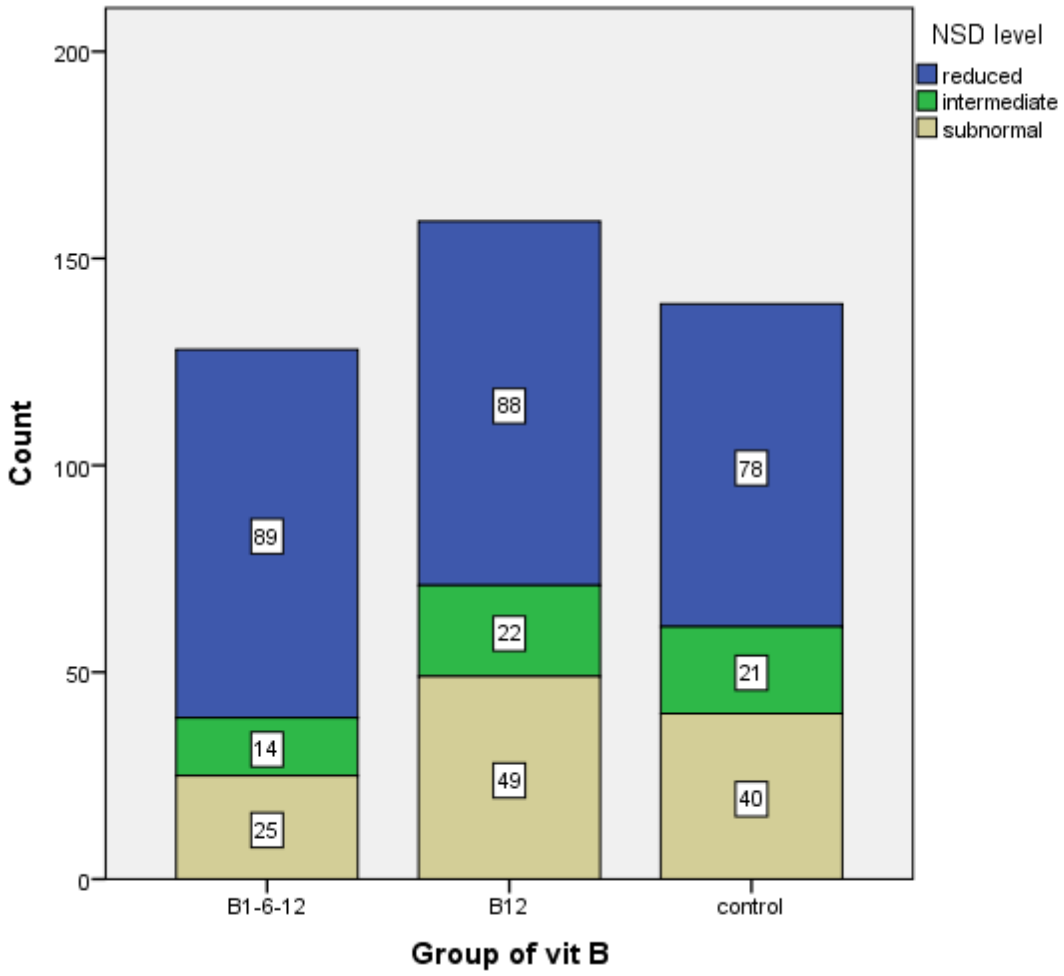


Figure 2 Area counting defined by grading of inferior alveolar nerve injury among 3 group at immediate postoperation

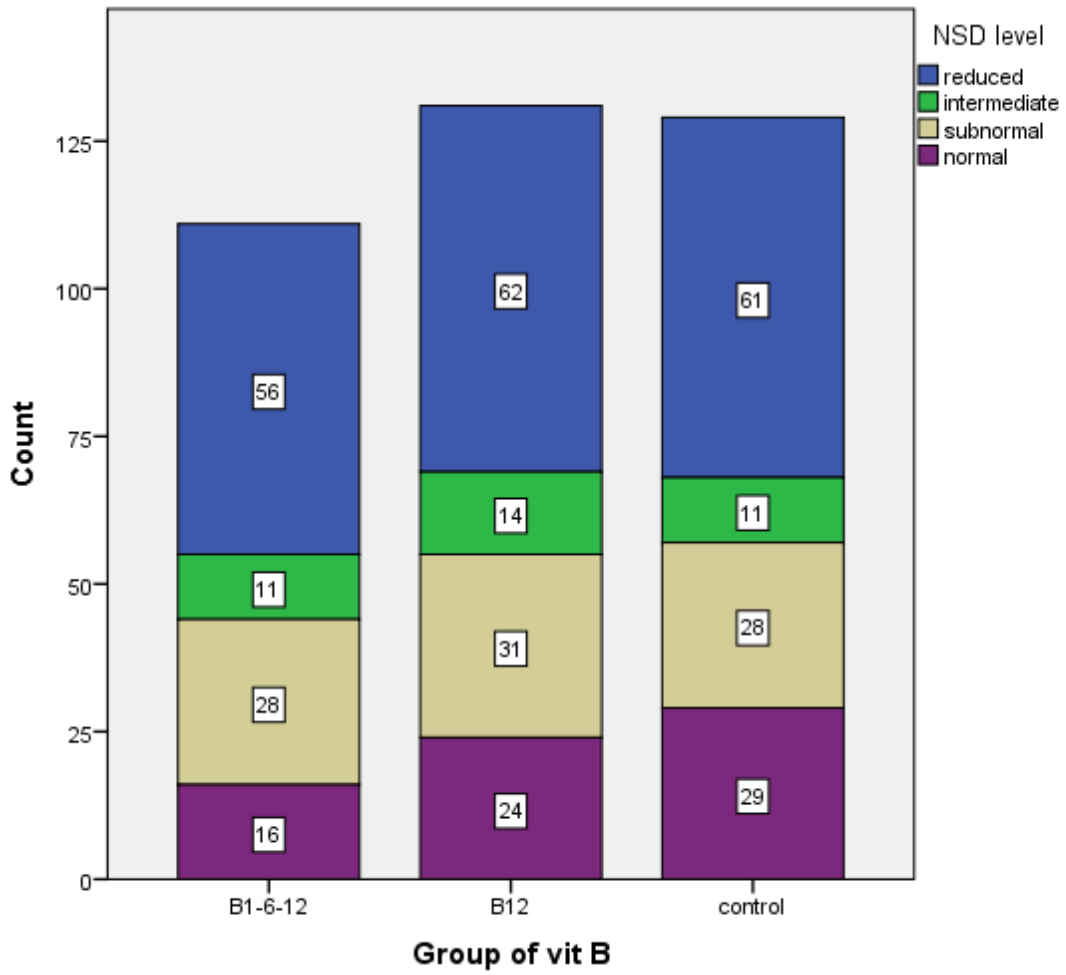


Figure 3 Area counting defined by grading of inferior alveolar nerve injury among 3 group at 1 week

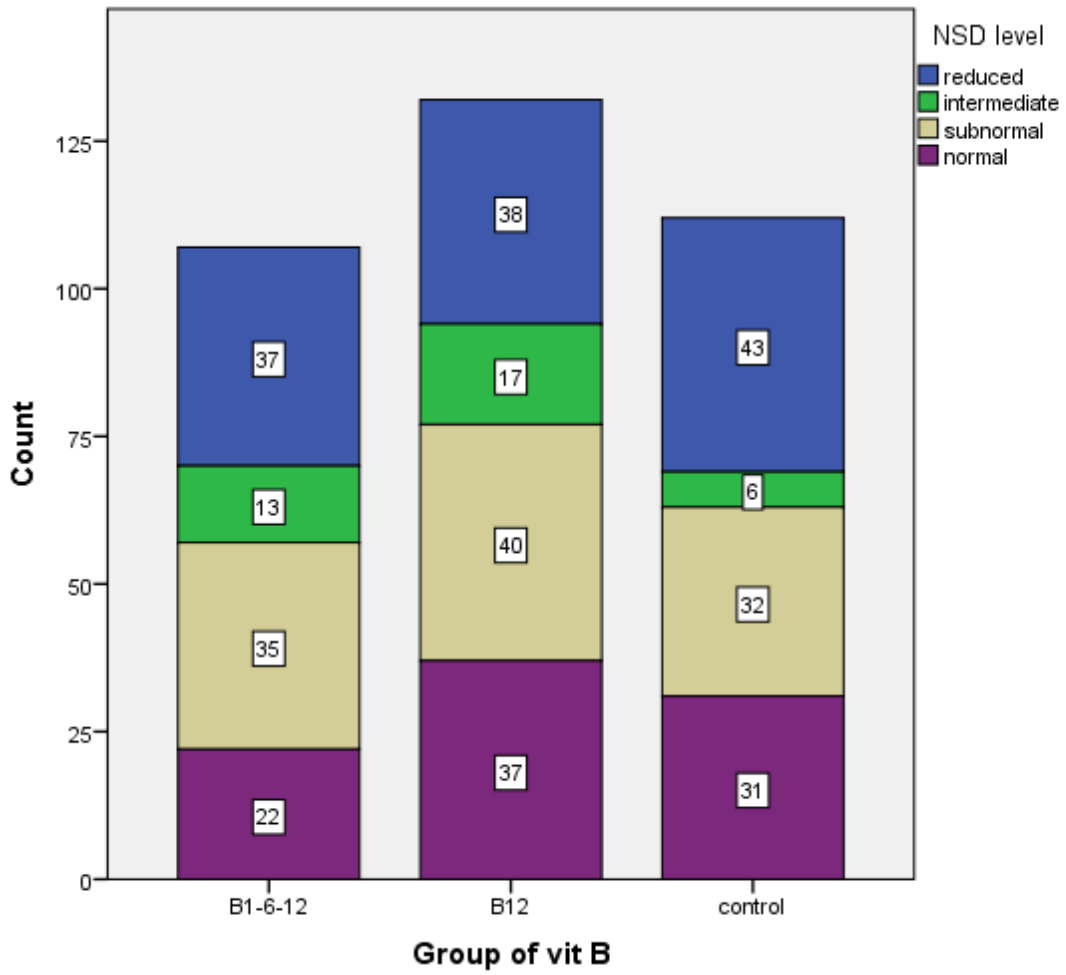


Figure 4 Area counting defined by grading of inferior alveolar nerve injury among 3 group at 1 month

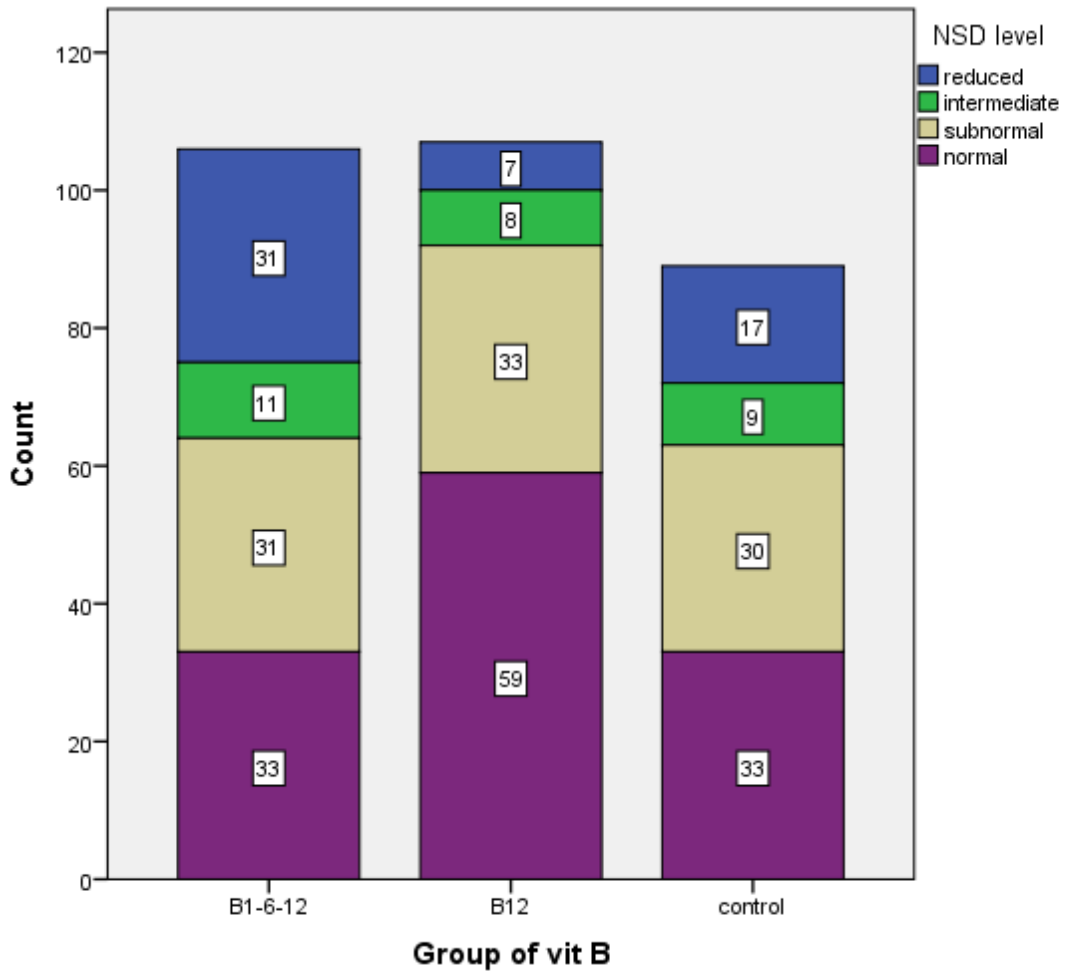


Figure 5 Area counting defined by grading of inferior alveolar nerve injury among 3 group at 3 months

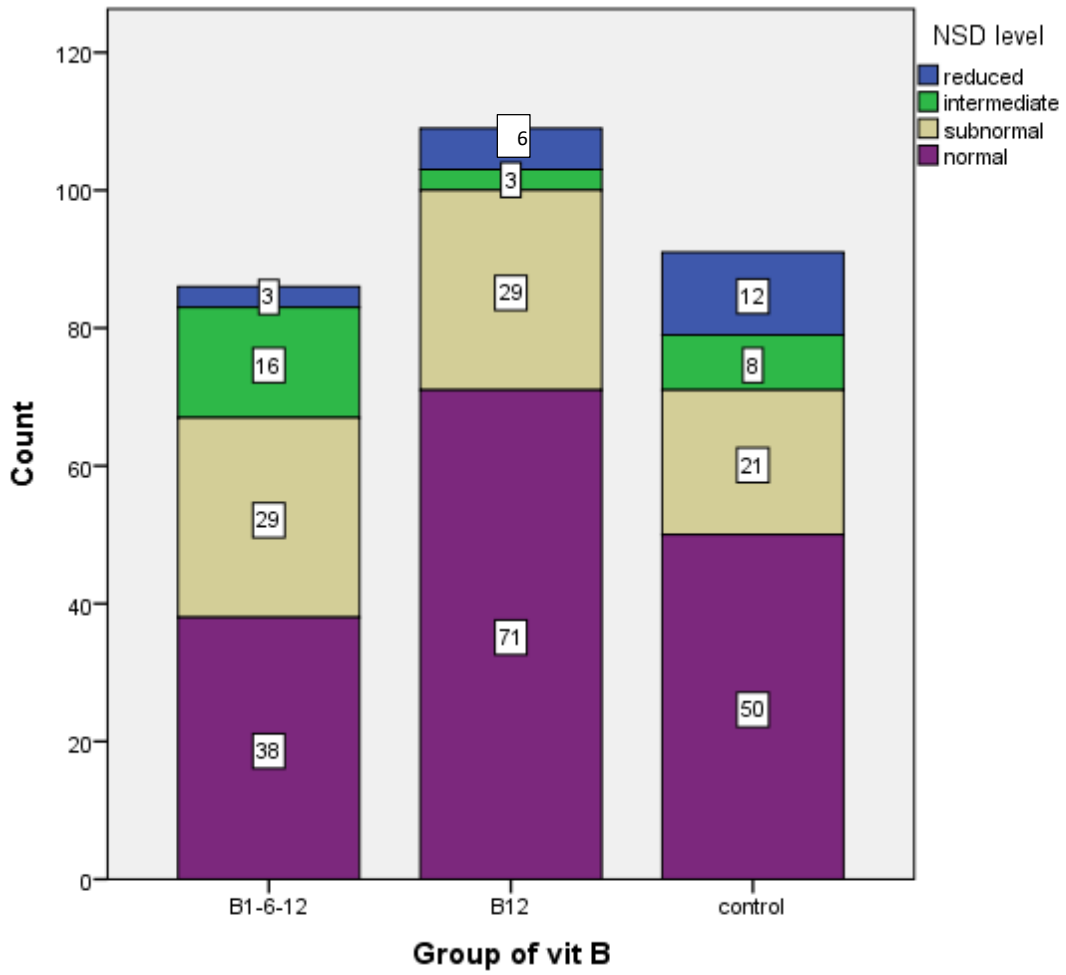


Figure 6 Area counting defined by grading of inferior alveolar nerve injury among 3 groups at 6 months

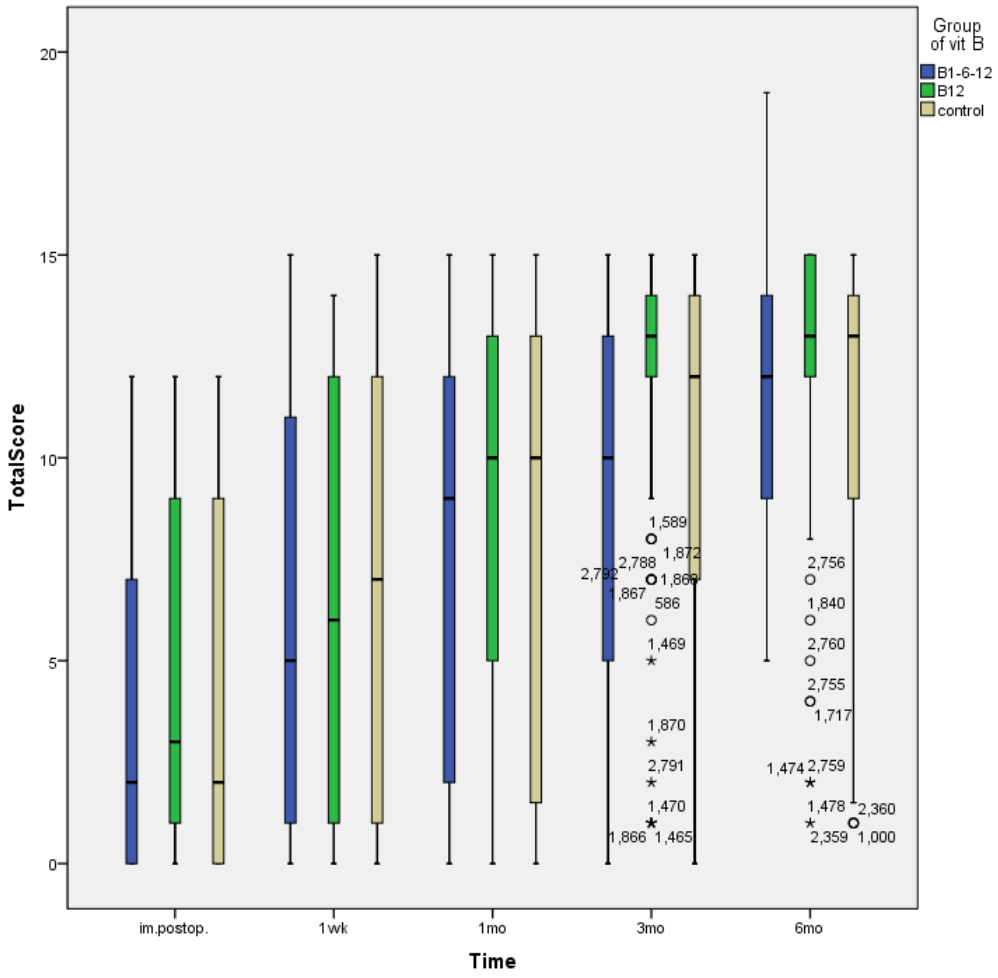


Figure 7 Global Sensitivity Score at follow up time reported with median ± interquartile rank

We calculated recovery proportion from GSS and we used nonparametric analysis. The result showed mean ± interquartile rank for among three group comparing at 1 week (Figure 8), 1month (Figure 9), 3months (Figure 10) and 6 months (Figure 11).

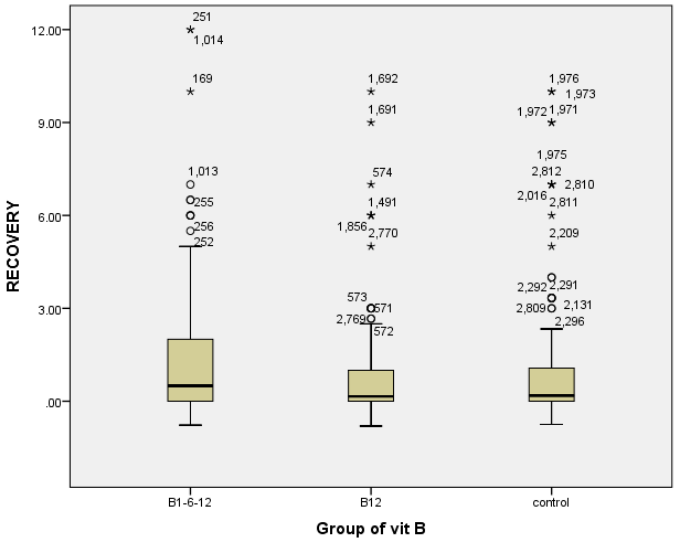


Figure 8 Median ± interquartile rank of recovery proportion among 3 groups at 1 week

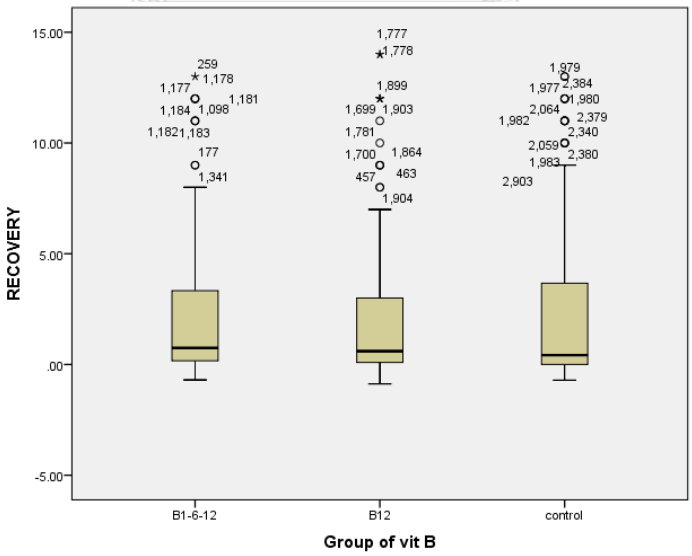


Figure 9 Median ± interquartile rank of recovery proportion among 3 groups at 1 month

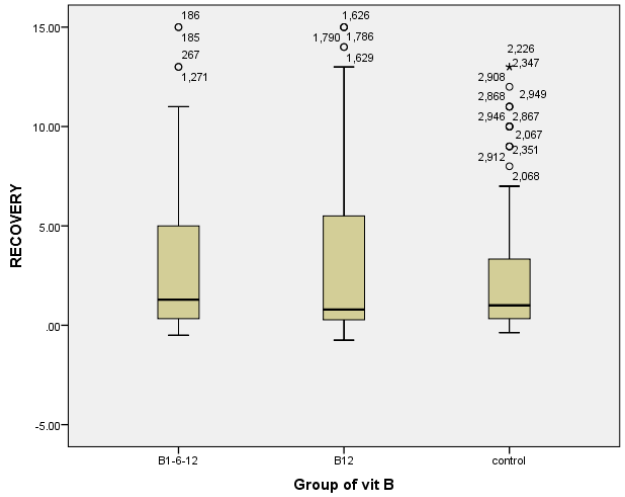


Figure 10 Median ± interquartile rank of recovery proportion among 3 groups at 3 months

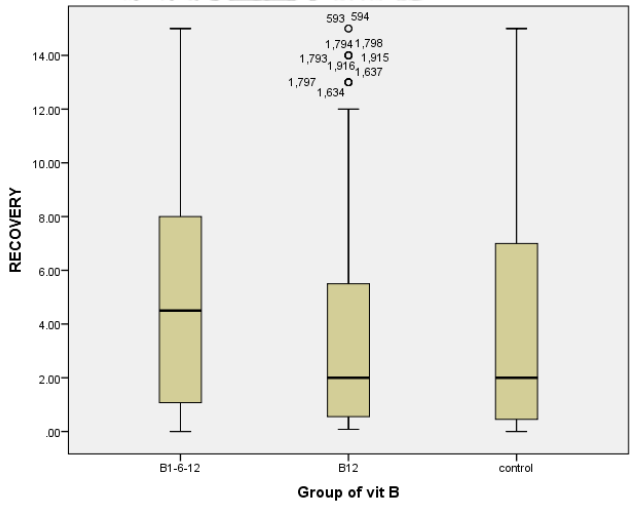
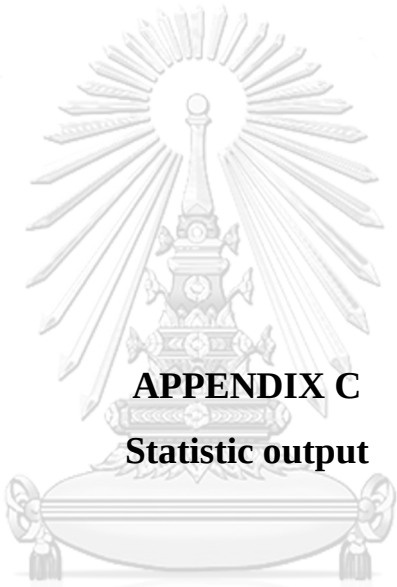


Figure 11 Median ± interquartile rank of recovery proportion among 3 groups at 6 months



APPENDIX C
Statistic output

One-Sample Kolmogorov-Smirnov Test

		age
N		75
Normal Parameters[a,b]	Mean	26.6000
	Std. Deviation	5.87942
Most Extreme Differences	Absolute	.181
	Positive	.181
	Negative	-.098
Test Statistic		.181
Asymp. Sig. (2-tailed)		**.000[c]**

a. Test distribution is Normal.

b. Calculated from data.

c. Lilliefors Significance Correction.

Table 1 Distribution of data (age of patients)

Test Statistics[a,b]

	age
Chi-Square	.056
df	2
Asymp. Sig.	**.972**

a. Kruskal Wallis Test

b. Grouping Variable: Group

Table 2 Comparing age of patients among 3 group with Kruskal Wallis H test

Group * gender

Crosstab

Count

		gender		
		male	female	Total
Group	B1-6-12	10	15	25
	B12	12	13	25
	Control	8	17	25
Total		30	45	75

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.333[a]	2	**.513**
Likelihood Ratio	1.340	2	.512
Linear-by-Linear Association	.329	1	.566
N of Valid Cases	75		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.00.

Table 3 and 4 Comparing gender of patients among 3 groups by Chi-Square test

Group * type of operation (1jaw or 2 jaws)

Crosstab

Count

		typeop		
		1 jaw	2jaw	Total
Group	B1-6-12	19	6	25
	B12	17	8	25
	Control	17	8	25
Total		53	22	75

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.515[a]	2	**.773**
Likelihood Ratio	.525	2	.769
Linear-by-Linear Association	.381	1	.537
N of Valid Cases	75		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.33.

Table 4 and 5 Comparing type of operation among 3 groups by Chi-Square test

Group * direction

Crosstab

Count

		direction				
		setback	advance	rotation	setback+rotation	Total
Group	B1-6-12	18	1	0	6	25
	B12	19	1	3	2	25
	Control	19	0	2	4	25
Total		56	2	5	12	75

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.836[a]	6	**.442**
Likelihood Ratio	8.007	6	.238
Linear-by-Linear Association	.134	1	.714
N of Valid Cases	75		

a. 9 cells (75.0%) have expected count less than 5. The minimum expected count is .67.

Table 6 and 7 Comparing direction of mandible among 3 groups by Chi-Square test

Group * operation time

Crosstab

Count

		optime		
		<180min	>180min	Total
Group	B1-6-12	12	13	25
	B12	11	14	25
	Control	10	15	25
Total		33	42	75

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.325[a]	2	.850
Likelihood Ratio	.325	2	.850
Linear-by-Linear Association	.320	1	.571
N of Valid Cases	75		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.00.

Table 8 and 9 Comparing operation time among 3 groups by Chi-Square test

Group * blood loss

Crosstab

Count

		bloodloss		
		<300ml	>300ml	Total
Group	B1-6-12	6	19	25
	B12	12	13	25
	Control	13	12	25
Total		31	44	75

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.729[a]	2	**.094**
Likelihood Ratio	4.919	2	.085
Linear-by-Linear Association	3.988	1	.046
N of Valid Cases	75		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.33.

Table 10 and 11 Comparing blood loss among 3 groups by Chi-Square test

Test Statistics[a,b]

	NSD Area
Chi-Square	2.000
df	2
Asymp. Sig.	**.368**

a. Kruskal Wallis Test

b. Grouping Variable: Group

Table 12 Comparing amount of neurosensory disturbance(NSD) among 3 group by Kruskal Wallis H test

One-Sample Kolmogorov-Smirnov Test

		RECOVERY	TotalScore
N		1722	1737
Normal Parameters[a,b]	Mean	1.9810	7.85
	Std. Deviation	3.49789	5.316
Most Extreme Differences	Absolute	.292	.145
	Positive	.292	.139
	Negative	-.230	-.145
Test Statistic		.292	.145
Asymp. Sig. (2-tailed)		.000[c]	**.000[c]**

a. Test distribution is Normal.

b. Calculated from data.

c. Lilliefors Significance Correction.

Table 13 Distribution of recovery proportion data and GSS by using Kolmogorov-Smirnov Test

Test of normality used Kolmogorov-Smirnov test as described in Table 13 at confidence interval of 95%. The significant was <0.001, mean non-normal distribution. Thus, recovery proportion were compared intragroup with Friedman test then post hoc with Wilcoxon signed rank test. Among 3 group comparing, we used Krukal Wallis H test and post hoc with Mann Whitney U test.

At immediate postoperation, GSS among 3 group were different significantly (p=0.083) so we used recovery proportion for comparing nerve healing as described in Table 14.

Test Statistics[a,b]

	RECOVERY	TotalScore
Chi-Square	.000	4.968
df	2	2
Asymp. Sig.	**1.000**	**.083**

a. Kruskal Wallis Test

b. Grouping Variable: Group of vit B

Table 14 Comparison of GSS and recovery proportion among 3 groups at immediate postoperation by using Kruskal Wallis H test

Intragroup comparison of vitamin B1-6-12 on the passing time were significantly increased at all period that using Friedman test and post hoc with Wilcoxon Signed Rank test. The significant difference were described in Table 15.

Test Statistics[a]

	wk1 - impostop	mo1 - wk1	mo3 - mo1	mo6 - mo3
Z	-6.527[b]	-2.829[b]	-2.657[b]	-5.006[b]
Asymp. Sig. (2-tailed)	**.000**	**.005**	**.008**	**.000**

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 15 Comparing recovery proportion of vitamin B1-6-12 between duration using Wilcoxon Signed Rank test

Intragroup comparison of vitamin B12 on the passing time were significantly increased almost all duration that using Friedman test and post hoc with Wilcoxon Signed Rank test. The significant difference were described in Table 16.

Test Statistics[a]

	wk1 - impostop	mo1 - wk1	mo3 - mo1	mo6 - mo3
Z	-5.960[b]	-5.372[b]	-5.779[b]	-.110[c]
Asymp. Sig. (2-tailed)	**.000**	**.000**	**.000**	**.913**

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

c. Based on positive ranks.

Table 16 Comparing recovery proportion of vitamin B12 between duration using Wilcoxon Signed Rank test

Intragroup comparison of control group on the passing time were significantly increased at all the time that using Friedman test and post hoc with Wilcoxon Signed Rank test. The significant difference were described in Table 17.

Test Statistics[a]

	wk1 - impostop	mo1 - wk1	mo3 - mo1	mo6 - mo3
Z	-6.886[b]	-3.301[b]	-3.324[b]	-3.135[b]
Asymp. Sig. (2-tailed)	**.000**	**.001**	**.001**	**.002**

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 17 Comparing recovery proportion of control group between duration using Wilcoxon Signed Rank test

Recovery proportion were compared among 3 groups at immediate postoperation (p=0.128), 1 week (p=0.77), 1 month (p=0.728), 3 months (p=0.55) and 6 months (p=0.055) as described in Table 18, 19, 20 and 21 respectively. We found no difference by using Krukal Wallis H test.

Test Statistics[a,b]

	RECOVERY
Chi-Square	4.114
df	2
Asymp. Sig.	**.128**

a. Kruskal Wallis Test

b. Grouping Variable: Group of vit B

Table 18 Comparing among 3 groups with Krsukal Wallis H test at 1 week

Test Statistics[a,b]

	RECOVERY
Chi-Square	.522
df	2
Asymp. Sig.	**.770**

a. Kruskal Wallis Test

b. Grouping Variable: Group of vit B

Table 19 *Comparing among 3 groups with Krsukal Wallis H test at 1 month*

Test Statistics[a,b]

	RECOVERY
Chi-Square	.634
df	2
Asymp. Sig.	**.728**

a. Kruskal Wallis Test

b. Grouping Variable: Group of vit B

Table 20 Comparing among 3 groups with Krsukal Wallis H test at 3 month

Test Statistics[a,b]

	RECOVERY
Chi-Square	5.790
df	2
Asymp. Sig.	**.055**

a. Kruskal Wallis Test

b. Grouping Variable: Group of vit B

Table 21 Comparing among 3 groups with Krsukal Wallis H test at 6 month

At 6 months were vitamin B1-6-12 group were higher recovery proportion than control group (p=0.038) as described in Table 22. Moreover, vitamin B1-6-12 group were higher recovery proportion than vitamin B12 group (p=0.33) as described in Table 23.

Test Statistics[a]

	RECOVERY
Mann-Whitney U	3196.500
Wilcoxon W	7661.500
Z	-2.072
Asymp. Sig. (2-tailed)	**.038**

a. Grouping Variable: Group of vit B

Table 22 Comparing between vitamin B1-6-12 and vitamin B12

Test Statistics[a]

	RECOVERY
Mann-Whitney U	3567.000
Wilcoxon W	9132.000
Z	-2.135
Asymp. Sig. (2-tailed)	**.033**

a. Grouping Variable: Group of vit B

Table 23 Comparing between vitamin B1-6-12 and vitamin B12

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