การพัฒนาและประเมินประสิทธิภาพของถุงมือที่มีการติดตั้งอุปกรณ์ตรวจจับอาการสั่นและอุปกรณ์ระงับอาการสั่นด้วยการกระตุ้นกล้ามเนื้อมือด้วยไฟฟ้า ในผู้ป่วยโรคพาร์กินสันที่มีอาการมือสั่นในขณะพักเป็นอาการเด่นและอาการมือสั่นนั้น ไม่ตอบสนองต่อการรักษาด้วยยารับประทาน

นางอรอนงค์ จิตรกฤษฎากุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาอายุรศาสตร์ ภาควิชาอายุรศาสตร์
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2560

Development of Parkinson's glove for detection and suppression of hand tremor at rest among the tremor-dominant Parkinson's disease patients with medically intractable tremor.

Mrs. Onanong Jitkritsadakul

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Medicine
Department of Medicine
Faculty of Medicine
Chulalongkorn University
Academic Year 2017

Thesis Title	Development of Parkinson's glove for detection and suppression of hand tremor at rest among the tremor-dominant Parkinson's disease patients with medically intractable tremor.
By	Mrs. Onanong Jitkritsadakul
Field of Study	Medicine
Thesis Advisor	Professor Roongroj Bhidayasiri
Thesis Co-Advisor	Assistant Professor Rattana Rattanatharn
	Dr. Chusak Thanawattano

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(Dr. Soradech Krootjohn)

อรอนงค์ จิตรกฤษฎากุล : การพัฒนาและประเมินประสิทธิภาพของถุงมือที่มีการติดตั้งอุปกรณ์ตรวจจับอาการสั่นและอุปกรณ์ระงับอาการสั่นด้วยการกระตุ้นกล้ามเนื้อมือด้วยไฟฟ้า ในผู้ป่วยโรคพาร์กินสันที่มีอาการมือสั่นในขณะพักเป็นอาการเด่นและอาการมือสั่นนั้น ไม่ตอบสนองต่อการรักษาด้วยยารับประทาน (Development of Parkinson's glove for detection and suppression of hand tremor at rest among the tremor-dominant Parkinson's disease patients with medically intractable tremor.) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ศ. นพ. รุ่งโรจน์ พิทยศิริ, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ. พญ. รัตนา รัตนาธาร, อ. ดร. ชูศักดิ์ ธนวัฒโน, 113 หน้า.

การศึกษานี้มีวัตถุประสงค์เพื่อประเมินประสิทธิภาพของการกระตุ้นกล้ามเนื้อด้วยกระแสไฟฟ้า ในการรักษาอาการมือสั่นในผู้ป่วยโรคพาร์กินสันที่มีอาการมือสั่นในขณะพัก เป็นอาการเด่นและอาการมือสั่นนั้นไม่ตอบสนองต่อการรักษาด้วยยารับประทาน การศึกษานี้ประกอบด้วยการศึกษา 2 ระยะ โดยการศึกษาระยะที่ 1 เป็นการหาค่าการ กระตุ้นและการตำแหน่งที่เหมาะสมในการกระตุ้นกล้ามเนื้อ และ การศึกษาระยะที่ 2 เป็นการทดสอบประสิทธิภาพของถุงมือพาร์กินสันในการลดอาการมือสั่นเปรียบเทียบกับถุงมือหลอกการศึกษาระยะที่ 1 เป็นการศึกษาแบบกึ่งทดลองที่มีผู้ป่วยเข้าร่วมการศึกษาจำนวน 34 รายที่มีอาการมือสั่นในขณะพักโดย จากการศึกษาพบว่าการกระตุ้นกล้ามเนื้อด้วย กระแสไฟฟ้าสามารถลดอาการมือสั่นในขณะพักได้จริงอย่างมีนัยสำคัญทางสถิติที่ประเมินจากการลดลงของสัญญาณสั่นจากเครื่องมือวัดอาการสั่นที่เป็นมาตรฐานการศึกษาระยะที่ 2 เป็นการพัฒนาถุงมือพาร์กินสันซึ่งเป็นอุปกรณ์ที่ประกอบ ด้วยเซนเซอร์วัดอาการสั่น และเครื่องกระตุ้นกล้ามเนื้อด้วยกระแสไฟฟ้า ที่จะทำงานร่วมกันเพื่อลดอาการสั่นที่เกิดขึ้นร่วมกับเป็นการทดสอบประสิทธิภาพ ของถุงมือพาร์กินสันในการลดอาการมือสั่นเปรียบเทียบกับถุงมือหลอก ในผู้ป่วยโรคพาร์กินสันที่มีอาการมือสั่นใน ขณะพักเป็นอาการเด่น จำนวน 40 ราย ที่ได้รับการสุ่มแบ่งเป็นผู้ป่วยในกลุ่มถุงมือพาร์กินสันจำนวน 20 ราย และ กลุ่มถุงมือหลอกจำนวน 20 ราย โดยพบว่าผู้ป่วยที่ใช้ถุงมือพาร์กินสันมีอาการสั่นของมือ ขณะพักลดลงอย่างมีนัยสำคัญ โดยที่ไม่เปลี่ยนแปลงของความถี่ของอาการสั่น โดยผลจากการศึกษาทั้ง 2 การศึกษานี้สนับสนุนถึงประสิทธิภาพ ของการกระตุ้นกล้ามเนื้อ ด้วยไฟฟ้า ในการระงับอาการมือสั่นในผู้ป่วยโรคพาร์กินสัน ที่อาจเป็นอีกทางเลือกหนึ่ง ของการรักษาอาการสั่นในอนาคต

ภาควิชา อายุรศาสตร์	ลายมือชื่อนิสิต .....
สาขาวิชา อายุรศาสตร์	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
ปีการศึกษา 2560	ลายมือชื่อ อ.ที่ปรึกษาร่วม .....
	ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5774766330 : MAJOR MEDICINE
KEYWORDS: PARKINSON'S DISEASE / TREMOR SUPPRESSION / ELECTRICAL MUSCLE STIMULATION

ONANONG JITKRITSADAKUL: Development of Parkinson's glove for detection and suppression of hand tremor at rest among the tremor-dominant Parkinson's disease patients with medically intractable tremor.. ADVISOR: PROF. ROONGROJ BHIDAYASIRI, CO-ADVISOR: ASST. PROF. RATTANA RATTANATHARN, DR. CHUSAK THANAWATTANO, 113 pp.

The objectives of this study were to determine the efficacy of an electrical muscle stimulation (EMS) as a treatment for drug resistant tremor in PD patients by identifying of the most suitable stimulation protocols for tremor reduction and to seek out for the best location for placement of the surface electrodes (phase 1) and developing the Parkinson's glove and test for its efficacy in suppression of hand tremor at rest among the tremor-dominant Parkinson's disease patients with medically intractable tremor (phase 2). From phase 1 study, 34 PD patients with classic resting tremor was recruited. The suitable stimulation protocol and the best location for stimulating were identified. Compared to before stimulation, we observed a significant reduction in tremor parameters during stimulation. From phase 2 study, the Parkinson's glove was developed and tested for its efficacy compare with a sham glove among 40 PD patients with intractable hand tremor in a randomized-controlled study. Forty PD patients were randomly allocated into 20 patients in the Parkinson's glove group and 20 patients in the sham glove group. During intervention, Parkinson's glove group showed significant tremor reduction compared to a sham group determined by reduction in the tremor amplitude parameters, but not with tremor frequency. Parkinson's glove might become a therapeutic option for tremor reduction among those PD patients with medically intractable tremor.

Department:	Medicine	Student's Signature	.....
Field of Study:	Medicine	Advisor's Signature	.....
Academic Year:	2017	Co-Advisor's Signature	.....
		Co-Advisor's Signature	.....

ACKNOWLEDGEMENTS

I would like to send my greatly appreciation my advisor, Prof. Bhidayasiri and my two co-advisor, Dr. Thanawattano and Assist. Prof Rattanatharn for their patience and extensive support in overcoming numerous obstacles I have been facing through my research.

I wish to thank to Prof. Phanthumchinda, Assist. Prof. Asawavichienjinda, Prof. Asawanonda, and Dr. Krootjohn for their kindly suggestion to improve this research.

Nevertheless, I am also grateful to the Parkinson's disease patients who participated in this study and all staff members at The Center of Excellence for Parkinson's Disease and Related Disorders, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, for their kind supports and considerations.

This study was supported by the 100th anniversary Chulalongkorn University Fund for Doctoral Scholarship, the 90th anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund), and the Cerebos award 2016.

Last but not the least, I would like to thank my family: my parents, my sister, and my husband for supporting me spiritually throughout writing this thesis and my life in general.

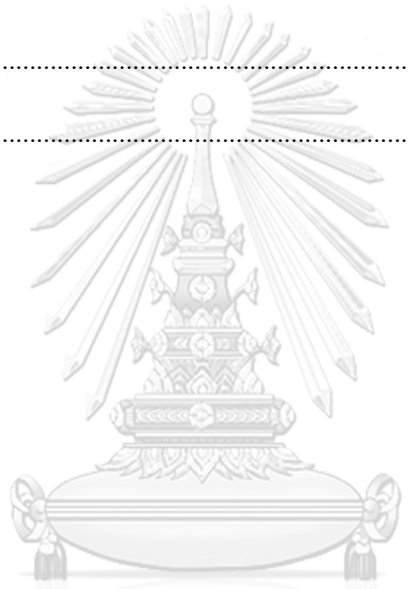
CONTENTS

Page

Page

Page

Page



LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Background and rationale

A definition of tremor is an involuntary, rhythmic and oscillatory movement involving parts of body caused by synchronize or alternate muscle contractions. (1-3) Classification of tremors according to their phenomenology were divided into two categories: resting tremor and action tremor (2). A resting tremor is a tremor that occurs in a body part that completely lack of voluntary movements and fully supported against gravity. (2) Action tremor occurs during muscle contraction and voluntary movement. Action tremors can be subdivided in 4 categorical groups including; postural, kinetic, task-specific, and isometric tremors (2). A tremor is the most common abnormal movement disorders that can be occurred from a physiological and pathological in origin (4). In some pathological forms of tremors such as Parkinson's disease (PD), essential tremor (ET), and dystonic tremor (DT), the tremors likely present in a high amplitude, certain frequency and contain features that can be distinguished from each other. Asymmetrical resting tremor is often seen in PD patients, while bilateral action tremors are usually seen in ET patients. Dystonic tremors may occur in a body part relevant with dystonia (2, 3).

Parkinson's disease is common neurodegenerative disorder, which is commonly characterized by its four predominantly motor symptoms as following: resting tremor, rigidity, bradykinesia, and postural instability (5). Parkinson's disease was first described for its particular characteristics by James Parkinson, who stated in the first paper publication called "An Essay on the Shaking Palsy" (6). He described the peculiar characteristics in a series of 6 patients as a key statement:

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward and to pass from a walking to a running pace: the senses and intellects being uninjured." (6)

By this statement, Dr. Parkinson described the specific PD symptoms, especially the resting tremor (the tremulous motion in parts not in action) that was particularly noticed and could be specific characteristic to this disease (6). The amplitude of resting tremor usually increases during mental stress (or mental load) and during movements of multiple body parts such as walking (2). PD tremors or parkinsonian tremors may have heterogeneous manifestations. Both resting and postural/kinetic tremors can be seen (2, 7). PD tremors were classified into 3 types based on the consensus criteria of the Movement Disorders Society, as follows; (2, 7) (Fig 1)

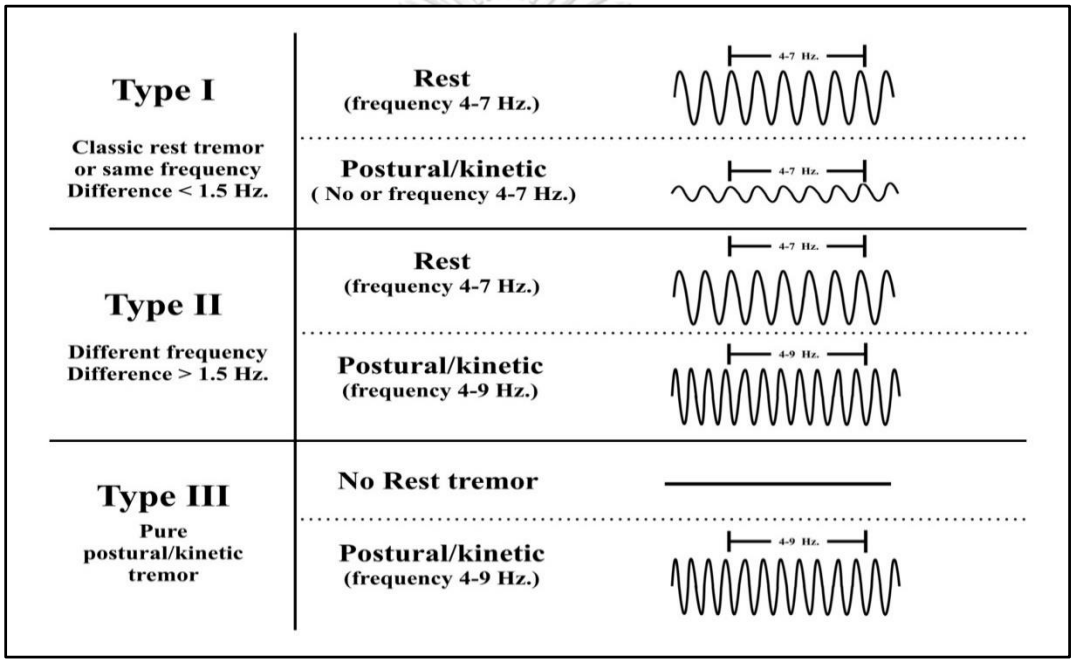


Figure 1: The figure shows three types of PD tremors based on the consensus criteria of the Movement Disorders Society

Type 1: classic resting tremor

This type of tremor is the most common form for Parkinson's disease. PD patients with type 1 tremors usually have resting component within the range between 4-6 Hz. frequencies that may occur with or without postural/kinetic tremors. However, higher tremor frequencies at up to 9 Hz. can be found in an early PD patient. However, tremor

frequencies for both resting and postural/kinetic position are similar and usually different less than 1.5 Hz.

Type 2: resting and postural/kinetic tremors of different frequencies

This type of tremor is uncommon. This tremor could considered as a combination of parkinsonian tremor and essential tremor. PD patients with type 2 tremors have both resting tremors and postural/kinetic tremors. However, the frequency of postural/kinetic tremors is usually higher than resting tremors more than 1.5 Hz.

Type 3: pure postural/kinetic tremor

This type of tremor is usually found in akinetic-rigid PD. PD patients with type 3 tremors have only postural/kinetic tremors within a range of 4-9 Hz. frequencies.

A type 1 tremor (or classic parkinsonian tremor) is the most common type of tremor in Parkinson's disease. It is usually noticed first, probably occurring in up to 70 percent of patients from western countries (8, 9). From the national Parkinson's disease registry in Thailand, the prevalence of resting tremors was found up to 68.6% of Thai PD patients (10, 11). The resting tremor in PD itself does not directly involve individually functional disabilities, but it usually contributes to stigmatization, shame feelings, and psychological concerns such as anxiety or depression (4, 12-15). The re-emerging tremor is one type of postural tremor in PD that presents at rest and re-expression again after maintaining posture. (16) This type of tremor had categorized as a type 1 classic parkinsonian tremor. (16) This type of tremor might occur during the maintenance of posture and is related with limitations in individual daily activities such as drinking and eating. Sometimes, it mimics with others causes of action tremors such as essential tremors and enhanced physiologic tremors (2, 9, 17, 18).

At the present time, PD treatment is mainly targets to control of tremor mechanisms (mainly with the central mechanism) by dopaminergic replacement with oral dopaminergic medications or functional neurosurgery. Traditional oral anti-parkinsonian medications such as levodopa remain the most efficacious medication compared to other oral dopaminergic medications (19). However, levodopa tends to

resolve specific motor symptoms such as bradykinesia and rigidity rather than tremors (17, 19, 20). Some Parkinson's disease patients reported no improvement or even worsen condition on their rest tremor after oral anti-parkinsonian medications, even with levodopa (17, 21). Because a resting tremor in PD often has debilitating symptoms and is easily noticed, those who had rest tremor refractory to dopaminergic medications often seek others medication or management to suppress tremors, such as trial in oral anticholinergic medication, beta-blocker therapy, or undergoing functional neurosurgery such as the deep brain stimulation in specific nuclei includes the thalamus, subthalamic nucleus (STN), and globus pallidus interna (GPi) (22-26). However, all of these managements forms for tremor reduction are related with adverse events including the risk of anticholinergic therapy in the elderly, such as arrhythmia, cognitive impairment, glaucoma, etc. Beta-blocker therapy is related with a high frequency of bradycardia but still lacks strong evidences to support its efficacy. Surgical management may increase the fatal risks such as surgical risk, risk of device stimulation, and stimulation-related risk (26-28). Again, with the reason of rest tremor in PD is usually had debilitating symptoms, easily noticed, and may be interpreted as a problem in public appearance. However, traditional treatment is usually limited or related to adverse events (22-26, 29). Finding of new additional treatments for this problematic issue is required.

Currently, electrical muscle stimulation (EMS) is being gaining increasing interest as an alternative treatment option for resting tremor attenuation in conjunction with oral anti-parkinsonian medications. This method might serve itself as strong stimuli to reset the tremor mechanisms, resulting in the transient reduction of resting tremor. However, there has been little research reporting on its efficacy in suppression of resting tremors among PD patients. What literature exists mostly contains numerous limitations, as follows; all of them were lacked of statistical standard and recruited participants with a small sample size; some of them were conducted using patients with other types of tremors (such as essential tremors) without any comparative study to PD patients or controls; all of them used analysis of tremors mainly with inertial sensors (accelerometer or gyroscope) but without providing standard tremor parameters or neurophysiologic explanation (such as surface electromyography) to

evaluate motor function among those tremors before and during the performance of electrical muscle stimulation; and none of these established data confirmed the efficacy or feasibility of an ambulatory EMS system for the suppression of tremors available in over a long-term period (30-36)(Fig 2 & Fig 3). There have been some studies that developed a tremor suppression system, but their devices were really large in size due to intentionally using a laboratory-based system. Such a system is unable to provide the implementation of data on the efficacy of EMS for tremor suppression in an everyday usage (30, 37).

Based on the aforementioned, the objective of this study is to determine the efficacy of EMS for reduction of intractable tremors in Parkinson's disease. A secondary objective is to develop a portable device that integrates both a tremor analysis function and electrical muscle stimulation function in order to detect and suppress the resting tremor in Parkinson's disease. In order to reduce limitations as in previous studies, we will provide a method as follows; a sample size calculation, reduction of sample heterogeneity by recruiting only classic PD resting tremors, providing the quantitative tremor measurement with standard tremor analysis device, and reporting tremor outcomes in standard tremor parameters. Before using the glove, all subjects will receive a quantitative measurement of tremors with a combination of standard inertial sensors and surface electromyogram (surface EMG) to determine the most suitable protocol for stimulation (such as pulse amplitude, and duration for stimulation). The combination of inertial sensors with an accelerometer and gyroscope system will detect degree of motion change by linear or angular displacement of body parts, or its tremor amplitudes. It will also provide reliable outcomes for both quantitative and qualitative measurement of tremor in terms of 5 tremor parameters (Peak magnitude, RMS, Frequency, Angle, Q) (38-40).

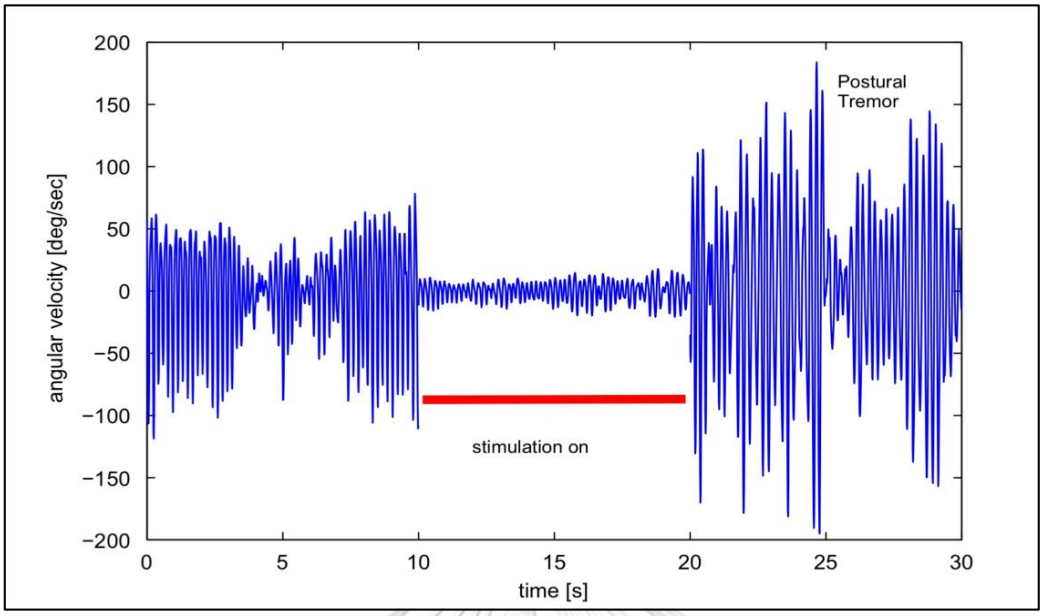


Figure 2: The figure of accelerometer represents the reduction of tremors during EMS (34)

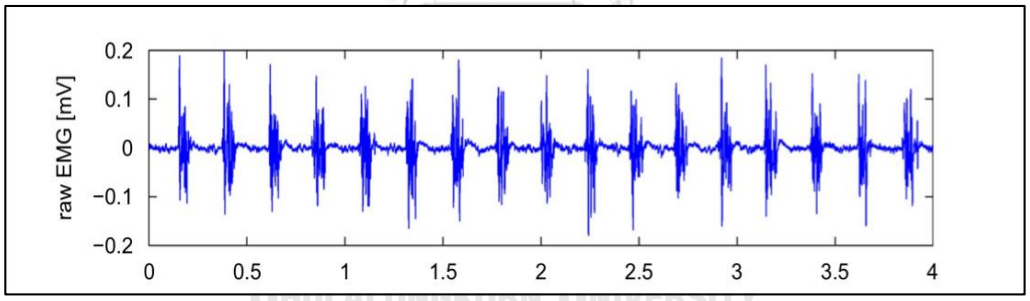


Figure 3: The surface EMG represents for tremor activity. (34)

The surface EMG will be recorded using an electromyography system**.** These systems are used and widely accepted in the global neuromuscular field. Surface EMG may provide information concerning the muscle activity (motor unit and synchronization) involved in the generation of tremors, probably physiologically differentiation for resting tremors in PD from the other types of tremors that may occur similarly at resting position such as dystonic tremor, show the relationship between involved muscles and tremor patterns, and revealing agonist and antagonist muscles, as well as, tetanic muscle contraction. However, traditional methods for the evaluation

of surface EMG are based on its amplitude and spectral analysis, which only supports qualitative outcomes and may not determine the differentiation between distinct patterns of EMG from different types of tremors(41). Therefore, the analysis of surface EMG based on dimensionality can be quantified using different motor features to determine the physiology of an underlying muscle. It may also help to more precisely diagnose Parkinson's disease (41, 42). The surface EMG and acceleration signal obtained from all patients in this study will be extracted and clustered into data in order to analyze using Matlab™ (MathWorks Inc.) (Fig 4). High-dimensional feature vectors will be performed later to determine the different efficacy in pulse amplitude of electrical muscle stimulation on feature vectors (35, 36, 41-43) (Fig 5).

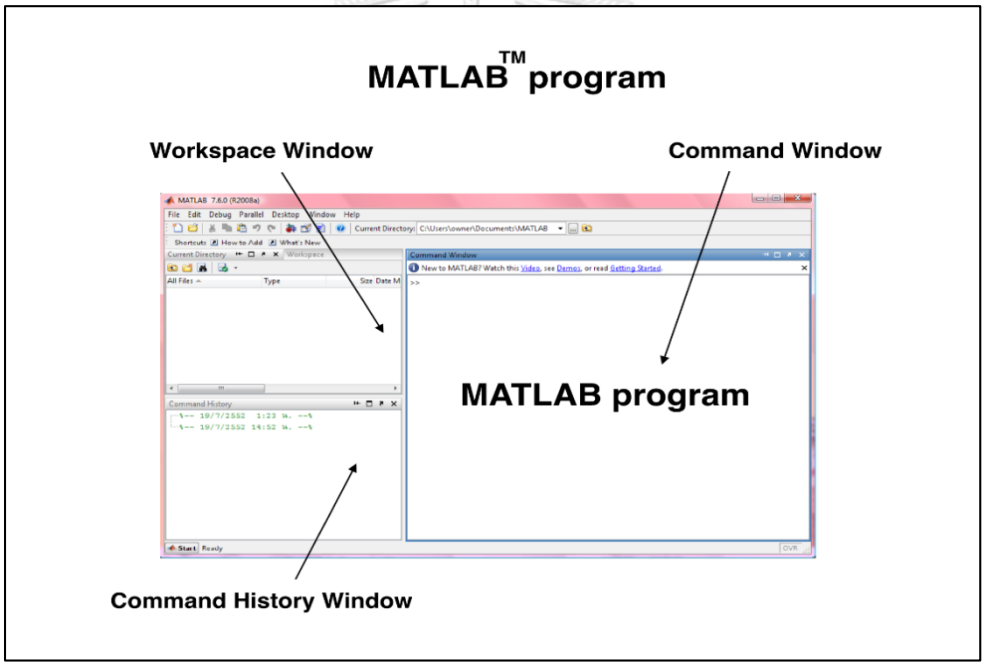


Figure 4: The Matlab™ program

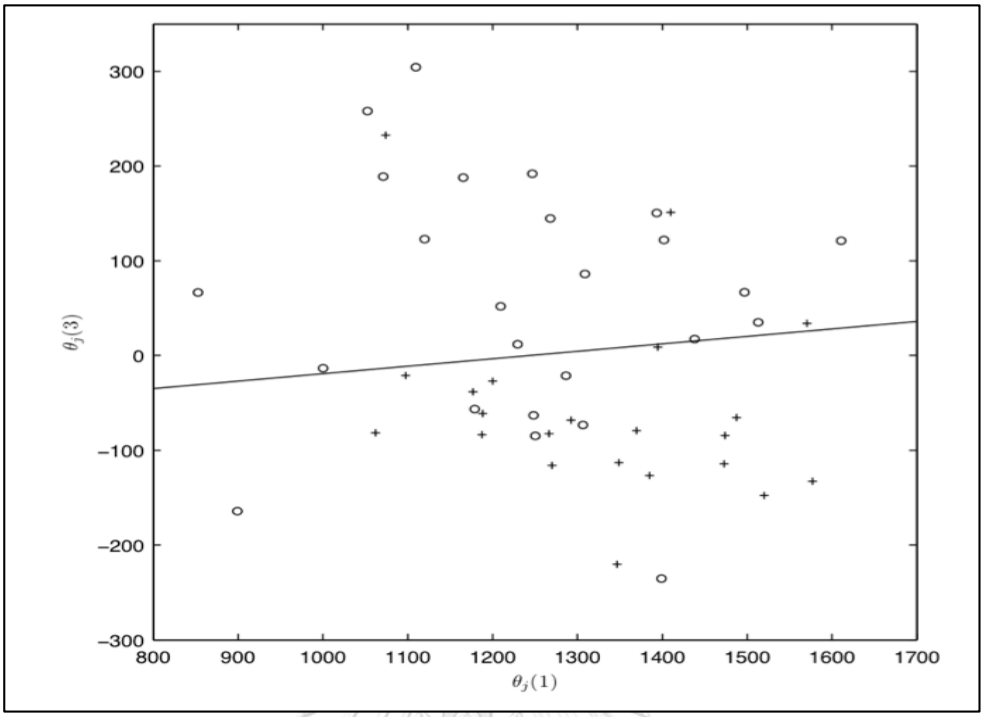


Figure 5: The analysis of surface EMG morphological signal from qualitative data in to quantitative data and its high-dimensional vector (Khahunen-Loeve transform) calculated by Matlab™ program (35)

For the device development, we incorporate The National Electronics and Computer Technology Center (NECTEC), Thailand, in developing a prototype model of the Tremor Detection and Suppression System device, which integrates both a tremor analysis device and an electrical muscle stimulation device in order to detect and suppress tremors, especially among those Parkinson's disease who have problematic, medically-intractable rest tremors. This novelty development is mainly intended for tremor reduction in everyday usage as a glove or "Parkinson's glove for tremor suppression" (Fig 6 & Fig 7).

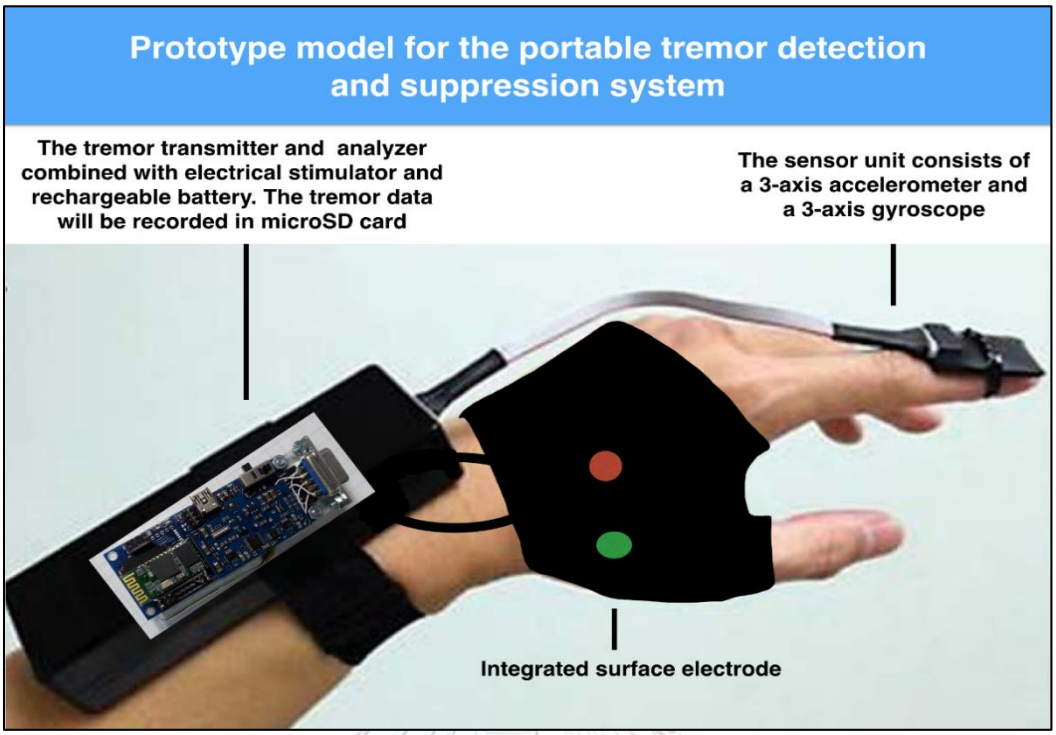


Figure 6: The prototype model for the tremor detection and suppression device (Parkinson's glove).

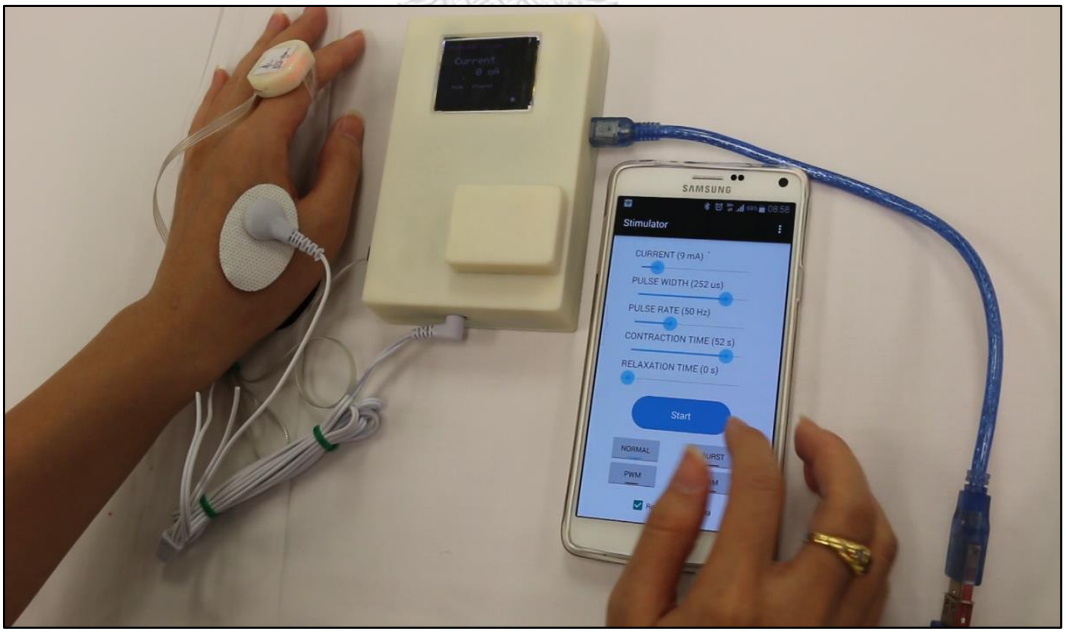


Figure 7: The prototype model for the tremor detection and suppression device (Parkinson's glove)

Research Questions

This study is composed of 2 phases:

Phase 1: Development of a Parkinson's glove for detection and stimulation of hand tremors at rest

Phase 2: Test for the efficacy of a Parkinson's glove for the suppression of hand tremors at rest among tremor-dominant Parkinson's disease patients with medically-intractable tremors

Phase 1: Development of Parkinson's glove for detection and stimulation of hand tremors at rest

Primary research question:

- What are the most suitable stimulation protocols (pulse width, frequency, and pulse amplitude) for a Parkinson's glove for suppression of rest tremors among tremor-predominant PD patients with medically-intractable tremors?

Secondary research questions:

- What is the most suitable stimulation duration for a Parkinson's glove that does not cause fatigue or pain of the hand muscles and can suppress rest tremors among tremor-predominant PD patients with medically-intractable tremor?
- Where are the most suitable areas for placement of the stimulation electrodes of a Parkinson's glove to suppress rest tremors among tremor-predominant PD patients with medically-intractable tremor?

Phase 2: Test for the efficacy of a Parkinson's glove for the suppression of hand tremors at rest among tremor-dominant Parkinson's disease patients with medically-intractable tremors.

Primary research question:

- Does the Parkinson's glove provide significant reduction of resting tremor amplitude as determined by incorporated accelerometer more than the sham glove among tremor-predominant PD patients with medically intractable tremors?

Secondary research questions:

- Does the Parkinson's glove provide significant reduction of re-emerging tremor amplitude as determined by incorporated accelerometer more than the sham glove among tremor-predominant PD patients with medically-intractable tremors?
- Does the Parkinson's glove provide significant improvement in quality of life as determined by a Parkinson's disease questionnaire with 8 items more than the sham glove among tremor-predominant PD patients with medically-intractable tremors?
- Does the Parkinson's glove relate to any adverse events more than the sham glove among the tremor-predominant PD patients with medically-intractable tremors?
- Does the Parkinson's glove reset or reduce the amplitude of parkinsonian tremors and confirm the hypothesis of modulation for the peripheral mechanisms in parkinsonian tremors?

Objectives

Primary objective for Phase 1:

- To identify the most suitable stimulation protocols (pulse width, frequency, and pulse amplitude) for a Parkinson's glove for suppression of rest tremors among tremor-predominant PD patients with medically-intractable tremors.

Secondary objectives for Phase 1:

- To identify the most suitable stimulation duration for a Parkinson's glove that does not cause fatigue or pain of the hand muscles and can suppress rest tremors among tremor-predominant PD patients with medically-intractable tremors.
- To identify the most suitable areas for placement of the stimulation electrodes of a Parkinson's glove to suppress rest tremors among tremor-predominant PD patients with medically-intractable tremors.

Primary objective for Phase 2:

- To determine an efficacy of the Parkinson's glove for detection of resting tremor amplitude compared to a sham glove in tremor-predominant PD patients with medically-intractable tremors.

Secondary objectives for Phase 2:

- To compare an efficacy for re-emerging tremor reduction between the Parkinson's glove and a sham glove among tremor-predominant PD patients with medically-intractable tremors.
- To compare improvement in quality of life scale between those using a Parkinson's glove and a sham glove among tremor-predominant PD patients with medically-intractable tremors.
- To compare the side effects between using the Parkinson's glove and a sham glove among tremor-predominant PD patients with medically-intractable tremors.
- To confirm the hypothesis of modulation for peripheral mechanisms with EMS (from the Parkinson's glove) that could be reset or reduced the amplitude of parkinsonian tremors.

Hypothesis

The Parkinson's glove is integrated with a tremor detection and suppression module (electrical muscle stimulation), which primarily effects EMS based on modulating the peripheral mechanisms of tremors, has effectiveness in tremor detection, properly in location for placement of electrode and the suitable stimulation protocol, and providing the suppression of rest tremors in combination with oral anti-parkinsonian medications among the tremor-predominant PD patients who suffered from medically-intractable tremors. Moreover, this device will not provide more adverse events than using the sham glove.

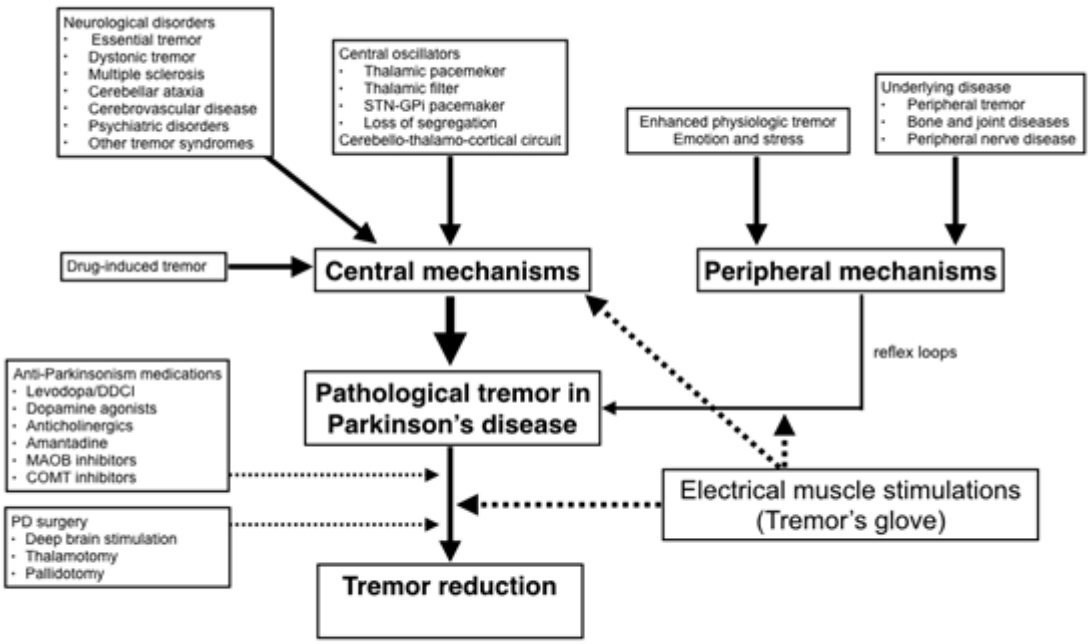
Assumption

- All PD patients who participated in each groups of this study are assumed to have similar tremor severity, disease severity, and no differences in other concurrently underlying diseases.
- All patients are assumed to continue their medicines regularly, as prescribed by their physicians, in order to determine the additional efficacy of the Parkinson's glove in the attenuation of tremor.

Key word

- Tremor suppression
- Electrical muscle stimulation
- Parkinson's disease

Conceptual framework



Operational definition

- Parkinson's disease: A parkinsonian syndromes that occurred in a patient who meets the Unified Parkinson's Disease Rating Society Brain Bank Clinical Diagnostic Criteria, as in Appendix-A (44).
- Tremor-predominant Parkinson's disease or classic rest tremors (type 1 tremors in PD) is the most common PD subtype according to an established criteria (2).
- Medically-intractable tremors are defined as intractable tremor that are medically unresponsive, despite the continued administration of combined conventional PD medications (45, 46).
- Essential tremor: A patient who fulfills all the TRIG classifications of essential tremor in Appendix-B (2).

- Dystonic tremor: A patient who fulfills the proposed the definitions of Appendix-C (2).
- Tremor rating scale (according to UPDRS as in Appendix-D): A clinical rating scale developed to evaluate the severity of parkinsonian tremors. The tremor scale is determined by rest tremor items, which are divided into 5 parts (head, arms, and legs). The total score is 20 points, with a higher score representing more severe tremor symptoms (47, 48).
- A resting tremor is defined as a tremor that occurs in body parts that are completely supported against gravity, without voluntarily muscle activation (2).
- An Action tremor is defined as a tremor that occurs during voluntary movement or voluntary muscle contraction. Action tremors can be subdivided into postural, kinetic, task-specific, and isometric tremors (2).
- A postural tremor is defined as a tremor that occurs in body parts that are voluntarily maintaining posture against gravity (2).

Expected Benefits and Applications

We hope that our study will provided greater understanding of tremor pathophysiology, which may lead to novel treatment of rest tremors in Parkinson's disease patients since it is a quite common and problematic issue and usually refractory to traditional medications. The EMS may become an alternatives or additional treatment for those PD patients to suppress their tremors without increasing risks.

Obstacle

This study needs the patients to use this device for a 14-day period (total of 3 follow-ups), though it may be quite difficult to recruit patients who are able to come to the hospital for all appointments. Thus, the investigators will make a

phone calls to each patient once per day in order to encourage the patients to correctly and continuously use the device.

CHAPTER II

LITERATURE REVIEW

Review of parkinsonian tremor pathology

Loss of dopaminergic neurons in substantia nigra pars compacta (SNc) relevant to a positive finding of intraneuronal inclusions that called Lewy bodies are the pathological hallmark of Parkinson's disease.(49) The pathology of tremor-predominant subtype showed less neuron degeneration in the lateral substantia nigra (A9) and locus ceruleus, and more neuron degeneration in the medial substantia nigra (retrorubral area) (A8), than in akinetic-rigid subtype.(50, 51) The degeneration of the retrorubral area might play a significant role in the presence of resting tremor in PD.(7) Tremor-predominant patients were found to have a slow disease progression, preserved cognition, and good prognosis than patients with a akinetic-rigid subtype.(52)

Review of tremor pathophysiology

Tremor results from complex interactions between central and peripheral mechanisms. There were many different types of tremor that have different pathophysiology. The two mechanisms for tremor generation are the combination of the central and peripheral mechanisms.(7, 53, 54)

Central mechanism

Many neurons located in the central nervous system can demonstrate oscillatory activity. Oscillatory activity referred to a rhythmic activity of neurons that occurred from the intrinsic properties of the ion channels within individual neurons.(55) Central oscillators usually referred to the basal ganglia neurons or their connectivity and the cerebello-thalamo-cortical circuit that make the spontaneous oscillations.(7, 56, 57) Physiologically, the central oscillators are driven tremor, but these oscillators may be developed in different pathological forms of tremor.(53, 54) Although locations of central oscillators are not well established, lesions in the basal ganglia nuclei and thalamus resulted in tremor reduction.(1, 58)

Peripheral mechanism

Peripheral mechanisms were called the mechanical-reflex mechanisms. (54) This structures were composes of mechanical resonance and feedback resonances.(54) Mechanical resonances are the mechanical factors of bone, muscle, and soft tissue that influence on tremor manifestation.(54) Changing mechanical factors by increasing/decreasing mass, external weight loading and increasing limb stiffness, usually effect to resonance frequency as following formula.(3, 53)

$$Frequency \approx \sqrt{\frac{K}{J}}$$

As equation, K is a stiffness and J is an inertia. Tremor frequency can be decreased by loading or adding weight and can be increased by adding stiffness.

Feedback resonance or the peripheral stretch reflex can be influenced on tremor manifestation.(53) The reflexes connected muscles to the central nervous system. Reflex loops are composed of central and peripheral loops.(53) Central loops referred to the connection between a higher segments of the spinal cord, brainstem, and higher brain, whereas, the peripheral loops referred to the connection between muscles and spinal motor neuron in the spinal cord and back.(53) The peripheral monosynaptic stretch reflex loop is a very simple loop where the Ia afferent fibers from the muscle spindle synapse directly with the spinal motor neurons, which further sends their axon to the extrafusal muscle fibers.(53) Theoretically, these reflex loops connected and oscillated continuously. Flexion movements will stretch and cause afferent transfer to elicit the reflexes in the antagonistic extensors. If extensor muscle is activated, a similar pattern occurs, causing an afferent transfer to the flexor muscles.(3). In certain circumstances, such as, the frequencies of the mechanical and reflex oscillations within the same range, the two frequencies will turn into the same frequency of an one system that we called the local mechanical-reflex mechanism.(53)

Review of tremor pathophysiology in PD

According to tremor pathophysiology in PD, a tremor is generated from the complex connection between central oscillators and peripheral mechanisms. The generation of tremor appears to result mainly from a central oscillator, which is thought to drive the tremor. However, the peripheral mechanism is thought to

modulate the tremor amplitude (53, 59). The specific location and physiology of related central oscillators for PD tremors are still inconclusive; some literatures support data on thalamus or within basal ganglia loop, which has been given much interested. The peripheral mechanism (or mechanical-reflex mechanism) is a combination of the mechanical resonance and feedback resonances (3, 53, 54). Mechanical resonances are the properties of bone, muscle, and soft tissue that have an influence on the frequency of vibration of body parts, whereas feedback resonances are the peripheral stretch reflexes or reflex loops that connect mechanical resonances to the central oscillators (54) (Fig 8 & Fig 9). The frequency of peripheral mechanism is inversely related with the mass and stiffness of the limbs, thus increasing external loading which usually influences tremor frequency.(53, 54, 59).

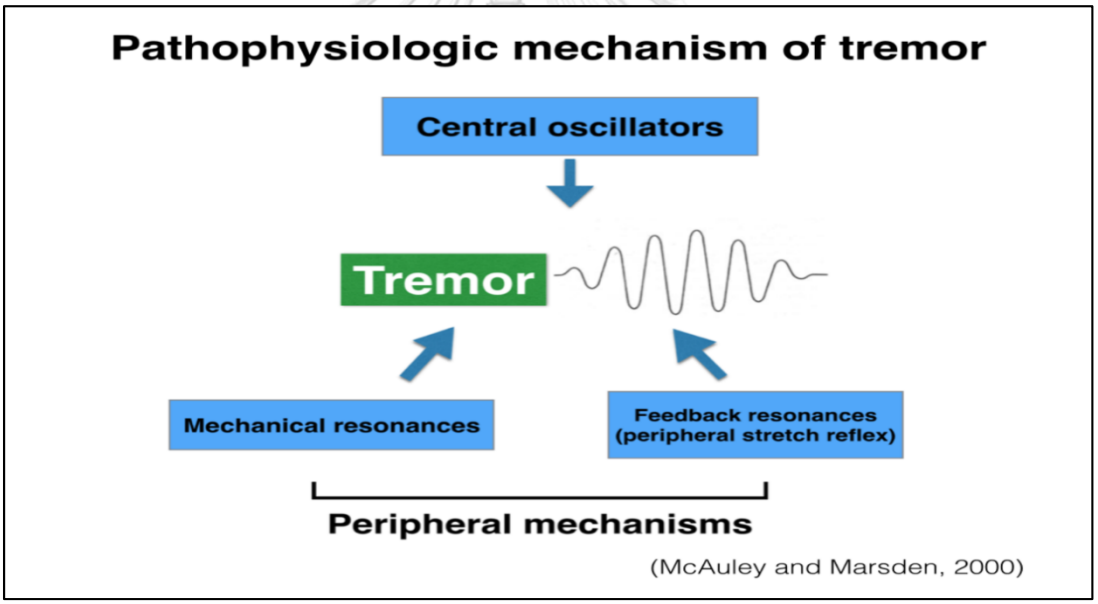


Figure 8: Pathophysiologic mechanism of tremor (54)

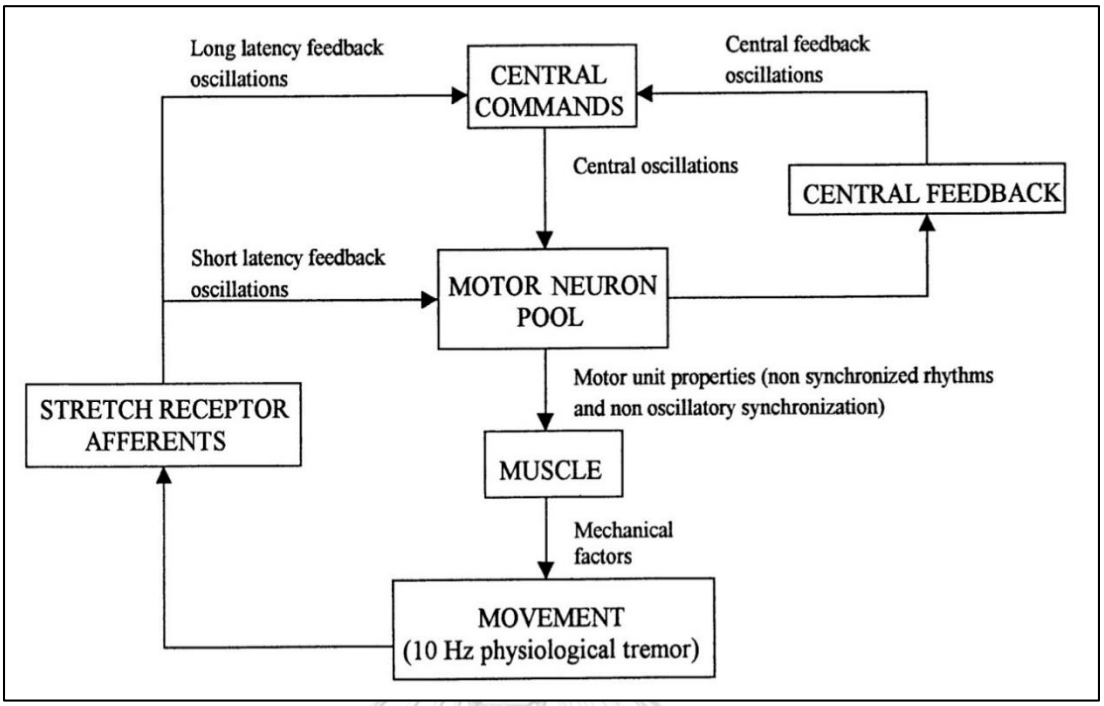


Figure 9: Proposed pathophysiologic mechanism of tremor (54)

Effect of central mechanisms in Parkinson's disease tremors

The central oscillators play a major role in rest tremor generation in Parkinson's disease, but the specific locations of these remain unclear (7). There are evidence supported that lesionning in several areas within the basal ganglia can reduce parkinsonian tremors. These findings suggests that these basal ganglia nuclei or their circuitry might be involved in resting tremors. Further, some of these nuclei were usually targeted lesions for surgery (DBS, pallidotomy, and thalamotomy).

There are five areas within the basal ganglia proposed as the possible parkinsonian tremors generation, including: (7, 57)

1. The thalamic pacemaker hypothesis
2. The thalamic filter hypothesis
3. The STN-GPi pacemaker hypothesis
4. The loss of segregation hypothesis
5. The connectivity between the basal ganglia and the cerebello-thalamo-cortocal circuit or "the d*immer-switch model"*

The mainstay traditional treatment in PD includes dopaminergic medications and functional neurosurgery, which were mainly targeting central oscillators.

Effect of peripheral mechanisms in parkinsonian tremors

Peripheral mechanisms are unlikely to generate tremors, but might be responsible for the modulation of tremor amplitude and/or frequency (3, 54, 60). From the study of Pollock, et al., cutting the posterior root of a patient with parkinsonism was found to not eliminate the tremor evenly attempted an entirely deafferented extremity, but there were changed in amplitude, rhythm, and rate (61). The data supports the notion that the reflexes may play a non-significant role in the generation and maintenance of tremors. An afferent denervation does not stop tremors, but might affect their frequency and amplitude. Many attempts at tremor reduction were conducted for alternative and traditional treatment options by targeting the modulation of peripheral mechanisms with electrical stimulation, which have been given much interest. Tremors can be modified when adding the mechanical condition at the periphery by such a strong stimuli, including peripheral nerve stimulation (62-64), as described in Table 1., and externally imposed movements of a joint (65, 66), as described in Table 2. However, both methods reported no promising tremor reduction or poor differentiation of rest tremors in PD from other types of tremors. Therefore, the possibility of modulating the peripheral mechanism has been decreased. Further, much interested and most studies or interventions for tremor reductions tend to target lesions within the central oscillators, especially in functional neurosurgery.

Review studies about peripheral nerve stimulation for tremor reduction

There have been 3 studies focused on peripheral nerve stimulation for the reduction of tremors (Table 1).

In 1969, Mones et al. studied on the peripheral nerve stimulation for attenuation of tremors in 5 PD patients. This study was conducted using the supra maximal median and ulnar nerve stimulation at the wrist. The needle electromyography recordings

(EMG) were made at the extensor digitorum longus muscle of the hand. Slightly changing in EMG intervals from mean 255 ms to 208 ms (ulnar) and from mean 245 ms to 202 ms (median) were observed during ipsilateral nerve stimulation. A limitation of this study is the low number of participants and its outcome could not represent significant tremor reduction after the performance of supra maximal nerve stimulation.

In 1980, Bathien et al. studied the peripheral nerve stimulation for attenuation of tremors in 14 ET and 10 PD patients. The study was conducted by using non-supra maximal radial nerve stimulation of the arm. The surface electromyography recordings (EMG) were made at the extensor indicis muscle of the hand. The stimulation-induced mean surface EMG silence duration in ET (92.1± 6.8 ms) and in PD (183.0 ± 16.8 ms.) was observed during radial nerve stimulation. A limitation of this study is the low number of participants. Its outcome could not represented the significance of tremor reduction during the performance of nerve stimulation.

In 1993, Britton et al. studied the peripheral nerve stimulation for attenuation of tremors in 10 ET, 9 PD, and 8 normal subjects mimicking tremors. This study was conducted by using non-supra maximal median nerve stimulation at the elbow. The surface EMG was made at the flexor carpi radialis m. at the forearms. Stimulation induced the inhibition of EMG activity with a duration ranging from 90-210 ms. Resetting index was calculated, but could not be used to differentiate the PD tremors from other types of tremors.

Review studies about mechanical perturbation for reduction of tremors

There were 2 studies about mechanical perturbation for the reduction of tremors (Table 2).

In 1981, Lee et al. studied mechanical perturbation at the wrist with a torque motor (Aeroflex T2W) 3.6 Nm, 100 ms duration for attenuation of tremors in 11 ET and 15 PD patients. The surface EMG was made at the flexor carpi radialis m. and extensor carpi ulnaris m. at wrist. Average EMG modulation from mechanical perturbation was calculated for the resetting index. Mean resetting index in ET group was 0.64 ± 0.14, and in PD group was 0.16 ± 0.19. This data confirmed that reflex mechanisms were

less important in Parkinsonian tremors. A limitation of this study was the low number of participants.

In 1992, Britton et al. studied mechanical perturbation at the wrist with a torque motor 0.38 Nm, 150 ms duration for attenuation of tremors in 18 ET and 13 PD patients. The surface EMG was made at the flexor carpi radialis m. and extensor carpi ulnaris m. at the wrist. Average EMG modulation from mechanical perturbation was calculated for the resetting index. ET patients had significant difference in the mean resetting index and tended to be more susceptible to modulation from the mechanical perturbation than Parkinson's disease patients. A limitation of this study was the low number of participants.

Table 1: The comparison of 3 studies about peripheral nerve stimulation for reduction of tremor

Studies	Design	Population	Stimulation	Patients	Tremor recording	Outcome
Mones (1969)	Descriptive	Hospital-based	Median n., Ulnar n. at wrist	5 PD	Electromyography (needle) extensor digitorum longus muscle at hands	Slightly changing in EMG intervals from mean 275 ms to 260 ms (ulnar) and 262 ms (median)
Bathien (1980)	Descriptive	Hospital-based	Radial n.	14 ET 10 PD	Electromyography (surface) at extensor indicis m. at forearms	Stimulation induced mean EMG silence duration in ET (92.1± 6.8 ms)and in PD (183.0 ± 16.8 ms.).
Britton (1993)	Descriptive	Hospital-based	Median n. at elbow	10 ET 9 PD 8 normal subjects mimicking tremors	Electromyography (surface) at flexor carpi radialis m. at forearms	Stimulation induced inhibition of EMG activities with duration range from 90-210 ms. Resetting index were calculated but can not be used to differentiate PD tremor from other types of tremor.
ET: essential tremor; PD: Parkinson's disease						

Table 2: The comparison of 2 studies about mechanical perturbation for reduction of tremor

Studies	Design	Population	Device	Patients	Tremor recording	Outcome
Lee (1981)	Descriptive	Hospital-based	Mechanical perturbation at wrist with a torque motor (Aeroflex T2W) 3.6 Nm, 100 ms duration	11 ET 13 PD	Electromyography (surface) at flexor carpi radialis m. and extensor carpi ulnaris m. at wrist	An average in EMG modulation from mechanical perturbation were calculated for the resetting index. Mean resetting index in ET group was 0.64 ± 0.14, and in PD group was 0.16 ± 0.19. These data were confirmed that reflex mechanisms were less important in Parkinsonian tremor.
Britton (1992)	Descriptive	Hospital-based	Mehanical perturbation at wrist with a torque motor 0.38 Nm, 150 ms duration	18 ET 13 PD	Electromyography (surface) at flexor carpi radialis m. and extensor carpi ulnaris m. at forearm	ET patients tended to be more susceptible to modulation from the mechanical perturbation than Parkinson's disease patients.
ET: essential tremor; PD: Parkinson's disease						

Review studies about electrical muscle stimulation for reduction of tremors

Recently, there have been a few studies in engineering fields claiming the efficacy of electrical muscle stimulation on rest tremor reduction in PD patients, some of which may probably lead to emerging interest in peripheral targeting on tremor reduction by electrical muscle stimulation, as described in Table 4.

Electrical muscle stimulation (EMS) has been an FDA approved device for physical therapy practice for many years. Its main proposes are for rehabilitating muscles such as after an injury or post-surgery, to prevent muscle atrophy. The therapeutic potential of EMS for rehabilitation recovery has been explored in some neurological disorders such as stroke, spinal cord injury, and evenly for tremor in PD (67). The recommendation for acceptable current intensity for safety reasons was published, as shown in Table 3.

Table 3: The effect of 60 Hz electrical shock current through the body on an average individual.

Current Intensity (mA)	Effect
1	Sensation threshold
5	Accepted as maximum harmless current intensity
10-20	"Let go" current before sustained muscular contraction
50	Pain. Possible fainting, exhaustion, mechanical injury. Heart and respiratory functions continue.
100-300	Ventricular fibrillation starts, but respiratory center remains intact. Usually result in death.

By clinical implementation of EMS to the pathophysiology of pathological tremor, EMS may probably provide tremor attenuation by serving itself as strong stimuli that may reset peripheral reflexes mechanism, which results in diminished tremors.

However, there is little literatures to support its efficacy on tremor suppression, especially among PD patients who had predominant rest tremors as a motoric feature. Therefore, we conducted a systematic review in order to identify related literature. The results are shown as below.

The process of systematic review

Data source and search

Literatures about the use of EMS for tremor reduction in Parkinson's disease and other types of tremors was searched electronically in MEDLINE and Thai Index Medicus databases at the initiation of the project by querying the 2 keywords phrases: 'Electrical muscle stimulation and Parkinson's disease' and 'Electrical muscle stimulation and tremor'. The study selection and selection process were shown as follows.

Study selection

Studies were included if they fulfilled the following selection criteria:

1. The study was conducted in patients with various types of tremors, which included Parkinson's disease tremors and/or other tremors with or without control subjects.
2. The study contained data related to the suppression of various types of tremors by using electrical muscle stimulation.
3. The study was available in full length in English language and published before the 30th November 2014.
4. Review articles, editorials, case reports, and clinical commentaries were excluded from the review process.

Selection process (Fig 10.)

1. If the study populations showed various types of tremors and electrical muscle stimulation, abstracts will be selected from database..
2. The chosen articles were selected for the full-length articles. The studies that fulfilled with the selection criteria were recruited.

3. The selected articles were identified relevant articles according to the reference lists
4. Statistical analysis or meta-analysis was not done due to the significant variability in study methodologies.

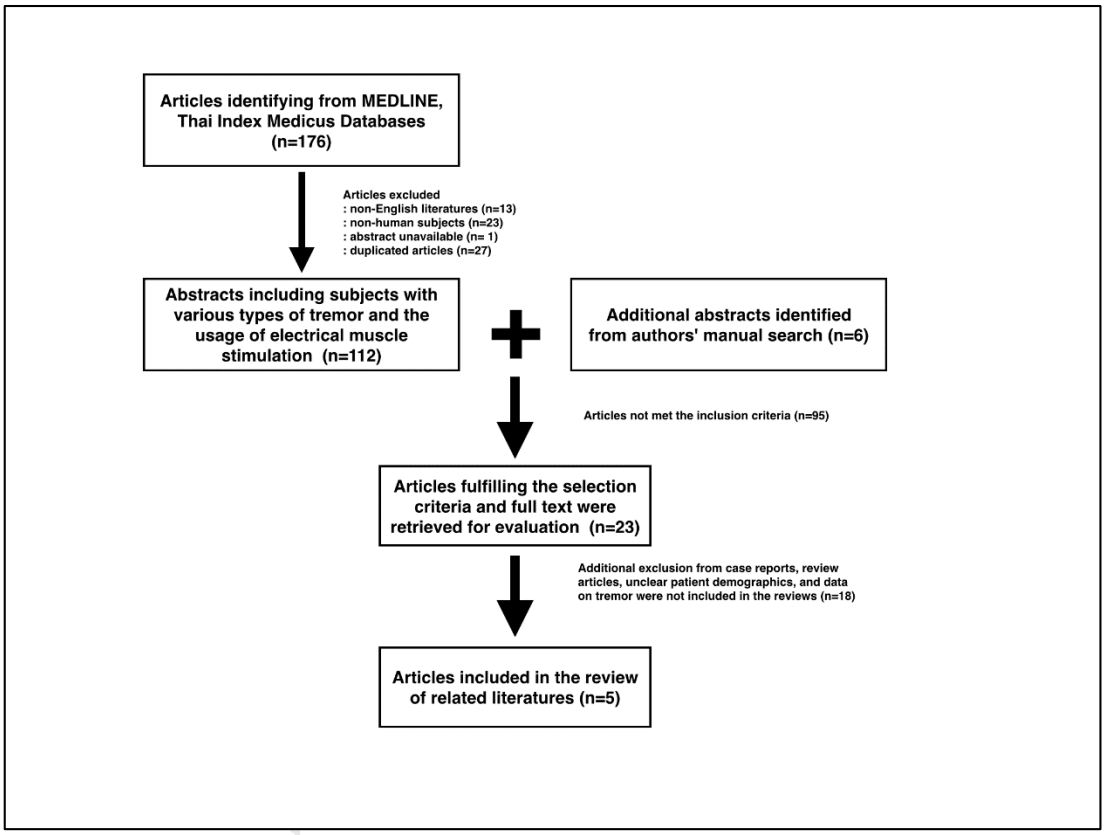


Figure 10: Selection process of related literatures

From 182 articles identified in the selection process, we found only 5 related articles about tremor suppression by electrical muscle stimulation, described in a comparison as in Table 4 & Table 5

In 1992, Javidan et al. (32) studied the functional electrical stimulation for attenuation of pathological tremors. This study was conducted using the tremor measurement system and functional electrical stimulation. The system was tested in 6 patients (4 with Parkinson's disease, 3 with Essential tremor, and 4 with cerebellar tremor from multiple sclerosis) and led to an average tremor reduction of 62%, 73%, and 38%, respectively. The limitation of this study was that the system did not provide

details for stimulation setting, results in standard tremor parameters for determination, or comparison of efficacy to the other studies.

In 2008, Zhang et al. (34) studied the functional muscle stimulation for the suppression of pathological tremors. This study was conducted using the tremor measurement system and functional electrical stimulation (Fig 11). The tremor measurement system was consisted of a Vicon motion capture system, Biopac EMG acquisition system, and accelerometers. The constant stimulation was a pulse width of 150-200 microsec, frequency of 20 Hz, and pulse amplitude of 30mA, which was delivered at the flexor carpi ulnaris and extensor carpi radialis muscles. The system was tested in 6 patients (4 PD, 2 rubral tremor, and 1 with psychogenic tremor) and led to an average tremor reduction of around 88%. However, the system was unable to achieve the good effectiveness in patients with psychogenic tremors. A limitation of this study was that the system did not provide results in standard tremor parameters for determination or comparison of efficacy to other studies.

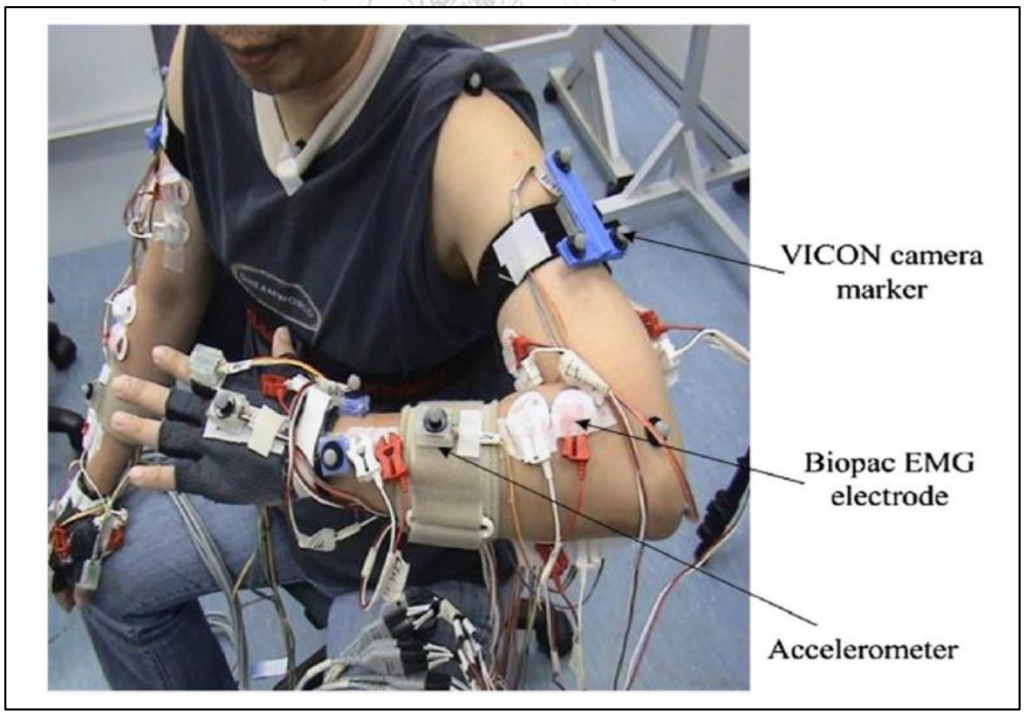


Figure 11: Tremor measurement system form the study of Zhang et al (34)

In 2011, Maneski et al. (33) studied the effect of EMS for suppression of pathological tremors (Fig 12). This study was conducted using the tremor suppression system and TremUNA stimulation. This system composed of the surface electrodes for the activation of the wrist flexors and extensors. The system was combined with a gyroscope to assess the angular rates of the forearm and hand. The constant stimulation was a pulse width of 250 microsec, frequency of 40 Hz, and pulse amplitude of 5-25 mA. The system was applied in 7 patients (4 PD and 3 ET) for the minimization of the wrist joint tremors, in which 6 reported a significant percentage of tremor reduction after using this system for an average 67 ± 13 %. However, this device could not reduce tremor in one essential tremor patient. The limitation of this study was that the system did not provide results in standard tremor parameters for determination or comparison of efficacy to other studies.

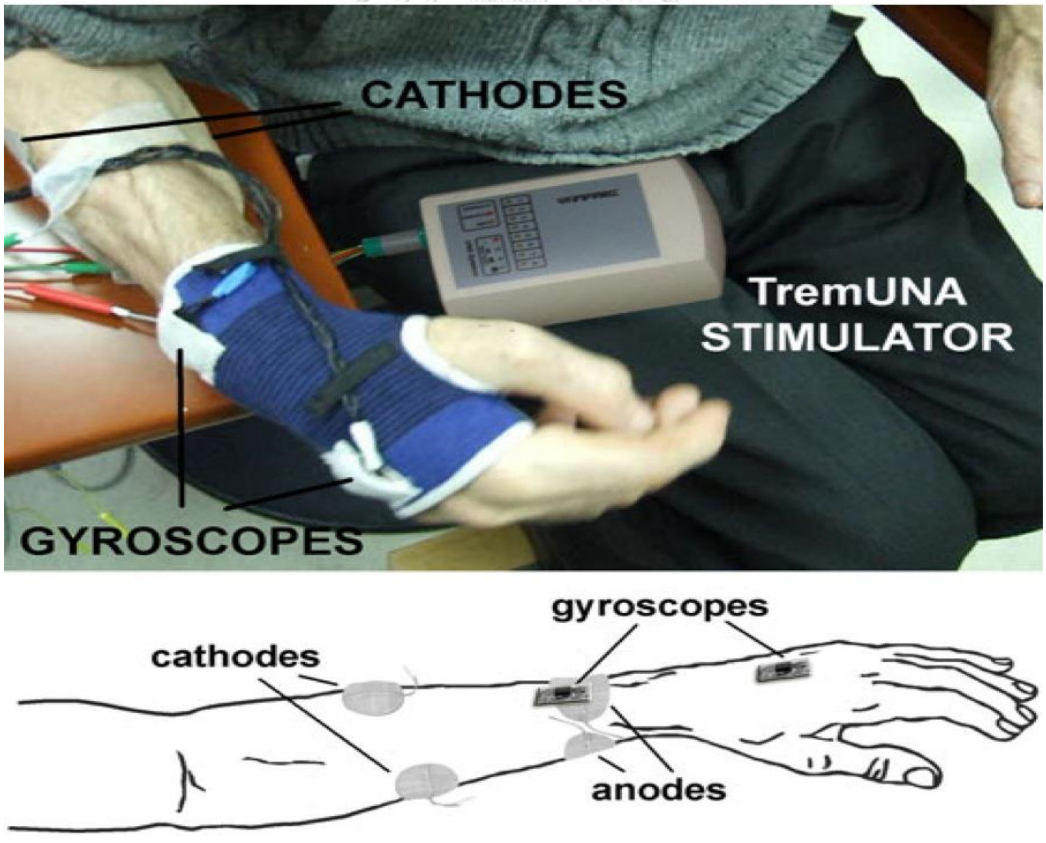
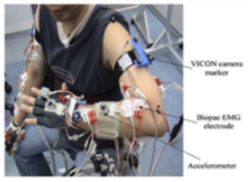
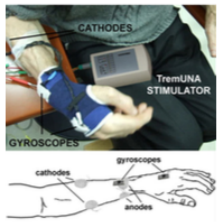
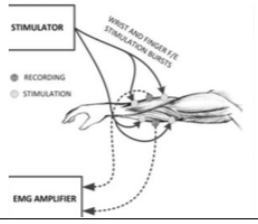


Figure 12: The TremUNA stimulation suppression system from Maneski et al (33)

In 2013, Gallego et al.(31) studied on the effect of EMS for suppression of pathological tremors. This study was conducted by using a neuroprosthesis device for tremor reduction. This system integrated a pair of solid gyroscopes for tremor parameterization and a multichannel monopolar neurostimulator for electrical muscle stimulation. The constant stimulation was a pulse width of 300 microsec., frequency of 40 Hz, and maximum tolerated pulse amplitude without pain was delivered to two muscles (at the flexor carpi ulnaris and extensor carpi radialis muscles). The neuroprosthesis provided the significant attenuation of tremors ($p<0.05$) in 6 patients (2 PD and 4 ET) and reduced the average tremor amplitude by up to a 52.33 ± 25.48 %. The limitation of this study was that the system did not provide the result in standard tremor parameters for determination or comparison of efficacy to other studies.

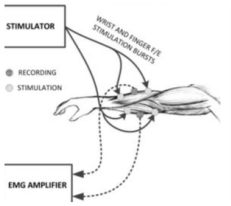
In 2013, Dosen et al.(37) studied electrical muscle stimulation for the suppression of pathological tremors. This study was conducted using the tremor suppression system for tremor detection based on the Iterative Hilbert Transform. EMS was delivered above the motor threshold (motor stimulation) and below the sensory threshold (sensory stimulation). The constant stimulation was a pulse width of 300 microsec., frequency of 100 Hz, and maximum tolerated pulse amplitude without pain was provided to all participants. The system was tested in 6 patients with predominant wrist flexion/extension tremors (4 PD and 2 ET tremor), which led to an average tremor reduction in the range of 46-81 % and 35-48 % in 5 patients. However, the system was unable to achieve any reduction of tremors in one essential tremor patient. The limitations of this study were that the system did not provide the results in standard tremor parameters for determination or comparison of efficacy to the other studies.

Table 4: The comparison of 4 studies about EMS as a treatment for reduction resting tremor in PD

Studies	Design	Setting EMS	Patients	Tremor recording	Outcome
Zhang (2010)	Descriptive	PW 150-200 mcs. F 20 Hz. PA 30 mA At extensor and flexor muscles at wrist joint	6 PD 2 Rubral 1 Psychogenic	Surface electromyography at extenxor carpi radialis longus m. and flexor carpi ulnaris m.at forearm 	FES provided average tremor reduction of 88%
Popovic (2011)	Descriptive	PW 250 mcs. F 40 Hz. PA 5-25 mA At extensor and flexor muscles at wrist joint	4 PD 3 ET	Accelerometer at wrist flexors and extensors 	FES provided average tremor reduction for all subtype of 61 ± 7 %
Gallergo (2013)	Descriptive	PW 300 mcs. F 40 Hz. PA : individuals at extenxor carpi radialis longus m. and flexor carpi ulnaris m.at forearm	2 PD 4 ET	Accelerometer at wrist flexors and extensors musles 	FES provided average tremor amplitude reduction up to a 52.33 ± 25.48 %.
Dosen (2013)	Descriptive	PW 300 mcs. F 100 Hz. PA: individuals At flexor and extensor muscles at wrist.	4 PD 2 ET	Accelerometer at wrist/finger flexors and extensors 	FES provided average tremor amplitude reduction up to 74 ± 8 % in motor stimulation and 57 ± 6 % in sensory stimulation.

EMS: electrical muscle stimulation; FES: functional muscle stimulation; PD: Parkinson's disease; ET: essential tremor; FCU: flexor carpi ulnaris muscle; ECRL: extensor carpi radialis longus muscle; PW: pulse width; f: frequency; PA: pulse amplitude; Individuals PA based on visual and tactile inspection of muscle contraction without patient discomfort.

Table 5: The study about EMS as a treatment for reduction postural tremor (or re-emergent tremor) in PD

Studies	Design	Setting EMS	Patients	Tremor recording	Outcome
Javidan (1992)	Descriptive	EMS setting: not mention, at wrist flexor and extensor muscles	4 PD 3 ET 4 cerebellar	Gyroscope at forearm flexors and extensors 	FES provided average tremor reduction of 62%, 73%, and 38%.
EMS: electrical muscle stimulation; FES: functional muscle stimulation; PD: Parkinson's disease; ET: essential tremor.					

Nowadays, there have been few literatures reported dealing with the effectiveness of EMS in the suppression of rest tremors among PD patients. Most of them contained numerously limitations as follows: all of them lacked a statistical standard and recruited participants with a small sample size. Some of them were conducted with patients having other types of tremors (such as essential tremors) without any comparative study with PD patients or controls. Further, all of them used analysis of tremors mainly with inertial sensors (accelerometer or gyroscope) without providing standard tremor parameters or neurophysiologic explanations (such as surface electromyography) to evaluate motor function in those tremors before and during the performance of electrical muscle stimulation. None used established data to confirm the efficacy and feasibility of ambulatory EMS system for suppression of tremors available over long-term use (30-36). Several studies have developed a tremor suppression system, but their devices were typically large in size due to intended use as a laboratory-based system. However, the study did not provide the implementation data on efficacy of EMS for tremor suppression in an everyday usage. (30, 37)

By the limitation of previous studies as discussed above, we identified the efficacy of EMS as an alternative option for treatment of tremor reduction by conducting a pilot study in 15 PD patients with classic rest tremors and 8 patients with dystonic tremors (DT) at rest. The stimulation protocol was performed in a quiet room with subjects instructed to sit comfortably in armchairs. Hand tremors at a resting position and postural position were assessed with a tremor analysis device and electrical muscle stimulator. Tremor parameters were collected both before and during EMS. The 4 tremor parameters were as follows: peak magnitude, the root mean square of the angular velocity (RMS), frequency, and tremor dispersion score (Q), as described in previous literatures (38-40). Two self-adhesive electrodes (size 1.5 inches x 1.5 inches) were placed over the thenar muscle and the 1st & 2nd interosseous muscles of the hand were the most affected by tremors (Fig 13).

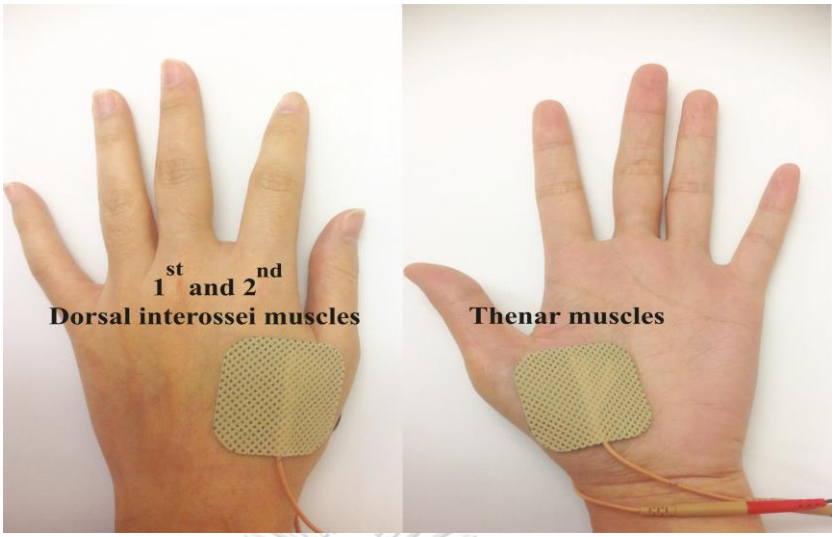


Figure 13: Electrode placement

EMS stimulation was performed at rest position as patients were asked to close their eyes and count backward for purposes of encouraging rest tremor. Pulse amplitude was slowly increased until tetanic muscle contraction (motor threshold) was found without pain or paresthesia (not until sensory threshold) (34). Differences in stimulation frequencies, as described in the previous literature, ranged from 30-100 Hz (31, 32, 35). In order to determine an optimal stimulation protocol, we evaluated the stimulation level of different frequencies in producing muscle contraction that can be functionally used for transient reduction of tremor. To avoid patient fatigue and muscle discomfort associated with high frequencies, we stimulated muscles within the 30-50 Hz frequency range (41, 42). The results of our pilot study with constant pulse amplitude, we found significant tremor reduction occurred during high frequency stimulation (50 Hz), as compared to low frequency stimulation (30 Hz) in both peak magnitude and RMS ($p<0.05$, each). Most patients reported more sustained muscle contraction without complications during higher frequency stimulation, as compared to lower frequency stimulation. (Fig 14) Consequently, a constant frequency of 50 Hz was applied to all subjects. Each patient examination took 30 minutes. Constant stimulation duration of 30 seconds for each session was shown to produce obvious tremor reduction. From clinical observation, tremor reduction was shown to last an average of 10 seconds after withdrawal of EMS.

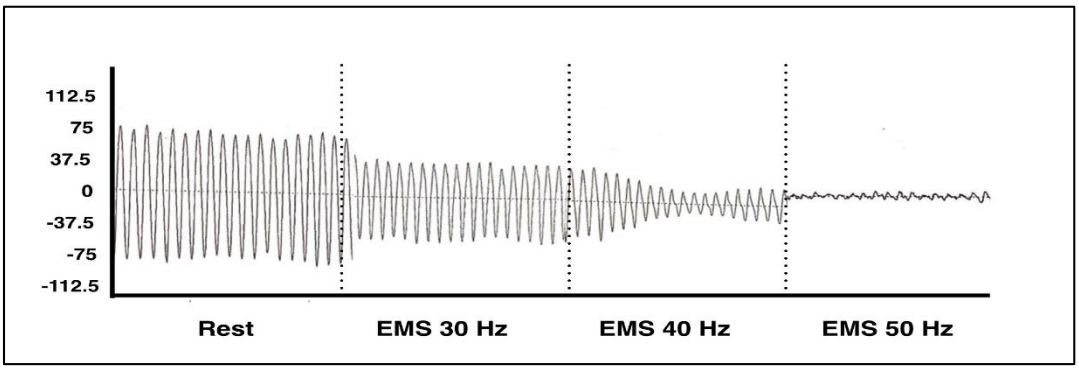


Figure 14: Accelerometer report in tremor amplitude reduction by EMS with constant pulse amplitude (15 mA) and different in pulse frequency (from pilot study)

The outcome of our pilot study showed promising rest tremor reduction in the PD group after stimulation as determined by tremor parameters, including peak magnitude and RMS angular velocity (p<0.001, each). However, this efficacy was not observed in the DT group (Fig 15 & Fig 16). The constant duration for 30 second for each session was shown obviously in tremor reduction. From clinical observation, this efficacy was shown to last for an average of 10 seconds after withdrawal of EMS.

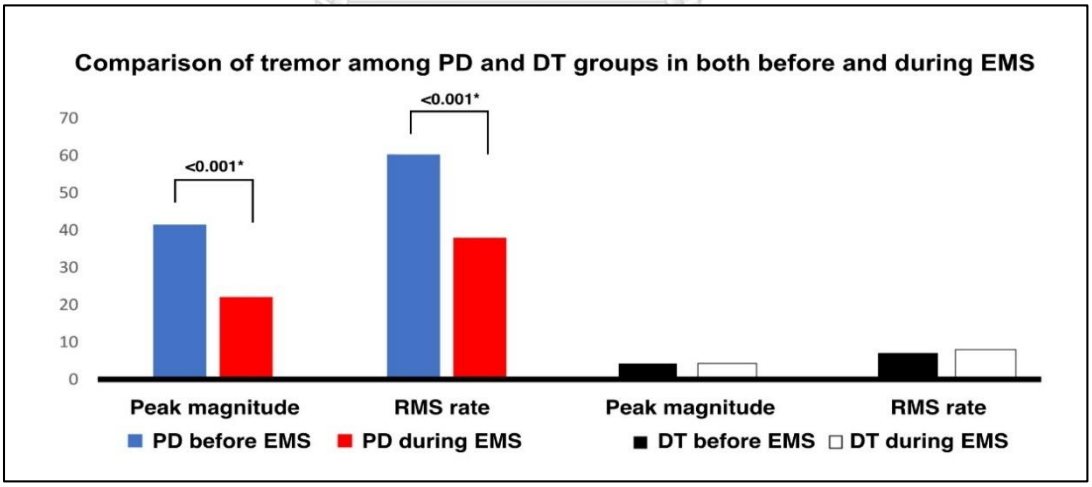


Figure 15: Comparison of tremor parameters among PD and DT groups, in both before and during EMS

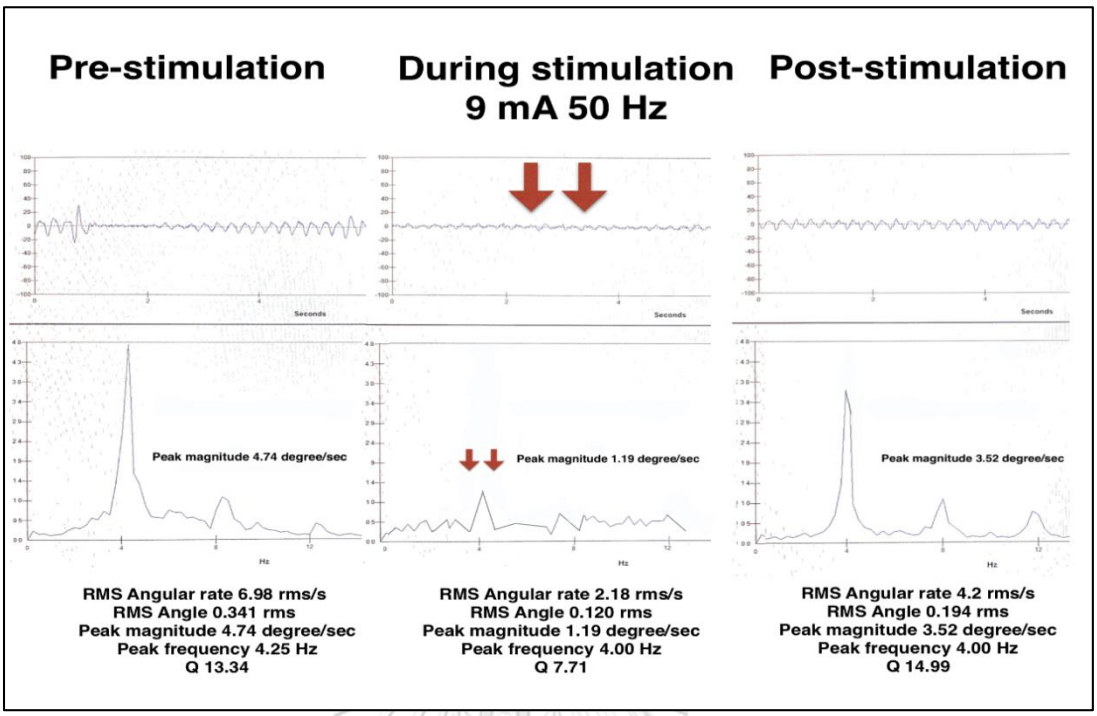
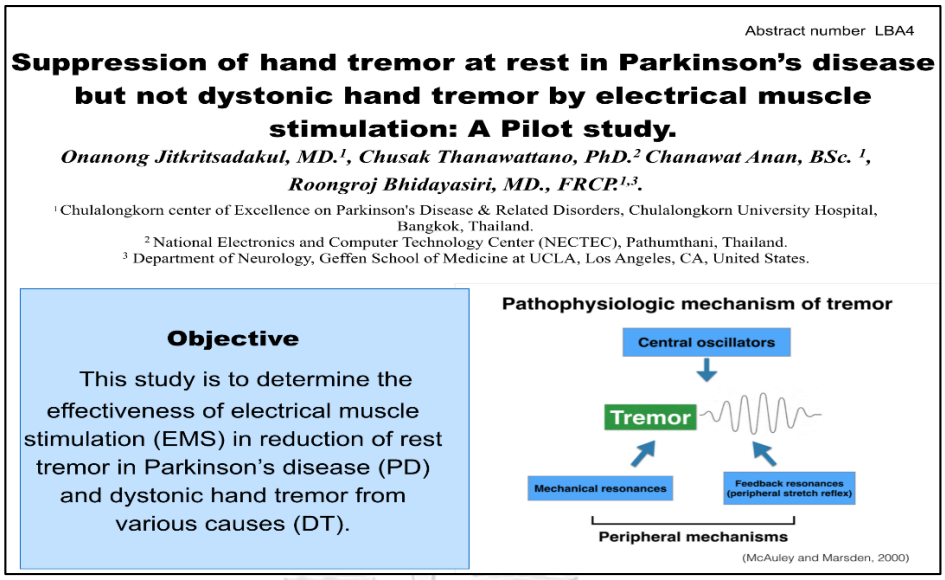


Figure 16: The efficacy of EMS on tremor from our pilot study

Interestingly, we found significant in tremor reduction occurred during the high frequency (50 Hz) when compared to low frequency (30 Hz) in both peak magnitude and RMS (p<0.05, each). Our pilot study was selected as the highlighted presentation at the 4th Asian and Oceanian Parkinson's Disease and Movement Disorders Congress (AOPMC) (68)(Fig 17).


Abstract number LBA4

Suppression of hand tremor at rest in Parkinson's disease but not dystonic hand tremor by electrical muscle stimulation: A Pilot study.

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Objective

This study is to determine the effectiveness of electrical muscle stimulation (EMS) in reduction of rest tremor in Parkinson's disease (PD) and dystonic hand tremor from various causes (DT).

Pathophysiologic mechanism of tremor

Figure 17: The pilot study was selected as the highlighted presentation at the 4th Asian and Oceanian Parkinson's Disease and Movement Disorders Congress.

According to our pilot study results and the pathophysiology of tremors that were discussed above, we would like to propose that EMS may provide effective rest tremor attenuation in addition to traditional oral anti-parkinsonian medications by serving itself as such a strong stimulus, enough to reset the peripheral mechanism. It may be able to modulate the central oscillators located in basal ganglia and later resulted in a transient tremor reduction.

CHAPTER III

METHODS

Research design

Phase 1: Descriptive study

Phase 2: Randomized-controlled trial. (Single blind, sham-controlled)

Research methodology

Study Population

- Target: Tremor-predominant Parkinson's disease (PD) patients.
- Population sample: Patients with the above condition who currently follow with an outpatient movement disorder clinic at King Chulalongkorn Memorial Hospital from 1st August, 2014 to 30th September, 2016.

Inclusion criteria

- Adults ≥ 18 year-old
- Patients who were diagnosed with Parkinson's disease according to the standard UKPDSBB criteria. Recruited patients needed to present with predominantly feature of intractable resting tremors.
- Informed consent

Exclusion criteria

- Patients with a history of systemic disease, such as, cardiac arrhythmia, renal failure, hepatic failure, and pregnancy. Patients who had a history or at risk of seizure, for example, patients with a stroke, .focal brain lesion, and encephalitis.
- Patients with a history of hand surgery with implanted screws or wires that prevented placement of a surface EMG or EMS, as well as those patients who were implanted for electrical devices such as cardiac pacemakers,

pulse generators of deep brain stimulation, and intrathecal baclofen pumps.

- Patients who cannot avoid the medication that may increase or decrease tremors such as antihistamines, benzodiazepine, illicit drugs, and thyroid hormone supplements.

Sample size calculation

The sample size calculation for the phase 2 study will be determined from the pilot study (phase 1: pilot and descriptive study).

The sample size is calculated using data from our pilot study in 20 PD patients with rest tremors between, before and during treatment. Ten of them were randomly assigned to use the EMS, whereas the other 10 patients were randomly assigned not to use EMS (sham study). The difference in delta RMS between, before and during EMS was used for calculation (Fig 18).

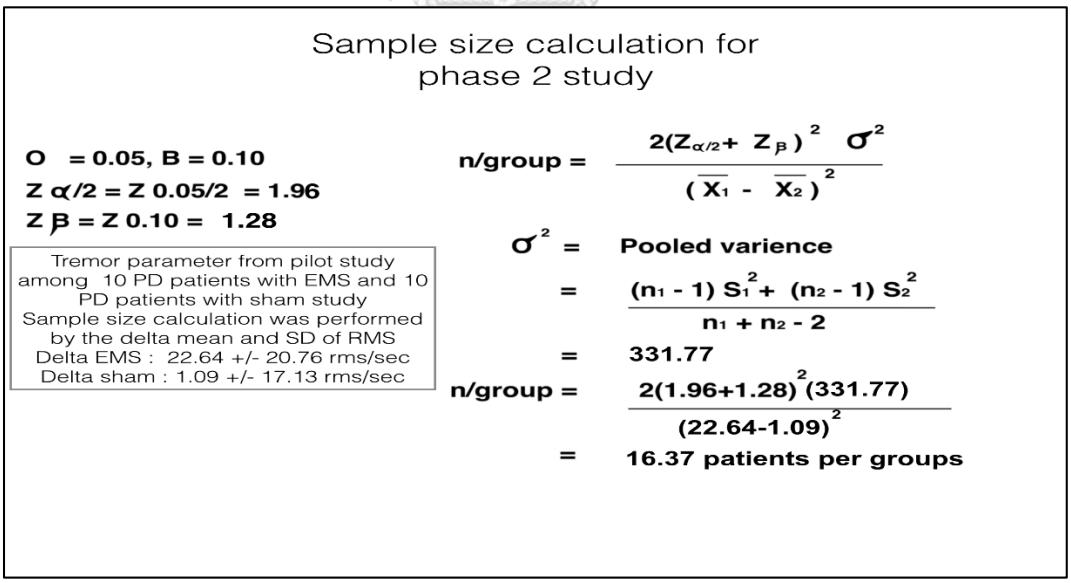

Figure 18: Sample size calculation for phase 2 study

Hence, our calculation sample size for comparison between PD with EMS and PD without EMS (sham study) is 16.37 patients per group. However, we would like to increase the sample size to 20 patients per group.

Method and sampling technique

Phase 1 study

- Tremor-predominant PD patients will be consecutively recruited from the outpatient movement disorder clinic at King Chulalongkorn Memorial Hospital.
- All subjects will be examined for severity of PD symptoms by a movement disorders specialist according the Unified Parkinson's Disease Rating Scale (UPDRS), especially for tremor items. Hoehn and Yahr (H&Y) score during the 'on period' will be given in order to determine any additional effect of EMS for suppression of tremors. Physical examinations of each patient will be recorded by video for later review.
- All subjects will be monitored for hand tremor at resting and postural positions. Tremor analysis with an accelerometer and gyroscope system and the surface EMG will be conducted. The surface EMG electrode will be placed over the thenar muscle of the hand, which is the most predominant side for tremors, for quantitative measurement and determination of tremor physiology.
- All surface EMG data and all data will be applied to The Matlab™ program (MathWorks Inc.) in order to modify the qualitative signals into quantitative parameters and perform the high-dimensional feature vectors, and later to determine the variety of efficacy in pulse amplitudes for electrical muscle stimulation on feature vectors.
- The most suitable stimulation protocols to get the maximum tremor reduction will be provided to each participants, including area placement, pulse width, frequency, pulse amplitude, and duration of stimulation.

- The tremor amplitude reduction as determined by the reduction of tremor parameters will be calculated by nonparameteric test (Wilcoxon-sign rank test). The results will be used for sample size calculation of the phase 2 study.

Phase 2 study

- All subjects will be provided the information concerning this research study and informed consent will be obtained from each subjects prior to participation.
- All PD patients will be randomly allocated into 2 groups (Parkinson's glove and sham glove) with a block randomization method.
- All PD subjects (in Parkinson's glove group and sham glove group) will be interviewed by a movement disorders specialist or a trained interviewer for their demographic and clinical data.
- All subjects will be examined for the severity of Parkinson's disease by a movement disorders specialist according the Unified Parkinson's Disease Rating Scale (UPDRS), especially for tremor items. A Hoehn and Yahr (H&Y) score during the 'on period' will be given in order to determine any additional effects of EMS for the suppression of tremors. Physical examinations of each patient will be recorded by video for later review.
- All subjects will be monitored for hand tremor at resting and postural positions. Tremor analysis with accelerometer and gyroscope system and the surface EMG will be conducted. The surface EMG electrode will be placed over the thenar muscle of the hand, which is the most predominant sided of tremors, for quantitative measurement and determination of tremor physiology.
- All surface EMG data and other data will be applied to The Matlab™ program (MathWorks Inc.) in order to modify the qualitative signals into quantitative parameters and performing the high-dimensional feature

vectors, which will later determine the different efficacy in pulse amplitudes of electrical muscle stimulation on feature vectors.

- All subjects will be stimulated for hand muscles with an electrical muscle stimulation (Intensity™ Twin Stim® III), with will be conducted by placement of 2 self-adhesive electrodes (size 1.5 inches * 1.5 inches) over the thenar muscle and 1^{st}&2^{nd} interrosseous muscles of the hand, which are the most predominant sided for tremors. The EMS will stimulate PD patients on the resting position, whereas the other tremors patients will be stimulated in both resting and postural positions. The pulse amplitude will be titrated slowly until providing a tetanic muscle contraction (motor threshold) without pain (all applied frequency of 50 Hz).
- All subjects will be instructed in how to use the Parkinson's glove and sham glove before their home-based treatment for a period of 2 weeks. During this periods, the patients need to visit the researchers for 3 consecutive appointments (baseline, 7^{th} day, and 7^{th} days after stopping the device) for assessment of the effectiveness of the Parkinson's glove overtime, including tremor parameters, tremor rating scale as determined by UPDRS tremor-5 items, and score of 8-items Parkinson's disease questionnaires for determination of general quality of life. A direct telephone call from a researcher will be provided to each patient every day.

Data Collection

- Demographic and clinical data: age, gender, clinical diagnosis, disease duration and severity score for each subject according to an established standard rating scale.
- Tremor parameters form the tremor analysis with accelerometer and gyroscope system, which will be collected both before and during EMS in 5 parameters including Peak magnitude, RMS, Angle, Frequency, and Q
- The pulse amplitude from EMS will be recorded for every titration in order to determine the efficacy of EMS at different pulse amplitudes.

- Tremor parameters and number of EMS times in tremor suppression form The Parkinson's glove and sham glove, which will be collected on an SD card for 14th day periods
- The times of Parkinson's glove in suppression of tremor will be counted automatically on the SD card, as well as the outcome of tremor suppression from EMS. The improvement of tremor rating scale determined by UPDRS tremor-5 items, an improvement of Parkinson's disease questionnaires 8-items (PDQ-8 items for determined the quality of life) will be collected at 3 consecutive follow up periods after using Parkinson's glove and sham glove at the baseline, on the 7th day, and 7 days after stopping the device)

Ethical considerations

All patients recruited in this study will be provided information on this research study and informed consent will be gained by every subjects. (Appendix-E) Tremor analysis device, surface EMG, and electrical muscle stimulation will be applied to all subjects, in which relate with low risks due to the standard of all machine (or devices) and the expertise of our technician. In the case of complications, such as pain, or discomfort in an examined area, the patient will be treated appropriately until better. The subjects' payment for those PD patients who accepted the use of the developed device for a 14-day period is 1,000 Thai Baht each.

Data Analysis

The statistical analysis in the phase 1 & 2 study is calculated from the SPSS program version 17. Categorical data will be analyzed for frequency and percentage. Continuous data will be analyzed by mean and standard deviation (SD). Non-parametric study would be preferable if the sample size was small or, in the case of distribution of data, did not present as normal distribution (determined by Kolmogorov-Smirnov test). Repeated ANOVA will be used for determination of the efficacy of different pulse amplitudes on tremor suppression and the efficacy of EMS at difference times during the follow up periods.

CHAPTER IV

RESULTS

This chapter result composed of two parts which phase 1 and phase 2. Each part was listed as follows:

Part 1: Phase 1 (Pilot, descriptive study)

Part 2: Phase 2 (Device development and A Randomized-controlled trial; single-blind, sham-controlled)

Part 1:

The objective of the phase 1 study was to identify of the most suitable stimulation protocols for tremor reduction and to seek out for the best location for placement of the surface electrodes.

How to identify the optimal stimulation protocol?

This pilot study was conducted in 15 PD patients with classic resting tremor according to the established criteria who were recruited from the outpatient movement clinic of the King Chulalongkorn Memorial Hospital between January to June 2015. The protocol was approved by the human Subjects Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The study was registered at the www.clinicaltrials.gov. All subjects gave their written informed consent before entering the study in accordance with the declaration of Helsinki.

We defined the suitable stimulation protocol that was capable of inducing tetanic muscle contraction without fatigue or paresthesia and able to reduce tremor directly by visual observation. The stimulation protocol was, firstly, performed in a quiet room with all subjects were asked to sit comfortably in an armchair. Tremulous hand at resting and postural position was assessed with a standard tremor analysis device (Fig. 19) and electrical muscle stimulator (Fig. 20). Tremor parameters were collected both before and during EMS; the 4 tremor parameters were, as follows: root

mean square of angular velocity (RMS), peak magnitude, frequency, and tremor dispersion score (Q) as described in the previous literatures (38-40).

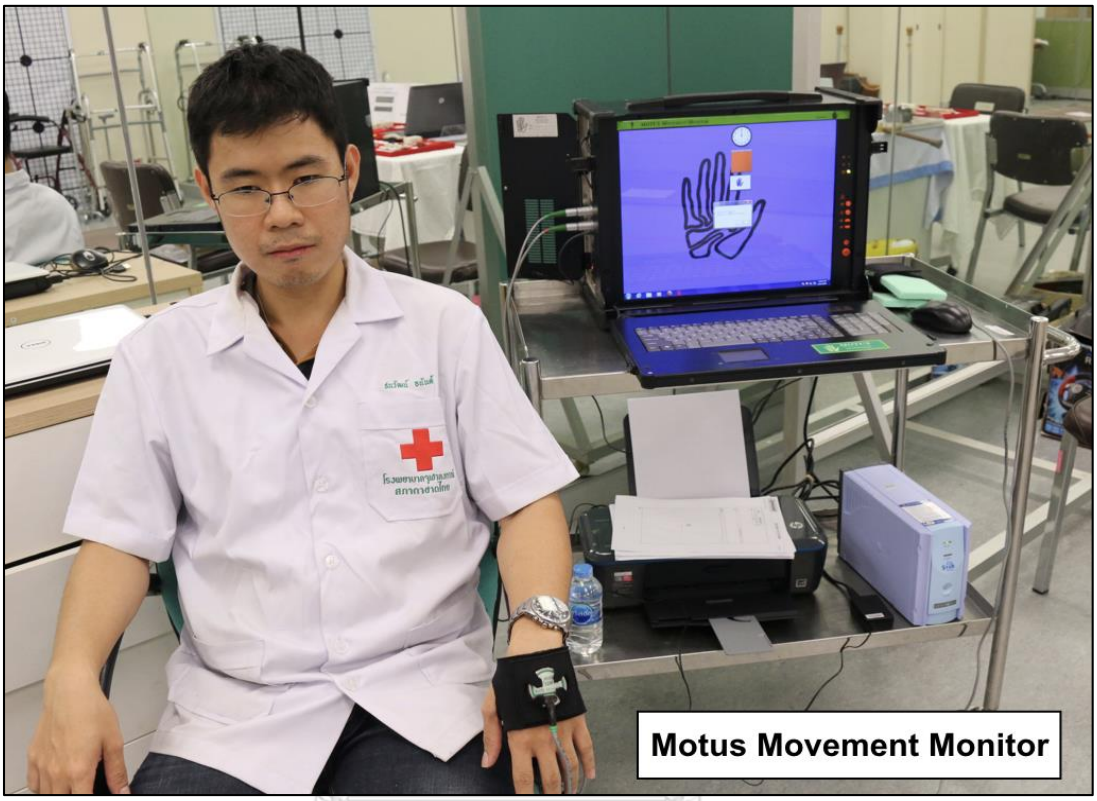

Figure 19: The tremor analysis device (Motus Movement Monitor, MOTUS Bioengineering Inc., CA, USA)

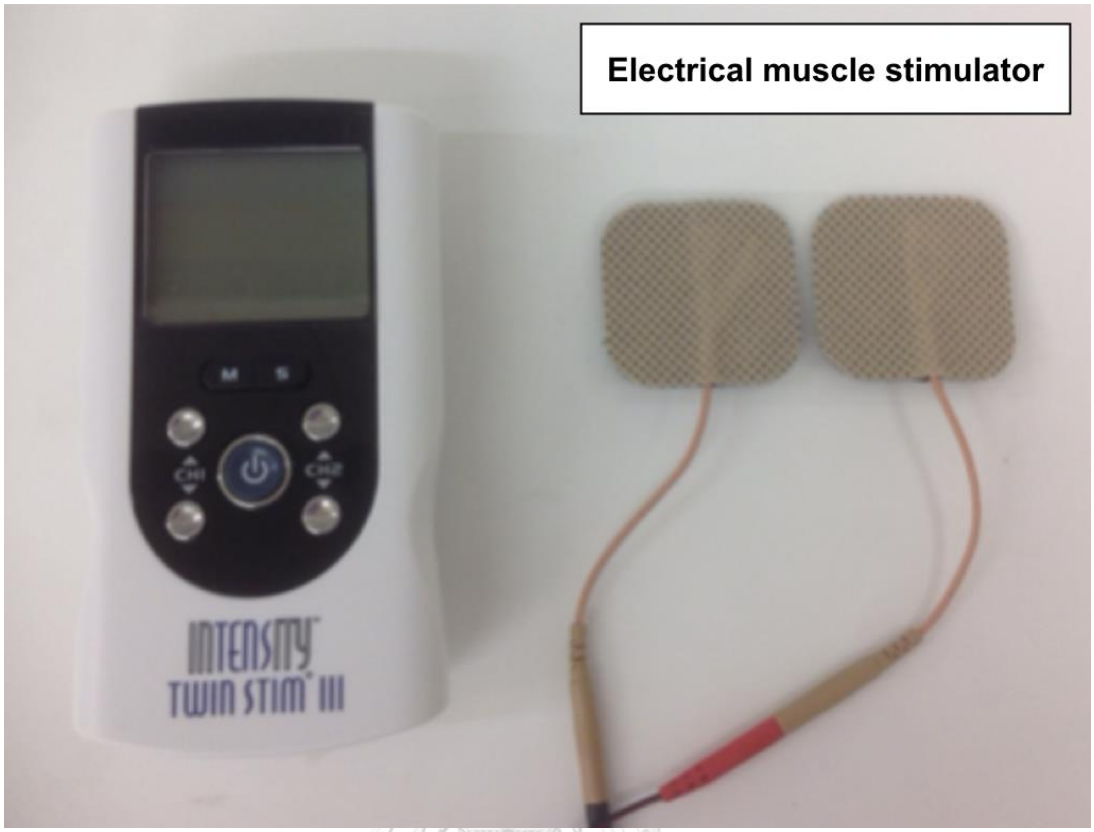

Figure 20: An electrical muscle stimulator (Intensity Twin Stim III, Current Solutions LLC, TX, USA

How to identify the optimal stimulation frequency?

Due to stimulation frequencies from previous literature were documented with the wide range of frequency between 20 and 100 Hz (69, 70), and resulted in difference outcome of muscle contraction and tremor reduction. Therefore, we targeted to identify the optimal stimulation frequencies. However, frequencies beyond 50 Hz were excluded as they were usually resulted to paresthesia and fatigue (71). Therefore, we performed a pilot study in another fifteen PD patients (separated from thirty-four previous recruited patients) by comparing the efficacy between 30 and 50 Hz. stimulation and results were summarized as in the Table 6. We provided the two stimulation setting as mentioned in previous literatures, including pulse width of 150 μs and pulse amplitude that provided a comfortable level to produce a muscle contraction. A slowly increasing of pulse amplitude in every 1 mA with a stimulation

duration of 30 seconds for each was provided to all participants until identify the optimal pulse amplitude which could produce a muscle contraction in either inducing a tetanic contraction without paresthesia or providing the maximum tremor reduction by visual observation. Based on the results of a pilot fifteen patients, the 50 Hz. stimulation was found effective in reducing tremor than 30 Hz. stimulation determined by peak magnitude and RMS angular velocity ($p<0.05$, each) (72) (Fig.21).

Table 6: Results of the EMS at 30- Hz and 50-Hz stimulation to the pilot patients to determine the suitable protocol.

No	Sex	Age (yrs)	Amp (mA)	RMS no stimulation	RMS 30 Hz.	RMS 50 Hz.	Peak no stimulation	Peak 30 Hz.	Peak 50 Hz.	Delta RMS 30 Hz.	Delta RMS 50 Hz.	Delta Peak 30 Hz.	Delta Peak 50 Hz.
1	F	64	9.00	153.93	105.70	90.38	91.48	48.21	47.00	48.23	63.55	43.27	44.48
2	M	70	17.00	15.21	6.30	6.85	9.49	3.15	2.41	8.91	8.36	6.34	7.08
3	M	47	12.00	73.36	34.92	20.08	57.00	19.57	12.01	38.44	53.28	37.43	44.99
4	F	74	9.00	4.52	3.15	1.21	3.22	1.32	0.29	1.37	3.31	1.90	2.93
5	F	69	9.00	45.61	71.37	62.20	28.49	19.58	18.51	-25.76	-16.59	8.91	9.98
6	M	68	10.00	71.71	62.69	36.74	64.98	38.35	27.66	9.02	34.97	26.63	37.32
7	M	63	12.00	11.58	5.71	2.25	8.02	2.63	0.60	5.87	9.33	5.39	7.42
8	M	59	7.00	49.77	47.45	23.47	44.66	41.05	14.01	2.32	26.30	3.61	30.65
9	M	56	10.00	93.24	82.79	87.34	71.92	69.68	54.09	10.45	5.90	2.24	17.83
10	M	81	9.00	13.66	1.54	1.02	10.16	0.53	0.35	12.12	12.64	9.63	9.81
11	F	67	9.00	6.98	3.84	2.18	4.74	3.12	1.19	3.14	4.80	1.62	3.55
12	F	63	7.00	5.28	3.10	1.48	3.69	1.19	0.25	2.18	3.80	2.50	3.44
13	M	70	11.00	91.08	57.77	34.94	61.14	54.03	26.72	33.31	56.14	7.11	34.42
14	F	81	15.00	30.09	9.64	6.39	27.16	6.27	4.68	20.45	23.70	20.89	22.48
15	M	69	8.00	48.15	24.14	14.24	37.66	17.17	7.73	24.01	33.91	20.49	29.93

F: female; M: male; Amp: pulse amplitude; RMS: the root mean square of the angular velocity; Peak: peak magnitude.
Delta RMS 30 Hz: RMS during no stimulation minus RMS during 30 Hz stimulation
Delta RMS 50 Hz: RMS during no stimulation minus RMS during 50 Hz stimulation
Delta Peak 30 Hz: Peak magnitude during no stimulation minus Peak magnitude during 30 Hz stimulation
Delta Peak 50 Hz: Peak magnitude during no stimulation minus Peak magnitude during 50 Hz stimulation
The stimulation at 50 Hz was more effective in the reduction of both peak magnitude and RMS of the angular velocity than the stimulation at 30 Hz (p=0.001 and p=0.005, respectively). The statistical analysis was performed by the Wilcoxon-Sign Rank test.

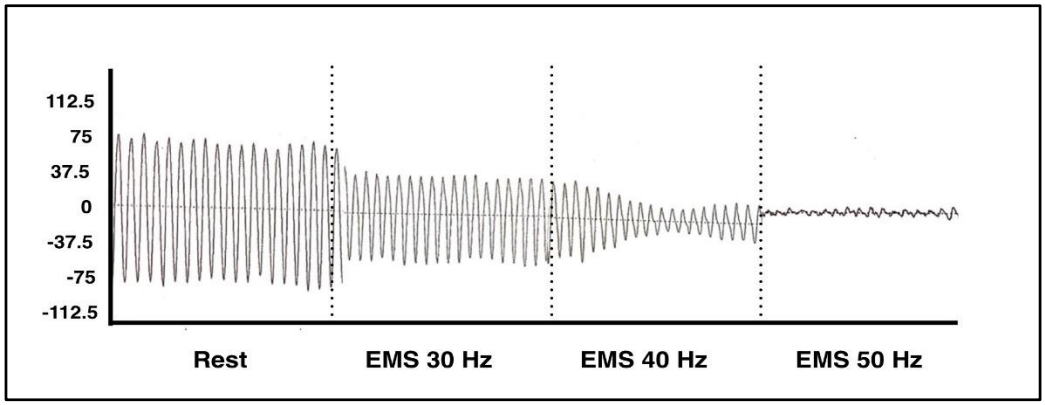

Figure 21: Gyroscopic report in tremor amplitude reduction by EMS with constant pulse amplitude (15 mA) and different in pulse frequency (from pilot study)

How to identify the optimal pulse width?

For determining the optimal pulse width, we compared the efficacy between PW 150 mcs and 300 mcs while remaining the other constant stimulation protocols including frequency of 50 Hz and a maximum pulse amplitude that produced the muscle contraction in a comfortable level among a pilot 15 patients. The results were summarized in the Table 7. There were no significant different in tremor reduction between PW of 150- and 300-mcs determining in both RMS of angular velocity and peak magnitude ($p>0.05$, each). However, the VAS during stimulation with PW 300 mcs was significantly higher than during stimulation with PW 150 mcs ($p<0.05$).

Table 7: Results of the EMS at the pulse width 150- and 300-microsecond stimulation among the pilot 15 patients to determine the suitable protocol.

No.	Sex	Age (yrs)	Amp (mA)	RMS no stimulation	PW 150	PW 300	Peak no stimulation	PW 150	PW 300	Delta RMS PW 150	Delta RMS PW 300	Delta Peak PW 150	Delta Peak PW 300	VAS PW 150	VAS PW 300
1	F	64	9.00	153.93	90.38	88.96	91.48	47.00	45.30	63.55	64.97	44.48	46.18	1	2
2	M	70	17.00	15.21	6.85	5.78	9.49	2.41	3.20	8.36	9.43	7.08	6.29	2	4
3	M	47	12.00	73.36	20.08	23.22	57.00	12.01	13.48	53.28	50.14	44.99	43.52	1	1
4	F	74	9.00	4.52	1.21	0.83	3.22	0.29	0.24	3.31	3.69	2.93	2.98	1	2
5	F	69	9.00	45.61	62.20	65.90	28.49	18.51	20.01	-16.59	-20.29	9.98	8.48	2	2
6	M	68	10.00	71.71	36.74	39.40	64.98	27.66	30.22	34.97	32.31	37.32	34.76	0	2
7	M	63	12.00	11.58	2.25	1.99	8.02	0.60	0.49	9.33	9.59	7.42	7.53	1	2
8	M	59	7.00	49.77	23.47	21.09	44.66	14.01	13.56	26.30	28.68	30.65	31.10	1	3
9	M	56	10.00	93.24	87.34	96.07	71.92	54.09	87.49	5.90	-2.83	17.83	-15.57	1	1
10	M	81	9.00	13.66	1.02	3.44	10.16	0.35	2.89	12.64	10.22	9.81	7.27	0	0
11	F	67	9.00	6.98	2.18	1.89	4.74	1.19	0.78	4.80	5.09	3.55	3.96	0	2
12	F	63	7.00	5.28	1.48	3.22	3.69	0.25	2.56	3.80	2.06	3.44	1.13	1	2
13	M	70	11.00	91.08	34.94	45.89	61.14	26.72	34.56	56.14	45.19	34.42	26.58	0	0
14	F	81	15.00	30.09	6.39	9.86	27.16	4.68	6.51	23.70	20.23	22.48	20.65	2	4
15	M	69	8.00	48.15	14.24	13.90	37.66	7.73	5.89	33.91	34.25	29.93	31.77	1	3

F: female; M: male; Amp: pulse amplitude; RMS: the root mean square of the angular velocity; Peak: peak magnitude; VAS: visual analog scale
Delta RMS PW 150: RMS during no stimulation minus RMS during PW 150 mcs. stimulation
Delta RMS PW 300: RMS during no stimulation minus RMS during PW 300 mcs. stimulation
Delta Peak PW 150: Peak magnitude during no stimulation minus Peak magnitude during PW 150 mcs. stimulation
Delta Peak PW 300: Peak magnitude during no stimulation minus Peak magnitude during PW 150 mcs. stimulation
There were no significant different in tremor reduction between PW of 150 and 300 mcs. determining in both RMS of the angular velocity and peak magnitude (p=0.078 and p=0.069, respectively). However, the VAS during stimulation with PW 300 mcs. was significantly higher than during stimulation with PW 150 mcs. (p=0.004).

Finally, a constant stimulation at a 50 Hz frequency, a 150 μs pulse width, and a maximum pulse amplitude that produced the motor response in a comfortable level were an optimal stimulation protocols for tremor reduction. This protocol also applied to the subsequent study for testing the efficacy of an EMS in a 34 PD patients. *(72)*

How to identify the suitable location for stimulating?

We defined the best location for stimulating as the location that EMS could be able to reduce tremor of the whole limb tremor. The surface EMG or electromyography was performed in 6 Parkinson's disease patients to determine muscle activities in both before and during stimulation.(72) Two disposable surface electrodes were placed to six muscles as following: biceps, triceps, extensor carpi radialis longus (ECRL), flexor carpi ulnaris (FCU), abductor pollicis brevis (APB), and dorsal interrossei (DI) as in previously published standard (34, 43). The placement of stimulating electrodes over the selected hands and forearm muscles were conducted with the EMS stimulator and the subsequent tremor reductions of the rest muscles were observed with EMG. The quantitative EMG signals were analyzed with analysis of amplitude. The amplitude of EMG signal was defined as the RMS signal in a 1-s duration. The average value of the amplitudes during before and during stimulation was used for analysis. We found that APB and DI muscles were the best locations for stimulating that could be observed a significant reduction of the RMS amplitude in the other limb muscles, especially with triceps and FCU muscles ($p<0.05$, each). Full results were shown in Table 8. We provided the figure shown the comparison of RMS reduction in all muscles (Fig.22) and sample EMG graph of 6 muscles of one patient (Fig. 23).

Table 8: The pilot EMG data in comparison of the root mean square calculated from EMG signal between before and during stimulation for each muscles

Muscles	RMS before stimulation	RMS during stimulation	*p*-value
Gyroscope data	58.10 (20.72)	32.30 (23.87)	0.028*
Biceps	35.46 (29.45)	24.76 (23.14)	0.075
FCU	49.47 (20.70)	29.22 (15.74)	0.046*
APB	124.98 (131.39)	43.70 (36.41)	0.075
Triceps	39.98 (23.49)	29.68 (18.59)	0.028*
ECRL	23.16 (4.55)	19.60 (6.28)	0.345
DI	158.95 (228.29)	128.26 (146.08)	0.753
The statistics were performed by Wilcoxon Sign Rank test and all parameters were reported in mean (SD); *: statistically significant RMS: root mean square of electromyographic signal, FCU:flexor carpi ulnaris muscle; APB: abductor pollicis brevis muscle; ECRL: extensor carpi radialis longus; DI: dorsal interrossei muscle			

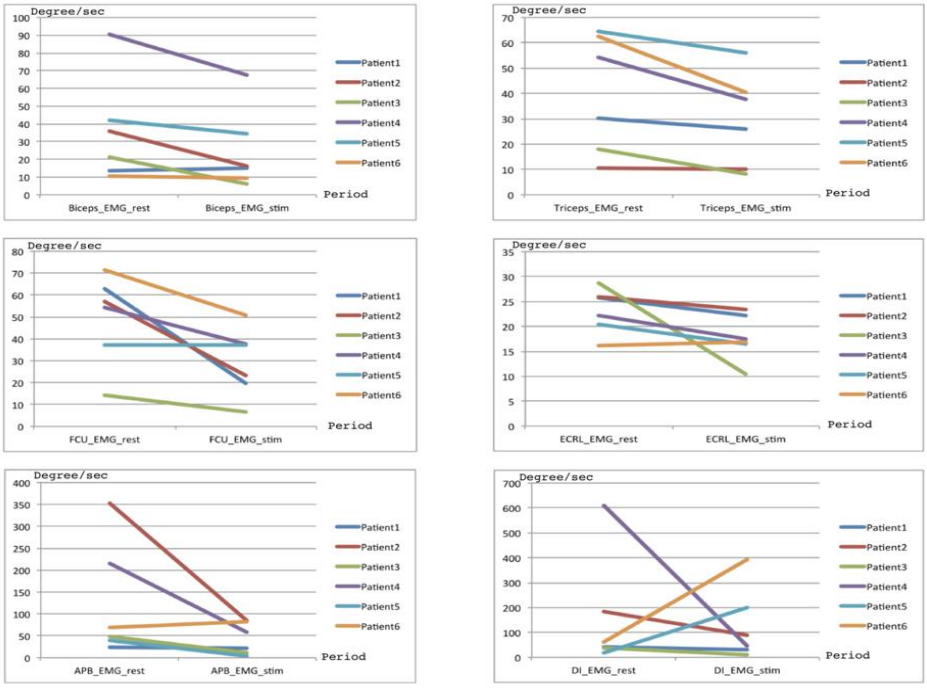

Figure 22: The figure shown the comparison of RMS reduction in all 6 muscles.

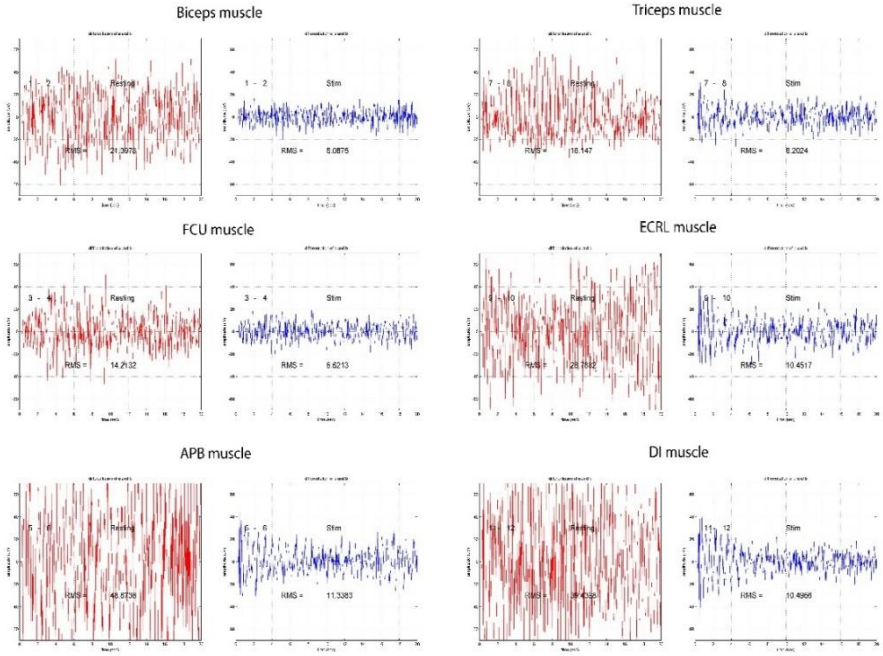

Figure 23: The figure shown the sample EMG graph of 6 muscles of one patient

Testing efficacy of EMS for PD tremor

The efficacy of EMS in parkinsonian tremor reduction was conducted in thirty-four PD patients. The optimal stimulation protocol and location for stimulating were provided for all participants as results from the pilot studies. The patient's characteristics are summarized (Table 9 and 10). All patients met the criteria for resistant tremor. More than 50% of patients were male and had a predominant tremor on right-sided.(72)

The kinematic analysis before stimulation showed a mean tremor frequency within parkinsonian tremor frequency range, but the tremor amplitude (determined by peak magnitude) was significant reduced when patients changed their hand position from resting to postural position ($p<0.05$). The reduction of tremor amplitude was consistent with classical rest tremor according to consensus criteria (2).

Table 9: Demographics data of all PD patients before EMS and tremor parameters between resting and postural positions.

Item	PD group (n= 34)		*p*-value
	Resting position before EMS	Postural position before EMS	
Age (year)	65.29 (8.72)		
Male gender (N, percent)	18 (52.9%)		
Tremor predominant on the right hand (N, percent)	21 (61.8%)		
Health insurance (Government reimbursement scheme) (N, percent)	21 (63.6%)		
TMSE score	27.24 (3.03)		
LED (mg)	716.27 (343.27)		
Disease duration (years)	6.67 (2.86)		
Average pulse amplitude (mA)	10.70 (3.09)		
Hoehn and Yahr score in the 'off' period	2.67 (0.91)		
Hoehn and Yahr score in the 'on' period	1.77 (0.67)		
UPDRS motor score in the 'off' period	27.29 (7.56)		
UPDRS motor score in the 'on' period	15.18 (3.81)		
UPDRS tremor score in the 'off' period	15.21 (1.87)		
UPDRS tremor score of the most affected hand in the 'off' period	3.76 (0.43)		
UPDRS tremor score in the 'on' period	10.59 (1.74)		
UPDRS tremor score of the most affected hand in the 'on' period	2.85 (0.50)		
Peak magnitude	34.96 (34.27)	2.63 (7.62)	$P<0.001^{\Phi *}$
RMS of the angular velocity	51.60 (51.07)	5.39 (11.66)	$P<0.001^{\Phi *}$
Frequency	4.81 (0.98)	5.82 (2.63)	$P=0.074^{\Phi}$
Q parameter	13.19 (4.40)	11.84 (5.04)	$P=0.162^{\Phi}$

$^{\Phi}$: Paired sample t-test; *: Statistically significant ($P<0.05$); parameters were reported in mean (SD); value in parentheses are shown as percentage; EMS: electrical muscle stimulation; PD: Parkinson's disease; TMSE: Thai Mental State Examination; H&Y: Hoehn and Yahr scale; LED: Levodopa equivalent dosage; RMS: Root mean square; Q: Tremor dispersion score; UPDRS: Unified Parkinson Disease Rating Scale

Table 10: Patient's characteristics for all PD patients.

Patient	Gender	Age (year)	Side of tremor	LED (mg)	Tremor frequency (Hz.)	Sensory threshold (mA)	Pulse amplitude (mA)	Current medications
1	F	69	Rt	450	4.00	4	10.00	1,2,5
2	F	63	Rt	1446.5	2.50	4	7.00	1,2,3,4,5
3	F	67	Rt	480	4.25	5	9.00	1,2,4,5
4	M	62	Rt	898.5	5.25	6	10.00	1,2,3,5
5	F	67	Lt	1225	3.50	5	15.00	1,2,6
6	M	81	Lt	1363.25	4.50	4	9.00	1,3,5
7	M	56	Rt	1596	4.75	5	13.00	1,3,5
8	M	59	Lt	1535	5.00	4	7.00	1,2,3,5
9	M	63	Rt	400	4.50	7	12.00	1,2,5
10	M	68	Lt	400	5.25	6	10.00	1,2,5
11	F	69	Rt	947.75	4.50	4	9.00	1,2,3,5
12	F	74	Lt	550	5.75	4	9.00	1,2,5
13	M	47	Rt	400	5.00	7	12.00	1,2,3,5
14	M	70	Lt	450	4.50	7	17.00	1,3,5
15	F	64	Lt	532	5.00	4	9.00	1,2,3,5
16	M	66	Rt	675	6.50	7	16.00	1,2,5
17	F	51	Rt	432.25	5.75	5	11.00	1,2,3,5
18	F	69	Lt	775	4.75	5	15.00	1,2,5,6
19	M	72	Rt	800	5.50	7	17.00	1,2,3,5
20	M	51	Lt	775	5.50	6	12.00	1,2,5,7
21	M	69	Lt	850	4.50	4	8.00	1,2,3,4,5
22	F	69	Rt	775	4.00	3	6.00	1,3,5
23	F	70	Rt	600	5.50	4	8.00	1,3,5,6
24	M	70	Rt	600	3.50	5	11.00	1,2,3,5
25	F	45	Lt	425	4.25	3	6.00	1,3,5
26	F	62	Rt	450	8.00	4	8.00	1,3,5,6
27	F	63	Rt	650	3.25	4	8.00	1,3,5
28	M	63	Lt	450	4.75	6	15.00	1,3,5
29	F	82	Rt	450	4.00	4	9.00	1,3,5,6
30	M	75	Rt	600	5.00	5	11.00	1,3,5,6
31	F	81	Rt	600	5.00	4	15.00	1,3,5,6
32	M	68	Lt	525	5.00	5	11.00	1,2,3,5
33	M	64	Rt	797.5	5.75	5	10.00	1,3,4,5,7
34	M	60	Rt	450	5.25	5	9.00	1,2,5

Gender: F=female, M=male; Ages were identified by current age. Side of tremor for the most affected hand; Rt: right side, Lt: left side; LED: levodopa equivalent dosage; UPDRS tremor: UPDRS tremor score of the most affected hand in ON period before stimulation. Current medications: Levodopa=1, DAs=2, COMTI=3, MAOBI=4, Anticholinergics=5, B-blockers=6, others=7
Levodopa: levodopa/carbidopa or levodopa/benserazide; DAs: Dopamine agonist; COMTI: Catechol-O-methyl transferase enzyme; MAOI: monoamine oxidase-B enzyme inhibitors; Sensory threshold: the weakest pulse amplitude that patient can detect.

During EMS, significant reduction in the RMS angular velocity and peak magnitude were found (p<0.05, each)(Table 11, Fig 24). However, the tremor frequency and Q parameter during stimulation were not significantly changed (p<0.05, each) (Figure 4.6). The UPDRS tremor score and the UPDRS tremor score of the most affected hand were significantly reduced during stimulation (p<0.05, each). Almost 50% tremor reduction determined from the tremor amplitude were noted. More than 60% of patients who improved their tremor at least 30% were identified from peak magnitude and RMS of angular velocity.(72)

A visual observation found the benefit of tremor reduction lasted for approximately 10-20 seconds after turn off the stimulator. However, the quantitative measurement was not performed in this study. We found no any adverse events among participants including; paresthesia, numbness, burning pain, or fatigue during EMS and at one-month follow-up.(72)

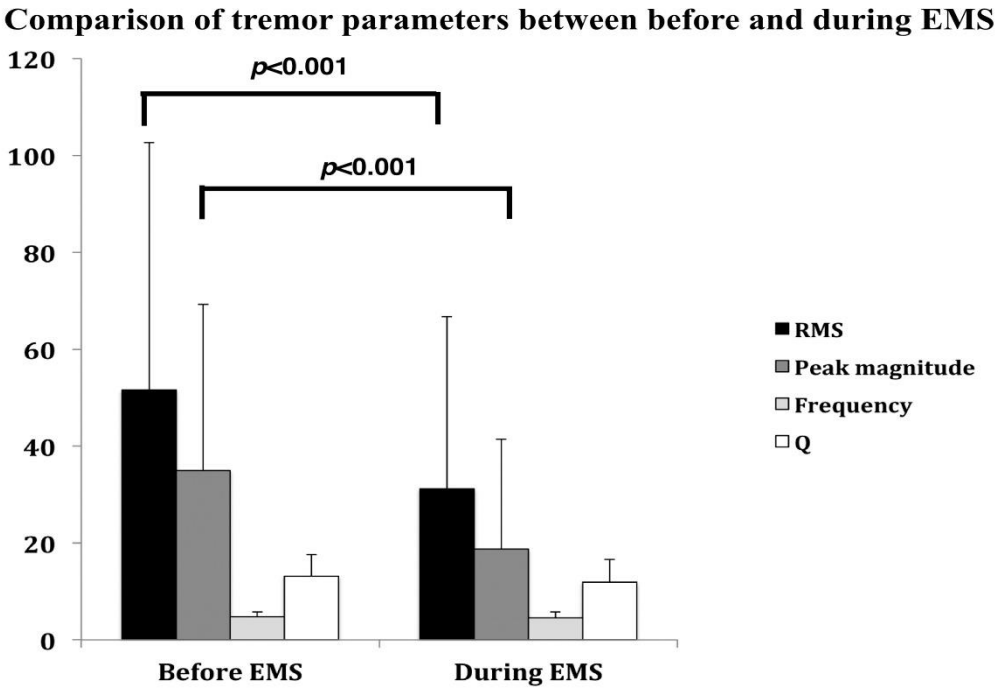

Figure 24: Bar graph shows the significant tremor reduction determined between before and during EMS.

Table 11: Demographics data of all patients and comparison of tremor outcomes between before and during stimulation

Item	Resting position before EMS	Resting position during EMS	*p*-value
UPDRS tremor score in the 'on' period	10.59 (1.74)	8.85 (2.19)	$P<0.001^{\Psi*}$
UPDRS tremor score of the most affected hand in the 'on' period	2.85 (0.50)	1.21 (0.94)	$P<0.001^{\Psi*}$
Peak magnitude	34.96 (34.27)	18.77 (22.61)	$P<0.001^{\Psi*}$
RMS of the angular velocity	51.60 (51.07)	31.19 (35.55)	$P<0.001^{\Psi*}$
Frequency	4.81 (0.98)	4.58 (1.24)	$P=0.126^{\Psi}$
Q parameter	13.19 (4.40)	11.94 (4.72)	$P=0.284^{\Psi}$
Mean percentage of RMS improvement	43.81 (33.15)		
Mean percentage of peak magnitude improvement	49.57 (38.89)		
Number of patient with at least 30% improvement of RMS during EMS (N, percent)	21 (61.8%)		
Number of patient with at least 30% improvement of peak magnitude during EMS (N, percent)	24 (70.6%)		

$^{\Psi}$: Paired sample t-test; *: Statistically significant ($P<0.05$); parameters were reported in mean (SD); value in parentheses are shown as percentage, EMS: electrical muscle stimulation; PD: Parkinson's disease; TMSE: Thai Mental State Examination; H&Y: Hoehn and Yahr scale; LED: Levodopa equivalent dosage; RMS: Root mean square; Q: Tremor dispersion score; UPDRS: Unified Parkinson Disease Rating Scale.

Part 2:

The objective of the phase 2 study was to develop the Parkinson's glove and test for its efficacy in hand tremor reduction among the tremor-dominant PD patients with medically intractable tremor.

No patent or previous invention describes a device that can detect, analyze and automatically suppress tremor signals of Parkinson's disease patients using electrical muscle stimulation. Therefore, we proposed a medical device that can perform these functions. This device can be used to treat many types of tremor occurring in several body parts of the body, for example, hands, arms, and legs.

Parkinson's glove development

The Parkinson's glove is a medical device that specially designed and incorporated both a tremor detection module and an EMS module into a glove. The glove is adjustable and can be use to detect and suppress the resting hand tremor (Fig. 25). A tremor detection module is a 6-axis gyroscope and accelerometer (MPU 6050 model from InvenSense, Inc.) which can track individual movements precisely in both angular and linear displacement. A tremor suppression module is an electrical muscle stimulator developed according to FDA standards. Combined electric muscle stimulation (EMS) provides electricity to the target muscles via the surface electrodes. In detail, the Parkinson's glove is placed on the most tremulous hand, and two embedded-surface electrodes are placed over DI muscle and the APB muscle. The tremor detection module is an inertial sensor which is inserted into a socket located at the dorsal part of the glove. The tremor detection module detects and transfers tremor signals to the microcontroller which then interprets the tremor signal and orders an electric muscle stimulation to release electricity according to previously defined electrical configurations set up by the investigator. Bluetooth communication occurs between a medical device combined with the tremor detection module and the tremor suppression module as a single portable unit. A microcontroller and the Android smartphone operate the Parkinson's glove function with data collected in the internal memory of the mobile phone. The Parkinson's glove consists of 3 components, including 1). An adjustable glove with embedded sensors and EMS, 2). control box placing on an individual waist belt, 3). Android smart phone with an installed device's application.

The control box is a small plastic container that composes of 3 components, as

following, microcontroller, Bluetooth's module, and batteries. Parkinson's glove is designed to be used as a portable lightweight and user-friendly device which can be controlled by an Android smartphone installed with the specific application. Total weight of Parkinson's glove and its components without the smart phone less than 300 grams. The patent application number of Parkinson's glove is 1701000170.

Figure 25: Figure A-C shows the component of Parkinson's glove. Figure A: 3 components of Parkinson's glove, including an adjustable glove, control box, and smart phone. Figure B-C demonstrated how a subject wore the Parkinson's glove.

Tremor detection module

The tremor detection module was positioned inside a pocket that was sewn onto the dorsal surface of the glove. The tremor detection module combines a 3-axis accelerometer and a 3-axis gyroscope, which together measure linear and angular displacements of tremor via complex 6-axis MotionFusion algorithms (MPU-6050;

InvenSense, Inc., San Jose, CA, USA). The sampling rate was 100 Hz and data recording typically consisted of 10s of data (1,000 samples), which were further processed by Fourier Transform algorithm for waveform analysis and calculated for amplitude and frequency.

EMS module

EMS module was splaced in a leather socket placing on an individual waist belt. An EMS module was designed in accordance with approved EMS standards and delivered electrical stimulation to the affected muscles via two self-adhesive electrodes (size: 1.5 * 1.5 inches) that were located inside the glove over the APB and DI muscles, which were the hand muscles most affected by tremor. An electricity source of EMS module was derived from two lithium-ion batteries. A suitable, custom-designed stimulation protocol was developed for each patient in the Parkinson's glove group using a continuous stimulation frequency of 50 Hz. The most effective pulse amplitude was identified by slowly increasing electricity until seen tetanic muscle contractions without paresthesia (above the motor, but below the sensory threshold). In patients bilaterally affected, the glove was worn on the most tremulous hand.

Full disclosure of Parkinson's glove development

1. Figure 26 shows the structure of the Parkinson's glove as a medical device combining the tremor detection module and the tremor suppression module in a single portable unit. The tremor detection module is an inertial sensor which is inserted into a socket located at the dorsal part of the glove. The glove is placed on the most tremulous hand and two embedded-surface electrodes are placed over DI muscle and APB muscle.
2. The tremor detection module is an inertial sensor (1) composed of a 6-axis gyroscope and accelerometer that is fitted to the body parts. The sensor sends a tremor signal to the digital-to-analog converter (2) which changes the signal from digital to analog for transmission to the first processor or microcontroller (3). This, then sends the signal in the appropriate format to the other units including the power supply (4), the display device (9), and the wireless communication module (10).

3. The power supply (4) receives an order from the microcontroller (3) to release muscles (8) when the signal reaches the specified range of tremor frequencies. The power supply (4) receives the high voltage from the capacitor (7), which receives the voltage from the upstream converter (6). The upstream converter receives the electrical discharge from the power source (5). The average resistance of the surface electrode is 1 kΩ.
4. The display device (9) is responsible for displaying data from the microcontroller (3) composed of tremor signals from the 6-axis gyroscope, accelerometer and the muscle stimulation data.
5. A wireless communication module (10) receives the tremor signal data and the muscle stimulation data from the microcontroller (3) and transmits all the signals to the wireless communication module (11) of the smartphone (12). The smartphone installed with the Parkinson's glove application represents the second processor (12). This operates the Parkinson's glove, displays the results, and stores tremor signals and muscle stimulation data in its internal memory (14).
6. The wireless communication module (11), the second processor (12), the user interface of a display device (13), and the internal memory (14) are all parts of the smartphone.
7. If the calculated tremor signals fall within the specific tremor frequency, the second processor (12) transmits the analyzed tremor signals back to the microcontroller (3) to automatically control the power supply and release the electrical discharge (4) via an electrode placed on the skin above the muscle (8). Continuous working of the first and second processors occurs via the wireless communication set (10 and 11) and all results are stored in the internal memory of the smartphone.
8. The device is attached to the two electrodes inside the glove and to the socket of an individual's belt to suppress tremors of the arms, legs, arms, and body. The Parkinson's glove is designed to be a small, lightweight device that can be handled or used on a daily basis.

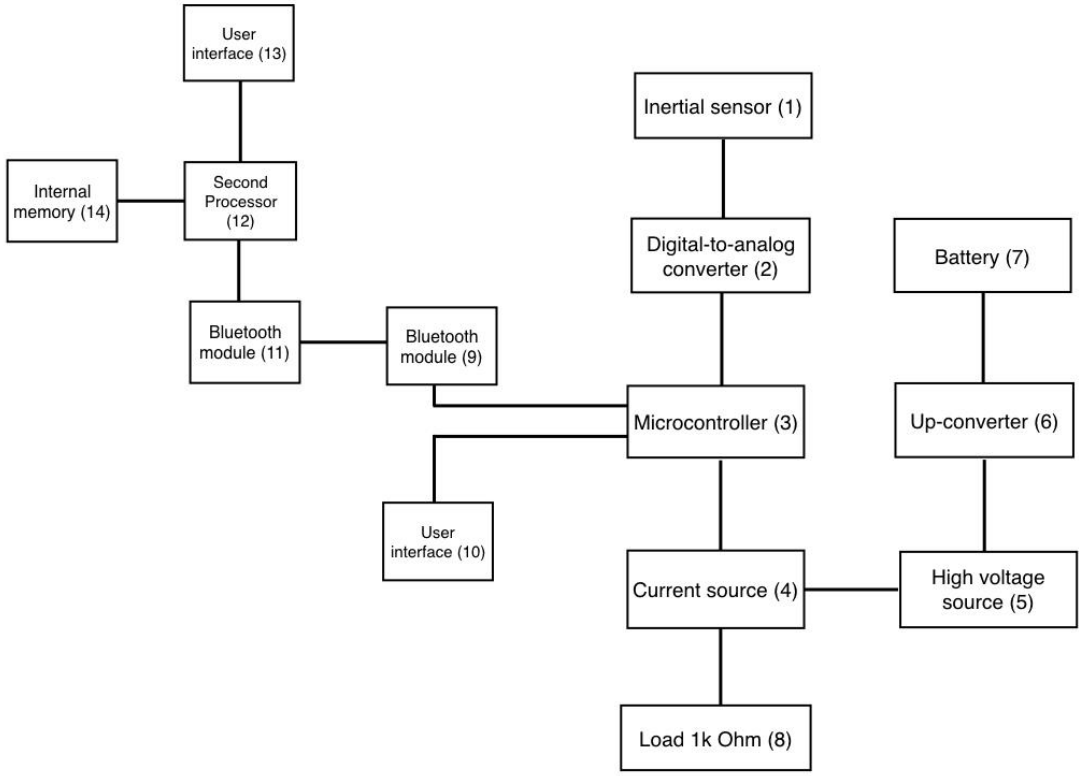

Figure 26: The full disclosure of an operating system of the Parkinson's glove development

Modes of stimulation

The Parkinson's glove could be operated in either an automatic or manual stimulation. The control panel was developed as an Android-based smart phone application with a Bluetooth's connection in the Parkinson's glove so the investigators could control and adjust the stimulation settings, as needed. The real-time tremor parameter and stimulation protocol with the sampling rate were each 100 Hz. Data was automatically recorded via a Bluetooth to save in the internal memory of a smart phone, including digital-output X-, Y-, and Z-axis angular rate sensors, triple-axis digital-output accelerometers, pulse amplitude, pulse width, pulse frequency, and mode of stimulation. This data was then exported in a comma separated values (CSV) file to be used to calculate a root mean square angular velocity and root mean square tremor frequency.

For an automatic mode, the tremor detection module and the EMS module are integrated to detect tremors and to automatically deliver a 10-second duration of electrical stimulation to reduce the shaking of hand muscles if tremor frequencies reach the classic rest tremor frequency of 4-7 Hz. In the manual program mode, the tremor detection module and the EMS module are independent of each other, and the EMS module will deliver continuous electrical stimulation to the trembling hand muscles in a customized configuration determined by the investigators.

A manual mode was directly operated by investigators to deliver stimulation to each participant. The most effective stimulation protocols (including pulse amplitudes and other stimulation parameters) was identified as a given parameter that gets the maximum tremor reduction and extended period of tremor reduction after stimulation was discontinued.

A sham glove

The sham glove is produced with identically materials and visibly similar to the Parkinson's glove (Fig. 27). The sham glove consists of 3 major components; 1). An adjustable glove that embedded inertial sensors without EMS module's connection, but a series of LED lights was installed that will be flashed on the control box interface mimicking EMS, 2). The control box that is suitably contained in a leather socket placing on an individual waist belt, and 3). Android smart phone that installed device's application. The total weight of a sham glove and its components are identical to the Parkinson's glove.

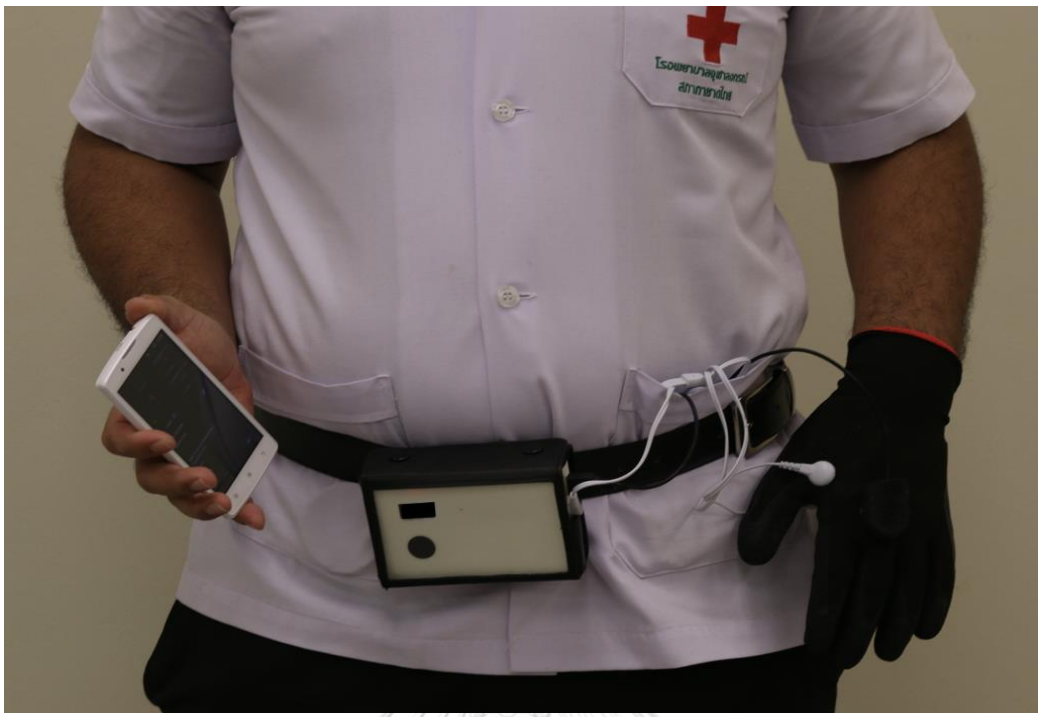

Figure 27: Figure showed the similarity of the sham glove to the Parkinson's glove.

Testing efficacy of Parkinson's glove

This was a double-blind, 1:1 pair-designed, randomized controlled study comparing the additional benefit of using a Parkinson's glove compared to a sham glove in 40 Parkinson's disease patients who satisfy the criteria of classic resting tremor and resistant tremor. All subjects were recruited from the outpatient movement clinic of the King Chulalongkorn Memorial Hospital between January 2016 and August 2016. During that period, the center enrolled patients in pairs using a simple random sampling method, with one patient randomly assigned to Parkinson's Glove group and the other to sham glove group, which 20 participants were allocated in the Parkinson's glove group and the rest were allocated to sham glove group. The protocol was approved by the human Subjects Ethics Committee of the Faculty of Medicine, Chulalongkorn University. All subjects gave their written informed consent before entering the study.

Demographic and baseline clinical characteristics are summarized in Table 12. From 40 patients (20 patients per group), all were tremor predominant subtype, as confirmed by kinematic studies for classic resting tremor according to consensus criteria (2). There were no significant differences between groups for age, gender, disease duration, TMSE score, LED dosage, or disease severity scores, including H&Y, UPDRS scores in both 'off' and 'on' periods, as follows (p.>0.05 for each); UPDRS-tremor score (a sum score of the UPDRS items 16, 20, and 21 is a range between 0-32 points), UPDRS III-tremor score (a sum score of the UPDRS items 20 and 21 is a range between 0- 28 points), UPDRS resting tremor of the most affected hand (item 20 is a range between 0- 4 points), UPDRS resting tremor of the other hand (item 20 is a range between 0- 4 points), UPDRS resting tremor of the most affected leg (item 20 is a range between 0- 4 points), UPDRS resting tremor of the other leg (item 20 is a range between 0- 4 points), UPDRS resting tremor of chin (item 20 is a range between 0- 4 points), UPDRS action/postural tremor of the most affected hand (item 21 is range between 0- 4 points), UPDRS action/postural tremor of the other hand (item 21 is a range between 0- 4 points), and UPDRS II (item 16 is a range between 0-4 points).

Table 12: Tremor parameters and outcome measurement during interventions between both groups.

Item	Parkinson's glove (N=20)	Sham glove (N=20)	*p*-value
Age (year)	63.15 (9.52)	63.20 (10.60)	0.718[φ]
Male gender (N, percent)	12 (60%)	8 (40%)	0.206[β]
Disease duration (years)	7.80 (3.58)	6.45 (2.48)	0.201[φ]
TMSE score	26.35 (2.75)	25.95 (3.23)	0.659[φ]
LED dosage	781.97 (304.40)	743.20 (400.64)	0.277[φ]
Hoehn and Yahr score-OFF period	2.55 (0.68)	2.77 (0.80)	0.327[φ]
Hoehn and Yahr score-ON period	1.67 (0.44)	1.75 (0.59)	0.659[φ]
Clinical rating scale-OFF period	Parkinson's glove	Sham glove	*p*-value
OFF UPDRS III	29.00 (11.06)	27.80 (9.39)	*P*=0.974[ε]
OFF UPDRS- resting tremor of the most affected hand (item 20)	3.75 (0.55)	3.65 (0.49)	*P*=0.478[ε]
OFF UPDRS-resting tremor of the other hand (item 20)	0.90 (1.20)	1.05 (1.09)	*P*=0.620[ε]
OFF UPDRS-resting tremor of the most affected leg (item 20)	1.10 (1.29)	1.10 (1.07)	*P*=1.000[ε]
OFF UPDRS-resting tremor of the other leg (item 20)	0.25 (0.63)	0.10 (0.44)	*P*=0.602[ε]
OFF UPDRS-resting tremor of chin (item 20)	0.85 (1.18)	0.50 (0.82)	*P*=0.478[ε]
OFF UPDRS-action/postural tremor of the most affected hand (item 21)	1.25 (0.85)	1.20 (0.95)	*P*=0.841[ε]
OFF UPDRS-action/postural tremor of the other hand (item 21)	0.15 (0.36)	0.25 (0.44)	*P*=0.602[ε]
OFF UPDRS III-tremor (item 20 and 21)	8.30 (3.75)	7.85 (2.77)	*P*=1.000[ε]
OFF UPDRS II (item 16)	2.55 (0.60)	2.40 (0.50)	*P*=0.529[ε]
OFF UPDRS-tremor (item 16, 20, and 21)	11.20 (4.42)	10.26 (3.15)	*P*=0.820[ε]
Clinical rating scale-ON period	Parkinson's glove	Sham glove	*p*-value
ON UPDRS III	16.15 (6.42)	16.75 (6.15)	*P*=0.758[ε]
ON UPDRS-resting tremor of the most affected hand (item 20)	2.40 (0.68)	2.40 (0.59)	*P*= 0.947[ε]
ON UPDRS-resting tremor of the other hand (item 20)	0.55 (0.82)	0.60 (0.68)	*P*=0.659[ε]
ON UPDRS-resting tremor of the most affected leg (item 20)	0.75 (1.07)	0.60 (0.59)	*P*=0.904[ε]
ON UPDRS-resting tremor of the other leg (item 20)	0.15 (0.36)	0.10 (0.31)	*P*=0.799[ε]
ON UPDRS-resting tremor of chin (item 20)	0.20 (0.41)	0.15 (0.36)	*P*=0.799[ε]
ON UPDRS-action/postural tremor of the most affected hand (item 21)	0.80 (0.77)	1.05 (0.82)	*P*=0.369[ε]
ON UPDRS-action/postural tremor of the other hand (item 21)	0.05 (0.51)	0.20 (0.41)	*P*=0.369[ε]
ON UPDRS-III tremor (item 20 and 21)	4.90 (2.49)	5.05 (2.03)	*P*= 0.883[ε]
ON UPDRS II (item 16)	1.50 (0.51)	1.85 (0.58)	*P*=0.108[ε]
ON UPDRS-tremor (item 16, 20, and 21)	6.40 (2.77)	6.90 (2.31)	*P*=0.620[ε]

[β]; Chi-square test, [ε]; Mann-Whitney U test, *; statistically significant; Parameters were reported in mean (SD); LED: levodopa equivalent dosage; MMSE: Mini-Mental State Examination; OFF: off state; ON: on state; UPDRS: The Unified Parkinson's Disease Rating Scale; UPDRS III (motor score): UPDRS III-tremor score (a sum score of the UPDRS items 20 and 21 is range between 0- 28 points); UPDRS resting tremor of the most affected hand (item 20 is a range between 0- 4 points); UPDRS resting tremor of the other hand (item 20 is a range between 0-4 points);UPDRS resting tremor of the most affected leg (item 20 is a range between 0- 4 points); UPDRS resting tremor of the other leg (item 20 is a range between 0- 4 points); UPDRS resting tremor of chin (item 20 is a range between 0- 4 points); UPDRS action/postural tremor of the most affected hand (item 21 is a range between 0- 4 points); UPDRS action/postural tremor of the other hand (item 21 is a range between 0- 4 points); and UPDRS II (item 16 is a range between 0-4 points); UPDRS-tremor score (a sum score of the UPDRS tremor items 16, 20, and 21 is a range between 0-32 points).

During stimulation, PD patients who assigned to the Parkinson's glove group showed a significant tremor reduction in RMS angular velocity for the X-, and Y-axis (p<0.05, each), a significant tremor reduction in RMS angular displacement for the X-, and Y-axis (p<0.05, each), and a significant tremor reduction in a peak magnitude for the X-, and Y-axis (p<0.05, each).

We also demonstrated markedly improvements in percentage of tremor reduction of the RMS angular velocity for the X-, Y-, and Z-axis (p<0.05, each), the RMS angular displacement for the X-, Y-, and Z-axis (p<0.05, each), the peak magnitude for the X-, Y-, and Z-axis (p<0.05, each). (Fig. 28).

Figure 28: A bar graph demonstrating a significant percentage reduction of various tremor parameters between the Parkinson's glove group and sham group. * shows significant difference ($p<0.05$). RMS angle; RMS angular displacement.

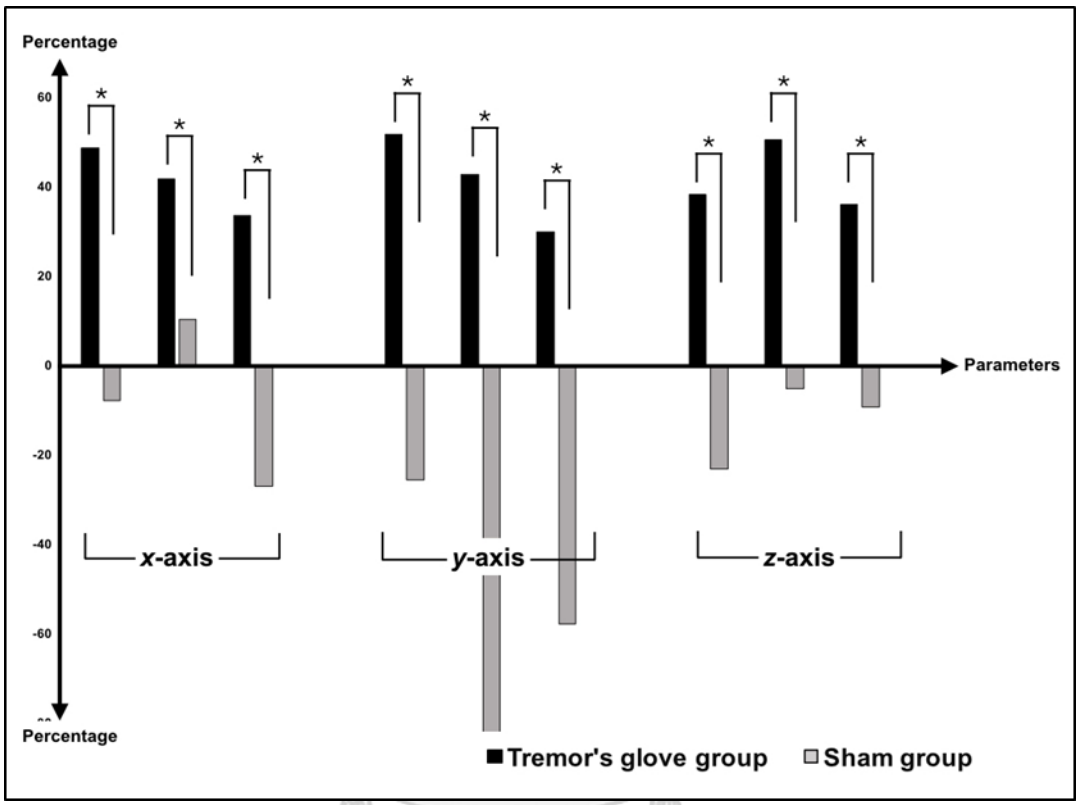

Table 13: Tremor parameters and outcome measurement during interventions between both groups

Objective measurements	Axis	Parkinson's glove	Sham glove	*p*-value
Reduction of the RMS angular velocity	X	6.81 (13.08)	-0.34 (7.59)	*P*=0.030[¥*]
	Y	9.22 (25.14)	2.38 (9.52)	*P*=0.013[¥*]
	Z	5.97 (14.90)	-1.58 (8.56)	*P*=0.060[¥]
Reduction of the RMS angle	X	0.40 (0.63)	-0.09 (0.47)	*P*=0.003[¥*]
	Y	1.56 (5.74)	0.42 (1.72)	*P*=0.030[¥*]
	Z	0.70 (2.52)	0.00 (0.57)	*P*=0.091[¥]
Reduction of the peak magnitude	X	14.59 (28.24)	-2.06 (18.59)	*P*=0.011[¥*]
	Y	22.61 (55.98)	5.18 (18.47)	*P*=0.004[¥*]
	Z	11.64 (27.36)	-1.25 (23.82)	*P*=0.072[¥]
Percentage reduction of the RMS angular velocity	X	48.65 (49.10)	-7.91 (68.39)	*P*=0.001[¥*]
	Y	41.54 (73.77)	10.13 (49.01)	*P*=0.011[¥*]
	Z	33.42 (56.72)	-27.14 (96.89)	*P*=0.015[¥*]
Percentage reduction of the RMS angular displacement	X	51.53 (41.75)	-25.73 (104.50)	*P*=0.001[¥*]
	Y	42.62 (48.51)	-82.08 (324.64)	*P*=0.023[¥*]
	Z	29.89 (66.02)	-57.97 (161.38)	*P*=0.028[¥*]
Percentage reduction of the peak magnitude	X	38.09 (81.64)	-23.14 (89.40)	*P*=0.002[¥*]
	Y	50.38 (63.92)	-5.35 (78.83)	*P*=0.002[¥*]
	Z	35.95 (58.46)	-9.25 (94.23)	*P*=0.046[¥*]

[¥]: Wilcoxon sign rank test; [¥]:Mann-Whitney U test; *:statistically significant; parameters were reported in mean (SD); X: x-axis; Y: y-axis; Z: z-axis; RMS: root mean square.

In a comparison of tremor parameters between before and during stimulation for each group (Table 14, Fig. 29), the Parkinson's glove group showed a significant reduction of tremor parameters for every axis (X-, Y-, and Z-axis) of RMS angular velocity ($p<0.05$, each), RMS angular displacement ($p<0.05$, each), and peak magnitude ($p<0.05$, each). However, the tremor frequency in every axis remained unchanged ($p>0.05$, each).

From Table 15, greater reductions in UPDRS tremor score, UPDRS-III tremor score, and UPDRS tremor score of the most affected hand were found only in Parkinson's glove group during stimulation ($p<0.05$, each). There were no improvements in any UPDRS tremor scores or tremor parameters among patients within the sham group ($p>0.05$ for each). In order to determine the effectiveness of tremor reduction after stimulation, the Parkinson's glove was set up manually with an average period of stimulation of almost 30 seconds. We found that patients remained tremor-free after discontinuation of stimulation for an average of almost 117 seconds.

Pain scores from visual analog scale (VAS) were significantly higher in the Parkinson's glove group than in the sham group ($p<0.05$).

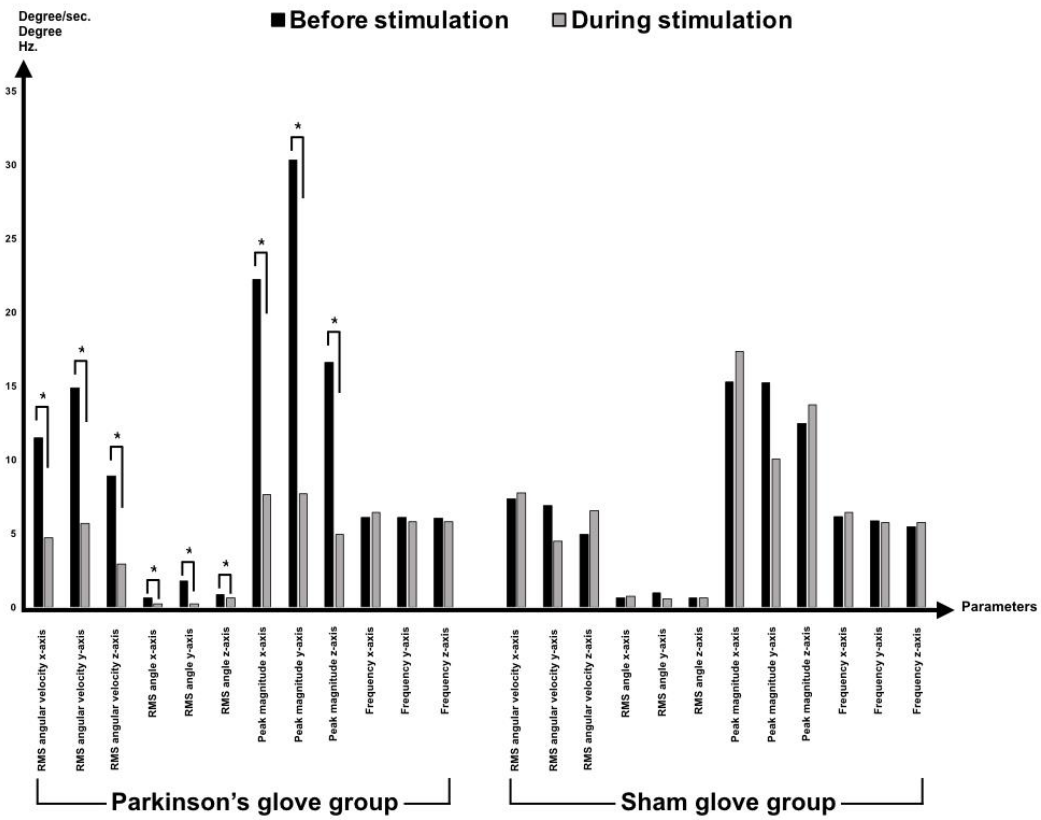

Figure 29: A bar graph comparing the significant difference of each tremor parameter between subjects in the Parkinson's glove group and sham group. * denotes statistically significant difference ($p<0.05$). RMS angle; RMS angular displacement. Represented units; RMS angular velocity (degree/sec.), RMS angle (degree), Peak magnitude (degree/sec.), frequency (Hz.).

Table 14: Tremor parameters between before and during interventions among both groups.

Objective measurements	Axis	Parkinson's glove		Sham glove		*p*-value
		Before intervention	During intervention	Before intervention	During intervention	
RMS angular velocity (degree/sec)	X	11.51 (15.76)	4.69 (11.62)	7.38 (9.92)	7.73 (11.11)	P_A= 0.416$^{\mu}$ P_B= 0.114$^{\mu}$ P_C= 0.004$^{\beta\bullet}$ P_D= 0.057$^{\beta}$
	Y	14.90 (28.71)	5.68 (16.42)	6.87 (11.33)	4.49 (5.34)	P_A= 0.414$^{\mu}$ P_B= 0.231$^{\mu}$ P_C= 0.002$^{\beta\bullet}$ P_D= 0.391$^{\beta}$
	Z	8.92 (16.55)	2.94 (6.43)	4.97 (6.20)	6.56 (12.46)	P_A= 0.925$^{\mu}$ P_B= 0.114$^{\mu}$ P_C= 0.010$^{\beta\bullet}$ P_D= 0.940$^{\beta}$
RMS angular displacement (degree)	X	0.63 (0.71)	0.23 (0.31)	0.66 (0.72)	0.75 (0.86)	P_A= 1.000$^{\mu}$ P_B= 0.046$^{\mu\bullet}$ P_C= 0.001$^{\beta\bullet}$ P_D= 0.852$^{\beta}$
	Y	1.79 (5.71)	0.22 (0.33)	0.97 (1.83)	0.55 (0.64)	P_A= 0.659$^{\mu}$ P_B= 0.063$^{\mu}$ P_C= 0.011$^{\beta\bullet}$ P_D= 0.926$^{\beta}$
	Z	0.85 (2.52)	0.15 (0.24)	0.62 (0.81)	0.62 (0.95)	P_A= 0.698$^{\mu}$ P_B=0.026$^{\mu\bullet}$ P_C= 0.019$^{\beta\bullet}$ P_D= 0.940$^{\beta}$
Peak magnitude (degree/sec)	X	22.23 (30.14)	7.63 (16.54)	15.26 (21.29)	17.33 (25.91)	P_A=0.414$^{\mu}$ P_B= 0.108$^{\mu}$ P_C= 0.002$^{\beta\bullet}$ P_D= 0.391$^{\beta}$
	Y	30.31 (63.87)	7.70 (19.66)	15.24 (24.09)	10.05 (12.85)	P_A=0.253$^{\mu}$ P_B= 0.242$^{\mu}$ P_C= 0.001$^{\beta\bullet}$ P_D= 0.737$^{\beta}$
	Z	16.60 (29.31)	4.96 (10.40)	12.48 (16.64)	13.73 (27.83)	P_A=0.862$^{\mu}$ P_B= 0.221$^{\mu}$ P_C= 0.002$^{\beta\bullet}$ P_D= 0.351$^{\beta}$
Peak frequency (Hz.)	X	6.10 (1.98)	6.46 (1.37)	6.13 (1.65)	6.42 (1.35)	P_A=0.986$^{\mu}$ P_B= 0.758$^{\mu}$ P_C= 0.490$^{\beta}$ P_D= 0.364$^{\beta}$
	Y	6.08 (2.19)	5.82 (1.39)	5.86 (1.81)	5.74 (1.60)	P_A= 0.495$^{\mu}$ P_B= 0.758$^{\mu}$ P_C= 0.472$^{\beta}$ P_D= 0.687$^{\beta}$
	Z	6.02 (1.81)	5.80 (1.67)	5.44 (1.94)	5.74 (1.60)	P_A= 0.253$^{\mu}$ P_B= 1.000$^{\mu}$ P_C= 0.556$^{\beta}$ P_D= 0.408$^{\beta}$

$^{\beta}$; Wilcoxon sign rank test, $^{\mu}$; Mann-Whitney U test, *; statistically significant, parameters were reported in mean (SD);X; x-axis, Y; y-axis, Z; z-axis

A; comparison parameters between 2 groups at before intervention

B; comparison parameters between 2 groups at during intervention

C; comparison parameters between before and during intervention among Parkinson's glove group

D; comparison parameters between before and during intervention among Sham glove group

Table 15: Outcome measurement between before and during interventions among both groups

Clinical measurement	Parkinson's glove		Sham glove		*p*-value
	Before intervention	During intervention	Before intervention	During intervention	
ON UPDRS- tremor	6.40 (2.77)	5.00 (2.80)	6.90 (2.31)	6.55 (2.41)	P_A= 0.620$^{\mu}$ P_B= 0.096$^{\mu}$ P_C<0.001$^{\beta*}$ P_D= 0.096
ON UPDRS-III tremor	4.90 (2.49)	3.50 (2.50)	5.05 (2.03)	4.70 (2.15)	P_A= 0.883$^{\mu}$ P_B= 0.102$^{\mu}$ P_C<0.001$^{\beta*}$ P_D= 0.102$^{\beta}$
ON UPDRS-resting tremor of the most affected hand	2.40 (0.68)	0.95 (0.76)	2.40 (0.59)	2.15 (0.87)	P_A= 0.947$^{\mu}$ P_B<0.001$^{\mu}$ P_C<0.001$^{\beta*}$ P_D= 0.059$^{\beta}$
Reduction of ON UPDRS-tremor during intervention	1.47 (0.74)		0.33 (0.72)		P<0.001$^{\mu*}$
Reduction of ON UPDRS-III tremor during intervention	1.60 (0.63)		0.33(0.72)		P<0.001$^{\mu*}$
ON UPDRS-resting tremor of the most affected hand during intervention	1.53 (0.74)		0.20 (0.56)		P<0.001$^{\mu*}$
Pulse amplitude (mA)		7.60 (3.59)		0.00 (0.00)	P<0.001$^{\mu*}$
Pulse width (μs)		150.00 (0.00)		0.00 (0.00)	P<0.001$^{\mu*}$
Pulse frequency (Hz.)		50.00 (0.00)		0.00 (0.00)	P<0.001$^{\mu*}$
Stimulation periods (seconds)		28.15 (22.19)		0.00 (0.00)	P<0.001$^{\mu*}$
Tremor reduction periods after off intervention (seconds)		116.90 (96.11)		0.00 (0.00)	P<0.001$^{\mu*}$
Visual analog scale		2.40 (1.04)		0.70 (0.65)	P<0.001$^{\mu*}$
Visual analog scale at 1month F/U		0.40 (0.50)		0.30 (0.47)	P=0.602$^{\mu}$

$^{\beta}$: Wilcoxon sign rank test; $^{\mu}$: Mann-Whitney U test; *: statistically significant, parameters were reported in mean (SD); X: x-axis; Y: y-axis; Z: z-axis

A: comparison parameters between 2 groups at before intervention; B: comparison parameters between 2 groups at during intervention

C: comparison parameters between before and during intervention among Parkinson's glove group; D: comparison parameters between before and during intervention among Sham glove group

VAS: visual analog pain scale; UPDRS: The Unified Parkinson's Disease Rating Scale; UPDRS-tremor score (a sum sore of the UPDRS tremor items 16, 20 and 21) is a range between 0- 32 points; UPDRS III-tremor score (a sum sore of the UPDRS tremor items 20 and 21) is a range between 0- 28 points, UPDRS resting tremor of the most affected hand (item 20) is a range between 0- 4 points.

We found moderate correlation between reduction in UPDRS tremor scores of the most affected hand and tremor parameters, including percentage of RMS angular velocity reduction for X-, Y-, Z-axis (*r*=0.427, r=0.558, and r=0.424, respectively), and percentage RMS angular displacement reduction for X- and Z-axis (*r*=0.434 and r=0.328, respectively), and percentage peak magnitude reduction for X- and Y-axis (*r*=0.437 and r=0.377, respectively) (Table 16). We also observed moderate to high correlation between pulse amplitude and a number of tremor parameters, including reduction of UPDRS tremor score (*r*=0.686) and reduction of UPDRS tremor score of the most affected hand (*r*=0.745). Similarly, stimulation times highly correlated with reduction of UPDRS tremor score of the most affected hand (*r*=0.662). We also observed that greater tremor reduction times were strongly correlated with higher pulse amplitude (r=0.750) and longer stimulation times (r=0.804).

No report of any serious side effects, including paresthesia, severe pain, burning pain, or fatigue at the placement sites during stimulation or at one-month follow-up visit was found. However, an erythematous rash under a surface electrode placement area with mild increasing of skin temperature at the same area was found in 5 patients in the Parkinson's glove group after a prolong, continuous stimulation more than 30 minutes, which all of them were female patients (Figure 30).

Table 16: Correlation results between clinical and tremor parameters

Parameters	Pulse amplitude	Stimulation periods	Tremor reduction periods	Delta UPDRS-tremor	Delta UPDRS-tremor, affected hand
Percentage RMS angular velocity reduction X-axis	0.469* (0.002*)	0.469* (0.002*)	0.643* (<0.001*)	0.331* (0.037*)	0.427* (0.006*)
Percentage RMS angular velocity reduction Y-axis	0.429* (0.006*)	0.429* (0.006*)	0.510* (0.001*)	0.391* (0.013*)	0.558* (<0.001*)
Percentage RMS angular velocity reduction Z-axis	0.390* (0.013*)	0.390* (0.013*)	0.504* (0.001*)	0.365* (0.002*)	0.424* (0.006*)
Percentage RMS angular displacement reduction X-axis	0.553* (<0.001*)	0.553* (<0.001*)	0.544* (<0.001*)	0.407* (0.009*)	0.434* (0.005*)
Percentage RMS angular displacement reduction Y-axis	0.407* (0.009*)	0.407* (0.009)	0.496* (0.001*)	0.218 (0.177)	0.295 (0.065)
Percentage RMS angular displacement reduction Z-axis	0.377* (0.016)	0.377* (0.016)	0.414* (0.008*)	0.295 (0.064)	0.328* (0.039*)
Percentage peak magnitude reduction X-axis	0.455* (0.003*)	0.455* (0.003*)	0.639* (<0.001*)	0.327* (0.039*)	0.437* (0.005*)
Percentage peak magnitude reduction Y-axis	0.482* (0.002*)	0.482* (0.002*)	0.561* (<0.001*)	0.256 (0.111)	0.377* (0.016*)
Percentage peak magnitude reduction Z-axis	0.311 (0.051)	0.311 (0.051)	0.521* (<0.001*)	0.213 (0.187)	0.281 (0.079)
Delta UPDRS-tremor	0.686* (<0.001*)	0.616* (<0.001*)	0.550* (<0.001*)	1.000 (*p*-value=NA)	0.830* (<0.001*)
Delta UPDRS-tremor, affected hand	0.745* (<0.001*)	0.662* (<0.001*)	0.651* (<0.001*)	0.804* (<0.001*)	1.000 (*p*-value=NA)
Pulse amplitude	1.000 (*p*-value=NA)	0.816* (<0.001*)	0.750* (<0.001*)	0.686* (<0.001*)	0.745* (<0.001*)
Stimulation periods	0.816* (<0.001*)	1.000 (*p*-value=NA)	0.804* (<0.001*)	0.616* (<0.001*)	0.622* (<0.001*)
Tremor reduction periods	0.750* (<0.001*)	0.804* (<0.001*)	1.000 (*p*-value=NA)	0.550* (<0.001*)	0.651* (<0.001*)

*: Statistically significant; All correlation were analyzed by Spearman's rho correlation; R :correlation coefficient; Values in parenthesis are shown as *p*-value. EMS: electrical muscle stimulation; RMS: root mean square of the angular velocity; UPDRS: The Unified Parkinson's Disease Rating Scale; Delta UPDRS-tremor: UPDRS-tremor score before intervention – UPDRS-tremor score during intervention; Delta UPDRS-tremor, hand: UPDRS resting tremor of the most affected hand before intervention–UPDRS resting tremor of the most affected hand during intervention.

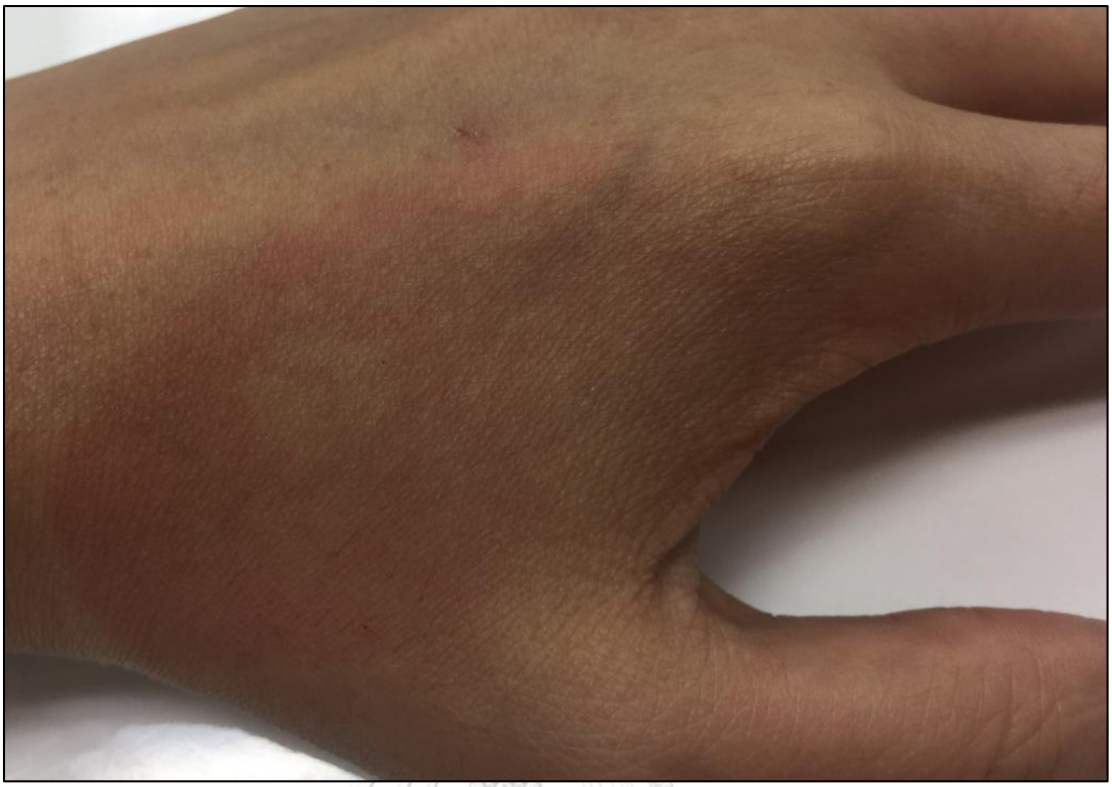

Figure 30: An erythematous rash under a surface electrode placement area with mild increasing of skin temperature at the same area was found in among Parkinson's glove group after stimulation.

CHAPTER V

DISCUSSION

This chapter of results composed of two parts which phase 1 and phase 2. Each part was listed as follows:

Part 1: Phase 1 (Pilot, descriptive study)

Part 2: Phase 2 (Device development and A Randomized-controlled trial; single-blind, sham-controlled)

Part 1:

The objective of the phase 1 study was to identify of the most suitable stimulation protocols for tremor reduction and to seek out for the best location for placement of the surface electrodes

Part 2:

The objective of the phase 2 study was to develop the Parkinson's glove and test for its efficacy in reduction of resting hand tremor among the tremor-dominant PD patients with medically intractable tremor.

Phase 1

From the phase 1 study, we found an effectiveness of EMS in reduction of resting hand tremor without significant adverse events that consistent with prior studies (30, 36). Tremor attenuation lasted for 10 seconds after stimulation; however, no direct quantitative measurement was obtained. We first evaluated the efficacy of EMS in the suppression of classic rest tremor in PD with a standard tremor analysis device and we provided constant stimulation parameters. Most of the PD patients presented with obvious tremor at resting position within a classic tremor frequency range. The classical range of tremor in PD frequency is between 4 to 7 Hz. The resting tremors showed completely disappeared after we requested the patients to change their hand position from rest to posture. This finding confirmed the diagnosis of classic rest tremor as described in established tremor criteria.(1)

After subjecting the hand muscle to electrical muscle stimulation (EMS), we observed a significant tremor amplitude reduction (determined by significant reduction in RMS and peak magnitude) that was consistent with the clinical tremor scale rating by UPDRS, but not with tremor frequency and Q parameter. This finding may help to further develop knowledge about the exact physiological mechanism of EMS in the suppression of rest tremor. The pathophysiology of tremor could provide a basis for understanding the complex connection between central and peripheral mechanisms (2, 6, 52, 53). Externally mechanical conditions at a periphery with intense stimuli (such as EMS) do not stop the tremor, but it may modify the tremor frequency and amplitude via peripheral mechanisms (2, 52, 60, 63).

The peripheral mechanism, including mechanical resonance (such as bone, joint, and soft tissue) and feedback resonance (represented as reflex mechanism), demonstrated the propensity to generate or modulate the tremor (53). In the past, we believed that reflex mechanisms might be responsible for assisting the driving mechanism and sustaining movement (53, 63). Therefore, some prior studies endeavored to evaluate and measure the effectiveness of peripheral nerve stimulation (62-64). However, the reflexes' mechanism may not be restricted in terms of stretch reflex and should be expanded to include the group of muscles involving with tremor (60). We believed that muscles had a propensity to generate tremor itself, and directly strong mechanical condition to muscle might be able to reset tremor evenly driven from central origin.

In phase 1 study, we postulate that muscle may be able to modulate the overall tremor, and that is described in 2 hypotheses. The first hypothesis relates to the efficacy of EMS-induced muscle contraction that may reset the peripheral mechanisms by the stretch reflex transfer along an Ia afferent in muscle fibers that are connected with spinal cord. This connection may be able to suppress the tremor via the function of inhibitory interneurons that are called Renshaw cells. Renshaw cells are located in the spinal cord and represented a negative feedback mechanism (73, 74). EMS may play a role in this connection by resetting the oscillatory mechanisms and resulting in the transient reduction of tremor. The second hypothesis proposes that EMS may provide persistent tetanic contraction of the hand muscles (causing 'dystonia-like'

hand posture) that masks the underlying tremor. However, from finding of 4 patients who presented with reduction of EMG signal without tetanic contraction of dorsal interrossei muscle, the EMS may be able to suppress tremor by serving itself as strong peripheral stimuli to reset the tremor mechanisms, more than providing the persistent tetanic contraction to the hand muscles until masking the underlying hand tremor. However, the tremor frequency which was generally dominated from central oscillators was unchanged, we believed that the effected of EMS may be restricted to modulate mainly within an interaction between central and peripheral, but may not have beyond effect to modulate the firing neuron in basal ganglia that responsibility for determining tremor frequency.

The strength of our phase 1 study could be able to recruit a high number of subjects to determine the effectiveness of electrical stimulation in rest tremor reduction without established adverse events compared with previous studies on various types of tremors, in which their data usually presented inconclusively due to small subject sample-size (30, 36, 72, 75, 76). Based on our findings, we propose that electrical stimulation may provide additional effectiveness for other therapies or provide an alternative treatment in rest tremor reduction among PD patients with medically intractable tremor.

Phase 2

The phase 2 study supported an efficacy of EMS in suppresion of resting tremor in 40 Parkinson's disease patients in a randomized, pair-designed, sham-controlled study by using a Parkinson's Glove and a shame glove, without any serious adverse events were observed. All of PD patients had obviously tremors at rest position with mean of tremor frequency was within the range of frequency between 4 to 7 Hz, and these rest tremors become almost disappeared after suggesting these patients to change their hand position form rest to postural positions, confirmatory the diagnosis of classic rest tremor (Class 1 tremor) in PD as described in an established tremor criteria.(1)

After wearing the Parkinson's glove, the patients had significant tremor amplitude reduction, which determined by UPDRS tremor score, UPDRS tremor score

of the most affected hand, and the RMS in all X-, Y-, and Z-axis, while remained unchanged in their tremor frequency. The reduction of the UPDRS tremor score of the most affected hand was significantly correlated with reduction in tremor severity form the RMS of the 3-axis gyroscope, especially with Y-axis. Additionally, we found greater tremor reduction times had highly correlated with higher in pulse amplitude, and longer in stimulation times. Therefore, the significant effectiveness of Parkinson's glove in reduction of parkinsonian tremor had been found during our study, which correlated in both clinical and objective measurements. These findings supported an effectiveness of EMS in tremor reduction, and the greater tremor reduction could be obtained if higher in pulse amplitude, and longer stimulation times were conducted.

The finding from phase 2 study supported the existing hypothesis on how explain the exact mechanism of EMS in suppression of rest tremor. Since resting tremor oscillators are located in basal ganglia (2, 77), the significant tremor reduction in every axis while the tremor frequencies remained unchanged supported the hypothesis of peripheral mechanisms that can modulate without directly resetting the central oscillators. Additionally, the variation of the extended period of a transient tremor reduction period after giving off the stimulation had found in our study which was correlated with the effect of pulse amplitude and stimulation times could support the mainly mechanism of peripheral mechanisms in tremor reduction rather than the central mechanisms (2, 77).

This study established the treatment options for resting tremor in PD that should not be limited to treatments that targeted on tremor circuitry involving basal ganglia and cerebellum as in medications or surgery. Currently, the evidence of EMS for tremor reduction is stronger and tremor can be modulated peripherally, using of an appropriate electrical current pulse. This method could lessen tremor severity and provided safety to patients with drug resistant PD tremor. Surface EMS may become the promising candidate for treatment in this groups of patients.

The strength of the phase 2 study is the ability to conduct a randomized-controlled trial with sham stimulation control in a selected number of PD patients with the homogeneous tremor patterns as confirmed by tremor analysis. Regards to the power of placebo effect in medical trials, we underwent a double-blind, randomized,

sham-controlled trial in order to exclude any placebo effects from EMS which we found a clear evidence for tremor reduction in both clinical ratings and tremor dynamics. Therefore, a large, RCT study to determine an efficacy of the Parkinson's glove with an improvement of an effect size and define for a specific stimulation protocol might be needed to further conduct. We propose that an EMS-based Parkinson's glove could provide an additional effectiveness in tremor reduction without a serious adverse event. This innovative device might become as an alternative treatment option for the tremor-dominant PD patients who are medically intractable or unwilling to undergo the more invasive surgical procedure such as the deep brain stimulation.

CHAPTER VI

CONCLUSION, LIMITATION AND SUGGESTIONS

Limitation of studies

There were some inherent limitations to our study. Firstly, the recruitment from a single-center and the small number of study participants. Secondly, the pain experienced by some subjects who receive EMS may uncover the double-blind design of this study and possible side effect with an erythematous rash was limited patient's usage for a long period. Thirdly, the efficacy has been limited to resting tremor among PD patients. Therefore, the results cannot be generalized to other forms of parkinsonian tremor as well as other tremor syndromes. Finally, the design of the Parkinson's glove that covers the whole hand and fingers may not be practical for using in a long period of time due to the heat and limitation of fine finger movement for daily activity. Perhaps exposure of the fingers may be more conducive.

Suggestion of studies

1. To avoid the possible side effects with pain from the Parkinson's glove that might be related with stimulation or heat, the automatic stimulation if tremor frequencies reach the targeted tremor frequency might reduce this sided effect.

2. A new design of the Parkinson's glove that partially covers over the dorsum and palm of hand likely reduced the possible side effect with increasing heat and allows freely movable fingers.

3. Development of the Parkinson's glove hardware with a stable EMS module might reduce this sided effect.

Future directions

Further study of possible resetting mechanisms relative to peripheral and central mechanisms, large randomized controlled trials to confirm the efficacy of Parkinson's

glove using improved performance and stimulation protocols is being planned. Treatment with a Parkinson's glove might be expanded to the others tremor syndromes such as others parkinsonian tremors (re-emerging tremor or walking tremor), essential tremor and dystonic tremor. In this study, the benefits of EMS in intractable tremor reduction seem to outweigh the minimal risks.

Conclusions

Our 2 studies provide an evidence of the efficacy of EMS in tremor reduction among PD patients with medically intractable rest tremor. Our study provides more insight into the role of peripheral mechanisms in tremorogenesis. Because of EMG results and unchanged in tremor frequency during EMS, we believed that the effected of EMS may be restricted to modulate mainly within an interaction between central and peripheral, but may not have beyond effect to modulate the firing neuron in the basal ganglia that responsibility for determining tremor frequency. Targeting peripheral mechanisms with strong stimuli may not be able to stop, but could modulate its tremor amplitude, even if it is mainly driven from a central origin. The efficacy of EMS in suppressing intractable resting hand tremor among PD patients was confirmed in a subsequent, randomized sham-controlled trial. The greater tremor reduction without serious adverse events was observed in Parkinson's glove group compared to a sham glove group. Parkinson's glove might become a therapeutic option for tremor reduction among those PD patients who had medically intractable resting tremor.

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APPENDIX

Appendix-A

The United Kingdom Parkinson's Disease Brain Bank Criteria

Step 1. Diagnosis of Parkinsonian Syndrome

Bradykinesia and at least one of the following

- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communication hydrocephalus on imaging study
- Negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease (Three or more required for diagnosis of definite Parkinson's disease in combination with step one)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

Appendix-B

TRIG classification for essential tremor

A. Definite essential tremor
1. Inclusion criteria (i) Tremor: Bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is visible and persistent. (Tremor of other body parts may be present in addition to upper limb tremor. Bilateral tremor may be asymmetric. Tremor is reported by patient to be persistent, although the amplitude may fluctuate, tremor may or may not produce disability. (ii) Duration: Longer than 5 years 2. Exclusion criteria (i) Other abnormal neurologic signs (with the exception of the presence of tremor and Froment's sign. the full neurologic examination should be normal for age)(ii) Presence of known causes of enhanced physiologic tremor. (iii) Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state (Many drugs acting on the central nervous system can produce tremor as a side effect. In people, drug-induced tremor is most often in the form of action tremor. Subjects should be drug-free for a period exceeding the known biologic effect of the drug.) (iv) Direct or indirect trauma to the nervous system within **3** months preceding the onset ***of*** tremor (This include5 head injury [direct or indirect]. and peripheral injury, if the anatomic distribution is the same as that of the tremor.) (v) Historic or clinical evidence of psychogenic origins of tremor. (The definition of psychogenic tremor is itself open to debate. Clinical features that may suggest this are unphysiological variations [>I Hz] in tremor frequency, unusual and inconsistent behavioral characteristics, and spontaneous remission. Psychiatric or social factors [multiple somatization. secondary gain. litigation or compensation pending] may support the diagnosis of psychogenic tremor.) (vi) Convincing evidence of sudden onset or evidence of stepwise deterioration
B. Probable essential tremor
1. Inclusion criteria: (i) The same as those for definite essential tremor. (Tremor may be confined to body parts other than hands. These may include head and postural tremor of the legs. However, abnormal posture of the head would suggest the presence of dystonic head tremor.) (ii) Duration longer than 3 years 2. 2. Exclusion criteria: (i) The same as for definite essential tremor. (ii) Primary orthostatic tremor (isolated. high-frequency [14-18 Hz] bilaterally synchronous tremor of the lower limbs on standing). (iii) Isolated voice tremor (because of the clinical difficulty of separating essential tremor of the voice from the speech disturbances of laryngeal dystonia and other dystonias of the vocal apparatus). (iv) Isolated position-hpecific or task-specific tremors. including occupational tremors and primary writing tremor. (v) Isolated tongue or chin tremor
C. **Possible essential tremor**
1. Inclusions (i) Type I a. Subjects who satisfy the criteria of definite or probable essential tremor but exhibit other recognizable neurologic disorders. such as parkinsonism, dystonia, myoclonus, peripheral neuropathy. or restless leg syndrome. b. Subjects who satisfy the criteria of definite or probable essential tremor but exhibit other neurologic sipnh of uncertain significance not sufficient to make the diagnosis of a recognizable neurologic disorder. Such signs may include mild extrapyramidal features, such as hypomimia, decreased arm swing, or mild bradykinesia. (ii) Type II Monosymptomatic and isolated tremors of uncertain relation to essential tremor. This includes position-specific and task-specific tremors, such as occupational tremors, primary writing tremor, primary orthostatic tremor, isolated voice tremor, isolated postural leg tremor, and unilateral postural hand tremor. 2. Exclusions The exclusions are the same as items *2 A* under Definite essential tremor. A further form of classification could be whether the tremor is familial or presumed sporadic.

Appendix-C

Proposed diagnostic criteria for dystonic tremor

Tremor in a body part affected by dystonia

1. Tremor in an extremity or body part that is affected by dystonia.
2. Focal tremors, usually with irregular amplitudes and variable frequency (mainly less than 7 Hz)
3. Mainly postural/kinetic tremors and usually not seen during complete rest.

Appendix-D

The Unified Parkinson's disease Rating Scale

I. Mentation, Behavior and Mood

1. Intellectual Impairment

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living

(for both "on" and "off")

5. Speech

0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting Food and Handling Utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in Bed and Adjusting Bed Clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (Unrelated to Freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when Walking
0 = None.
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory Complaints Related to Parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. Motor Examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face."
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at Rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands
(Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. Complications of Therapy
(In the past week)

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. Clinical Fluctuations

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

C. Other Complications

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis? (Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

Appendix-E

Consent form

 คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย	AF 10-05/4.0 เอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัย

การพัฒนาและประเมินประสิทธิภาพของถุงมือที่มีการติดตั้งอุปกรณ์ตรวจจับอาการสั่นและอุปกรณ์ระงับอาการสั่นก้วนการกระตุ้นกล้ามเนื้อมือด้วยไซฟฟ้า ในผู้ป่วยโรคพาร์กินสันที่มีอาการสั่นเป็นอาการเด่นและอาการสั่นไม่ตอยสนองต่อการรักษาด้วยยารับประทาน (Development of Parkinsonian's glove for detection and suppression of hand tremor at rest among the tremor-predominant Parkinson's disease patients with medically intractable tremor)

วันให้คำยินยอม วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้า นาย/นาง/นางสาว.....

ที่อยู่.....ได้อ่านรายละเอียดจากเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัยวิจัยที่แนบมาฉบับวันที่..... และข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยโดยสมัครใจ

ข้าพเจ้าได้รับสำเนาเอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัยที่ข้าพเจ้าได้ลงนาม และ วันที่ พร้อมด้วยเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัย ทั้งนี้ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย ระยะเวลาของการทำวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัย และแนวทางรักษาโดยวิธีอื่นอย่างละเอียด ข้าพเจ้ามีเวลาและโอกาสเพียงพอในการซักถามข้อสงสัยจนมีความเข้าใจอย่างดีแล้ว โดยผู้วิจัยได้ตอบคำถามต่าง ๆ ด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ารับทราบจากผู้วิจัยว่าหากเกิดอันตรายใด ๆ จากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่เสียค่าใช้จ่าย (และระบุด้วยว่าจะได้รับการชดเชยจากผู้สนับสนุนการวิจัยหรือไม่.....)

ข้าพเจ้ามีสิทธิที่จะบอกเลิกเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ โดยไม่จำเป็นต้องแจ้งเหตุผล และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคหรือสิทธิอื่น ๆ ที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะเมื่อได้รับการยินยอมจากข้าพเจ้าเท่านั้น บุคคลอื่นในนามของบริษัทผู้สนับสนุนการวิจัย คณะกรรมการพิจารณาจริยธรรมการวิจัยในคน สำนักงานคณะกรรมการอาหารและยาอาจได้รับอนุญาตให้เข้ามาตรวจและประมวลข้อมูลของข้าพเจ้า ทั้งนี้จะต้องกระทำไปเพื่อวัตถุประสงค์เพื่อตรวจสอบความถูกต้องของข้อมูลเท่านั้น โดยการตกลงที่จะเข้าร่วมการศึกษานี้ข้าพเจ้าได้ให้คำยินยอมที่จะให้มีการตรวจสอบข้อมูลประวัติทางการแพทย์ของข้าพเจ้าได้

ผู้วิจัยรับรองว่าจะไม่มีการเก็บข้อมูลใด ๆ เพิ่มเติม หลังจากที่ข้าพเจ้าขอยกเลิกการเข้าร่วมโครงการวิจัยและต้องการให้ทำลายเอกสารและ/หรือ ตัวอย่างที่ใช้ตรวจสอบทั้งหมดที่สามารถสืบค้นถึงตัวข้าพเจ้าได้

ข้าพเจ้าเข้าใจว่า ข้าพเจ้ามีสิทธิ์ที่จะตรวจสอบหรือแก้ไขข้อมูลส่วนตัวของข้าพเจ้าและสามารถยกเลิกการให้สิทธิในการใช้ข้อมูลส่วนตัวของข้าพเจ้าได้ โดยต้องแจ้งให้ผู้วิจัยรับทราบ

ข้าพเจ้าได้ตระหนักว่าข้อมูลในการวิจัยรวมถึงข้อมูลทางการแพทย์ของข้าพเจ้าที่ไม่มีการเปิดเผยชื่อ จะผ่านกระบวนการต่าง ๆ เช่น การเก็บข้อมูล การบันทึกข้อมูลในแบบบันทึกและในคอมพิวเตอร์ การตรวจสอบ การวิเคราะห์ และการรายงานข้อมูลเพื่อวัตถุประสงค์ทางวิชาการ รวมทั้งการใช้ข้อมูลทางการแพทย์ในอนาคตหรือการวิจัยทางด้านเภสัชภัณฑ์ เท่านั้น

 คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย	AF 10-05/4.0 เอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัย

ข้าพเจ้าได้อ่านข้อความข้างต้นและมีความเข้าใจดีทุกประการแล้ว ยินดีเข้าร่วมในการวิจัยด้วยความเต็มใจ จึงได้ลงนามในเอกสารแสดงความยินยอมนี้

.....ลงนามผู้ให้ความยินยอม

(.....) ชื่อผู้ยินยอมตัวบรรจง

วันที่ .....เดือน.....พ.ศ.....

การจัดการกับตัวอย่างทางชีวภาพ

☐ ไม่มีตัวอย่างชีวภาพ

☐ มีแต่ไม่มีการขอเก็บ

☐ มีและขอเก็บตัวอย่างชีวภาพที่เหลือไว้เพื่อการวิจัยในอนาคต

ข้าพเจ้า ☐ ยินยอม

☐ ไม่ยินยอม

ให้เก็บตัวอย่างชีวภาพที่เหลือไว้เพื่อการวิจัยในอนาคต

.....ลงนามผู้ให้ความยินยอม

(.....) ชื่อผู้ยินยอมตัวบรรจง

วันที่ .....เดือน.....พ.ศ.....

ข้าพเจ้าได้อธิบายถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการไม่พึงประสงค์หรือความเสี่ยงที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด ให้ผู้เข้าร่วมในโครงการวิจัยตามนามข้างต้นได้ทราบและมีความเข้าใจดีแล้ว พร้อมลงนามลงในเอกสารแสดงความยินยอมด้วยความเต็มใจ

.....ลงนามผู้ทำวิจัย

(.....) ชื่อผู้ทำวิจัย ตัวบรรจง

วันที่ .....เดือน.....พ.ศ.....

.....ลงนามพยาน

(.....) ชื่อพยาน ตัวบรรจง

วันที่ .....เดือน.....พ.ศ.....

Appendix-F

The certificate honored for the Best Abstract of the Year Award (academic center) from The Royal College of Physicians of Thailand, 2015

ราชวิทยาลัยอายุรแพทย์แห่งประเทศไทย

มอบให้เป็นเกียรติแก่

แพทย์หญิงอรอนงค์ จิตรกฤษฎาทุต

สำหรับผลงานวิจัย รางวัลชนะเลิศ

การประกวดผลงานวิจัย Best Abstract of the Year Award ประเภท Academic Center

สำหรับการประชุมวิชาการประจำปี ครั้งที่ ๓๑

เมื่อวันที่ ๒๑ เดือน มีนาคม พุทธศักราช ๒๕๕๘

ประธานราชวิทยาลัยอายุรแพทย์ฯ

ประธานคณะอนุกรรมการวิจัย

เลขาธิการราชวิทยาลัยอายุรแพทย์ฯ

Our phase 1 study was received the Best Abstract of the Year Award (academic center) from The Royal College of Physicians of Thailand during the 31st RCPT Annual Meeting, March 26-29, 2015, Bangkok. We felt extremely honored and appreciative for receiving this significant award, which boosted our confidence and inspiration to develop an innovation for helping PD patients with medically intractable tremor.

Appendix-G

The phase 2 study received the trophy award from the Cerebos Award 2016.

Our phase 2 study was received the Cerebos Award 2016 during the Cerebos Award Conference, November 23-24, 2016, Bangkok (Fig. 4.14). We felt extremely honored and appreciative again for receiving this significant award and its grant which boosted our confidence to develop a new prototype of a Parkinson's glove that is lesser in the side effect and more compatible to use.

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