Study Title:

Evaluating The Efficacy And Tolerability Of The Oral Combination Of Alpha Lipoic Acid And Vitamin B Complex Preparation In Carpal Tunnel Syndrome: a single center, randomized, double-blind, placebo-controlled trial.

Protocol Development Phase 1: 17th January 2023

Protocol Revisions Version 2 : 2nd February 2023

Protocol Revisions Version 3 : 1st April 2023

Study initiation date: 1st December 2023

Study completion date: 30th September 2024

Protocol by:

Dr. Anna Misyail Abdul Rashid
Internal Medicine Physician and Neurologist
Neurology Department, FPSK/HPUPM,
Universiti Putra Malaysia.
Version 3 :1/4/2023

1. **Research title:**

   Evaluating The Efficacy And Tolerability Of The Oral Combination Of Alpha Lipoic Acid And Vitamin B Complex Preparation In Carpal Tunnel Syndrome: a single center, randomized, double-blind, placebo-controlled trial.

2. **Principal investigator:**

   Dr. Anna Misyail Abdul Rashid

3. **Co-investigators**

   Dr. Nur Alya Zainal
   Assoc. Prof. Dr. Wan Aliaa Wan Sulaiman
   Dr. Azliza Ibrahim
   Dr. Abdul Hanif Khan Yusof Khan
   Dr. Janudin Baharin
   Dr. Collin Looi
   Pn. Musmarlina Omar

4. Introduction

Background of the study

Carpal Tunnel Syndrome (CTS) is one of the commonest peripheral neuropathy caused by compression of the median nerve at the level of the wrist. The patients typically present with symptoms of tingling and numbness of the hand in the distribution of the median nerve, which may range in its clinical severity (1). Treatment for CTS ranges from non-pharmacological and medical for mild to moderate cases, to surgical interventions in more severe cases. It poses an important workplace issue, causing significant loss of time from work and high medical cost, approximating to almost $30,000 for each injured worker (2).

Problem statement and study rationale

For mild to moderate CTS, literature shows conflicting evidence on efficacy of non-surgical approach, which includes non-pharmacologic treatment such as splinting, physiotherapy and ultrasound; as well as medical therapy which includes oral antiepileptics, combination of vitamins and local steroid injections. As such, current evidence do not recommend one treatment over the other (2,3). Of these available treatments, many patients do not like the invasive nature of steroid injections and long term side effect of steroids, and thus opt for oral

medications. For severe CTS however, the preferred treatment is surgical treatment via carpal tunnel release as the response to medical therapy maybe suboptimal (2).

Among the oral medications, anti-epileptic drugs such as gabapentin may cause significant side effect (i.e drowsiness) at a higher dose, which prevents its widespread use. As such, combination of vitamins and alpha lipoic acid are becoming more preferred due to its lower rate of side effects. We seek to determine the efficacy of Bionerv, which is an oral combination of alpha lipoic acid (300mg), methylcobalamin (500mcg), Vitamin B1 (39mg) and Vitamin B6 (8mg) on mild to moderate CTS.

5. Research Question(s)

a. What are the socio-demographic profiles of patients with CTS in Malaysia?
b. Are oral combination of alpha lipoic acid and vitamin B preparations for the treatment of CTS safe?
c. Does oral administration of a combination of alpha lipoic acid and vitamin B preparations improve symptoms of CTS?
d. Does oral administration of a combination of alpha lipoic acid and vitamin B preparations improve electrodiagnostic tests in patients with CTS?

6. Research objectives and hypotheses

General objective

a. To determine the oral efficacy of a combination of alpha lipoic acid and vitamin B preparations in treatment of mild to moderate CTS.

Specific objectives

a. To describe the socio-demographic profile of patients with mild to moderate CTS in Malaysia.
b. To examine the efficacy of oral combination of alpha lipoic acid and vitamin B in reducing symptoms of mild to moderate CTS.
c. To determine if treatment with of oral combination of alpha lipoic acid and vitamin B is associated with improvement of NCS in patients with mild to moderate CTS.

d. To evaluate tolerability of oral combination of alpha lipoic acid and vitamin B in patients with mild to moderate CTS

7. Literature review

CTS is due to local compression of the median nerve, causing conduction blocks within large myelinated nerve fibers. It reduces capillary blood flow to the median nerve through the swelling of the synovial tissue of the tendon, commonly at the level of the wrist (4). The reduction of blood flow in the endoneural capillary system then induces alteration in the nerve structure that is provoked by endoneural edema, venous congestion, ischemia, and subsequent metabolic abnormalities (5). It has been proposed that ischemia/reperfusion injury of the median nerve results in oxidative stress and inflammation of the subsynovial connective tissue, which play an important role in the evolution of idiopathic CTS.

Common associations include metabolic causes such as diabetic mellitus, hypothyroidism, rheumatoid arthritis and pregnancy; although up to 60% of cases may be idiopathic (6). The clinical severity of CTS may vary from numbness and tingling; to pain sensation in the distribution of the median nerve. Although CTS is a clinical diagnosis, NCS is often carried out to determine the severity of CTS as well as to have a quantitative measure of the physiological function of the median nerve, that is able to guide direction if treatment and provide prognosis for patients (7).

Mild to moderate CTS is usually treated conservatively, either with non-pharmacologic treatments (i.e : splinting, electrotherapy, physiotherapy) or medical treatment with oral anti-epileptics, analgesia, steroids or even local steroid injections. Although local steroid injections may reduce inflammation and is hypothesized to reduce local edema and subsequently compression neuropathy, systemic review fails to show sustained long term effect as compared to other treatment modalities (6). In contrast, severe CTS is usually treated surgically with carpal tunnel release (8).

The long term side effects from steroids, that includes Cushing's syndrome, resistant hypertension, acne and osteoporosis has caused clinicians to shy away from these medications**,** especially considering the chronic nature of CTS. There has been a recent interest in using oral

antiepileptics such as gabapentin by means of its efficacy in modulation of neuropathic pain of other etiology. However, results of randomized controlled trials failed to show sustained efficacy with regards to symptom control in CTS (2,9).

As such, the pharmacological treatment of CTS has been directed to neuroprotection, aiming to limit the injury and damage to the median nerve. Previously, vitamin preparations such vitamin B6 preparations were proven to mitigate neuronal problems as well as bridging anaesthesia to decrease pain threshold. However existing studies yield heterogenous outcomes, mainly due to limitations of study design and small sample size (9,10).

Of late, alpha lipoic acid (ALA) has gained interest due to its powerful scavenging activity, to metabolic support of nerve cells, as well as modulation of neurotrophic cytokines release. All together, these mechanisms reduce inflammation, improve functioning of the nerve fibers and promote neuroprotection and neuroregeneration (11,12). In a study involving rats, administration of ALA has shown to reduce infarct size, thus demonstrating its neuroproliferative and neurorestorative benefits. In this study, treatment with ALA increased proliferative cell lineage by 5 fold (13). Another study established neuroprotective property of ALA by means of increased expression of the proliferating cell nuclear antigen, which is a key regulatory protein for DNA repair. This study also exhibited anti-apoptotic of ALA against neurotoxicity which is a key aspect in cellular functioning (14).

This has led to the hypothesis of improved outcome if the medications are combined in a single preparation. As such, Bionerv was developed as a combination drug (Alpha Lipoic Acid (300mg), Methylcobalamin (500mcg), Vitamin B1 (39mg) and Vitamin B6 (8mg)) to simplify administration for patients. We would like to determine the efficacy of oral combination of alpha lipoic acid and vitamin B preparations versus placebo; with regards to symptom control and improvement on NCS parameters. Both groups are allowed to undergo physiotherapy which includes splinting, ultrasound and other non-pharmacologic treatment, as determined necessary by the clinician. The concomitant treatment that the patient is receiving is also recorded.

8. Conceptual framework

Intervention : Bionerv

Alpha Lipoic Acid (300mg), Methylcobalamin (500mcg), Vitamin B1 (39mg) and Vitamin B6 (8mg); two tablets once daily.

Placebo : Maltodextrin, Microcrystalline Cellulose , Tricalcium Phosphate , Silicon Dioxide , Magnesium stearate; two tablets once daily.

Independent variable

Age

Gender

Anthropometric data

(weight, height, body mass index)

Comorbidities

Severity of CTS

Laterality of CTS

Primary outcome

Electrodiagnostic improvement of median nerve on NCS:

i- Distal sensory latency (DSL)
ii- Sensory action potential (SNAP)
iii- Conduction velocity (CV)
iv- Distal motor latency (DML)
v- Compound Motor Action Potential (CMAP)

Secondary outcome

Tolerability of oral combination of alpha lipoic acid and vitamin B preparations

Boston Carpal Tunnel Questionnaires (BCTQ)

i-symptom severity scale (SSS)

ii-functional status scale (FSS)

Pain score (Visual analogue scale; VAS)

Quality of life score (SF 36 questionnaire)

9. Research methodology

This is a single center, randomized, double-blind, placebo-controlled trial conducted in University Putra Malaysia Teaching Hospital (HPUPM).
Study period : 6 months
Date of first subject enrolment :1st December 2023
Date of last subject completed: 30th September 2024

Target population : patients with symptoms of CTS
Sampling frame : all patients referred to Neurology Department for clinical and electrodiagnostic examination of CTS.
Sampling unit : patients with mild to moderate CTS
Sampling method : universal sampling

All patients that presented to Neurology Clinic or Neurophysiology Laboratory with symptoms of hand numbness/tingling or pain in the median nerve distribution undergo a thorough physical examination based on current international guideline for diagnosis and assessment of CTS (15). This includes :

- Personal characteristics (eg, age, sex, weight, height, body mass index)
- Range of motion of hand/wrist
- Observation of deformity, swelling, atrophy, skin trophic changes
- Manual muscle testing of the upper extremity (eg, examine for muscular atrophy, especially in the thenar muscle group), pinch/grip strength
- Sensory examination
- Provocative tests (eg, Phalen test, Tinel sign, median nerve compression test, reverse Phalen test)

These patients then undergo an NCS, to determine the severity of CTS. The NCS will be carried out using the machine *Natus, USA, Synergy on Nicolet EDX NCS EMG EP System*. The NCS protocol follows the American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation (AAN/AANEM/AAPMR) guidelines for diagnosis of CTS (15), which includes electrodiagnostic examination of :

- Sensory NCS studies to the median nerve with distal latency compared to the ulnar and radial nerve
- Median motor nerve conduction studies

If the clinical and NCS studies fulfil the diagnosis of CTS and fits the inclusion criteria for the study, they undergo randomisation into the treatment group or the control group. The treatment group will receive oral combination of alpha lipoic acid and vitamin B preparations, while the control group will receive a placebo. The treatment will be carried out for 6 months.

Treatment group will receive oral combination of alpha lipoic acid and vitamin B. Composition: Alpha Lipoic Acid (300mg), Methylcobalamin (500mcg), Vitamin B1 (39mg) and Vitamin B6 (8mg), 2 tablets taken once daily (Bionerv).

Control group will receive placebo drug. Composition: Maltodextrin, Microcrystalline Cellulose , Tricalcium Phosphate , Silicon Dioxide , Magnesium stearate, 2 tablets taken once daily.

Inclusion and exclusion criteria

Inclusion criteria

- Age more than 18 years old
- Subjects with symptoms and physical examination of CTS
- Fulfil the electrodiagnostic criteria of mild to moderate CTS, defined based on the Padua Scale (16):
    - Minimal : abnormal segmental and comparative tests only
    - Mild : abnormal digit/wrist sensory nerve conduction velocity (SNCV) and normal distal motor latency (DML)
    - Moderate : abnormal digit/wrist sensory nerve conduction velocity (SNCV) and abnormal distal motor latency (DML)

Exclusion criteria

- Pregnant or breast feeding women
- Patients with history of trauma in the dominant hand
- Patients with symptoms of CTS but has normal NCS

- Patients with electrodiagnostic criteria of severe or extreme CTS as defined in the Padua scale (16):
    - severe : absence of sensory response (SNAP) and abnormal distal motor latency (DML)
    - extreme : absence of motor (CMAP) and sensory responses (SNAP)
- Patients who are taking traditional or complementary medication for CTS

Study procedure

The patients were randomized to receive oral combination of alpha lipoic acid and vitamin B; Bionerv (alpha lipoic acid; 300mg, methylcobalamin; 500mcg, vitamin B1; 39mg and vitamin B6; 8mg), 2 tablets once daily or placebo drug (maltodextrin, microcrystalline cellulose, tricalcium phosphate, silicon gioxide, magnesium stearate) 2 tablets once daily.

During visit 1, a thorough history and physical examination were done, and demographic data was collected. Afterward, the patients were required to answer three sets of self-administered questionnaires: Boston Carpal Tunnel Questionnaire (BCTQ), Visual analogue score (VAS) and SF-36. The BCTQ is a specific questionnaire for assessing CTS that consists of two distinct scales, the Symptom Specific Scale (SSS) which has 11 items and the Functional Status Scale (FSS) containing 8 items. Each scale generates a final score ranging from 1 to 5, with a higher score indicating greater disability and poor symptoms control. BCTQ is a reliable questionnaire to assess CTS owing to its high cross-cultural adaptation and multilingual validity and reliability (17-18). The VAS is a visual scale with 0 scored as “no pain” and 10 as “worst pain imaginable” and serves as an excellent tool for pain score with excellent validity and reproducibility (19-20). The SF-36 is a quality-of-life questionnaire that comprises of 36 questions covering eight domains of health which are; Physical Functioning (PF), Role Limitations due to Physical Health, Role Limitations (RL) due to Emotional Problems (RE), energy/fatigue, emotional well-being, social functioning, pain, and general health (GH) where a higher score indicates a better outcome (21). After the administration of these questionnaires, they will be subjected for a nerve conduction study (NCS) to determine the severity of CTS. The NCS were performed by the same trained personnel to ensure consistency and

accuracy. A Patient-Reported Questionnaire to monitor any side effects were used to assess the tolerability of the drugs.

The patients were reassessed at Visit 2 (3 months post-treatment) and Visit 3 (6 months post-treatment). During each visit, they underwent physical examination, NCS, and were required to complete the three sets of questionnaires (BCTQ, VAS, and SF-36). They were also required to fill in the form regarding the side effects of the treatments. The investigators made a phone call and sent reminder message at the 6th and 18th week to ensure compliance, medication adequacy and follow up review. During the study, patients were allowed to undergo the standard of care treatment at our center such as physiotherapy.

Fig. 1 The visual analogue scale (VAS).

The quality of life questionnaires have become of recent interest. Although the BCTQ and VAS score are able to scale functional disability and pain, they are not constructed to determine the quality of life which encompasses emotional and social domains of everyday function. The SF 36 measures two distinct physical and mental dimension. It also can good validity and reproducibility and is useful in our clinical setting (22).

Randomisation

Patients' randomisation is done by an independent statistician using a random number generating programme (www.randomizer.org) into two groups (treatment and placebo) using mixed block randomization technique at the ratio of 1:1 i.e. group A and group B. The independent statistician will then code the treatment and the placebo into group A and group B. The written allocation of assignment for each participant with an identification number (code) was sealed in a brown opaque envelope. This envelope will be opened by the researcher on recruitment of a participant. The key coding to the allocation will be revealed by the independent statistician at the completion of the study. An independent statistician will label the treatment and placebo group as either group 'A' or group 'B'.

The participants are assigned to either treatment or placebo arm in a parallel intervention mode.

The principle of random allocation is employed to assign the participants to an intervention (i.e. treatment) and a control (i.e. placebo arm). To achieve an unbiased comparison group and to have a balanced randomization, permuted block randomization with a varying block size is used for the study. The sample size estimated for the study is 76. Hence, there are 19 blocks with a block size of four participants each and one-to- one allocation ratio is used. Random sequence generation is done with the help of a Research Randomizer, an online random number generator (Urbaniak & Plous, 2014). An external member, who is not directly involved in the study, generates the sequence. To have a strict implementation of the generated random sequence, the concealed allocation is achieved using sequentially numbered, opaque and sealed envelopes (SNOSEs). An aluminium foil is kept inside the envelope to prevent possible chances of deciphering. An external member, who is not directly involved in the study, would prepare the SNOSEs.

The final code is only known to the statistician and the document will be stored in a secure locked safe. The following information will be recorded during the randomization; study ID (assigned during the study initiation), investigator password (assigned during the initiation), subjects screening status, date of informed consent signed by subject, subject's ID no (e.g., Last 4 digits of IC), upon successful randomization, the subjects will be assigned randomization number and treatment. The subject's ID no. and randomization no. will be documented on the Patient Enrolment Log and Patient Identification List.

Blinding and emergency unblinding procedures

The participants and outcome assessor of the study is blinded about the allocation status of the participants. In the setting of an adverse event (AE), for which knowledge of the identity of the test drug is necessary to manage the subject's condition, the sealed emergency code key for that subject may be broken and the test drug identified by the medical monitor. The medical monitor will have a set of sealed emergency code keys (one for each subject) kept in a secured location and he/she will be accessible at all times by telephone. The medical monitor is medical officer who is working in the hospital. He/she is familiar with hospital system and is also aware of the study protocol. Should emergency unblinding be required, the investigator will call the medical monitor who will break the emergency code key for that subject, identify the test coil and inform the investigator. A detailed report with the date and reason for identifying the study drug will

be prepared by the medical monitor and attached to the case report form. This report must be signed by the medical monitor and the investigator. All unused sealed code keys will be accounted for at the end of the study.

Except in the case of emergency, the treatment blind will be maintained until all subjects have completed the treatment and the database has been cleaned and locked. Any broken code will be clearly justified and explained by a comment on the case report form, along with the date on which the code was broken.

Sample size estimation

Sample size calculation was performed using the study published by Pajardi et al. Sample size was calculated based on improvement to limitations of everyday activity among the patients with CTS as the outcome parameter (1.07 ± 1.27 vs 0.83 ± 0.81). The marginal error (α) was set at 0.05.

Sample size: $\frac{2\ SD\ ^2(Z\alpha/2 + Z\ \beta)\ ^2}{d^2}$

SD – standard deviation = from previous studies or pilot study

Zα/2 = Z 0.05/2 = Z 0.025 = 1.96 (From Z table) at 80 % power at type 1 error of 5 %

Z β = Z 0.20 =0/842 (From Z table) at 80 % power

d= effect size = difference between mean value

So, the formula:

sample size: $\frac{2\ SD^2(1.96 + 0.84)^2}{d^2}$

SD = 1.27

Za/2 = 1.96

Zb = 0.84

$d^2 = (0.81)^2 = 0.66$

$n = \frac{2(1.27)^2 (1.96+0.84)^2}{(0.81)^2}$

$$= \frac{2\ (1.61)\ (7.84)}{0.66}$$

= **38 in each arm (Total 76 patients)**

Operational definitions

Primary outcome measure

The primary outcome was the electrodiagnostic improvement of the median nerve on NCS before the before the intervention (visit 1) and at three-months (visit 2) and six- months (visit 3). The NCS parameters that are analysed were:

1. Distal sensory latency; DSL (normal value for DSL <3.5ms)
2. Sensory nerve action potential; SNAP (normal value for SNAP >2.5 μV)
3. Conduction velocity; CV (normal value for CV >50m/s)
4. Distal Motor Latency; DML (normal value for DSL <4ms)
5. Compound muscle action potential; CMAP (normal value for CMAP>4.0 mV).

Secondary outcomes measures

- Tolerability and safety of oral combination of alpha lipoic acid and vitamin B preparations
- The improvement of scores in Boston Carpal Tunnel Questionnaires (BCTQ) by the SSS scale prior to the intervention, at 3 months and at 6 months
- The improvement of scores in Boston Carpal Tunnel Questionnaires (BCTQ) by the FSS scale prior to the intervention, at 3 months and at 6 months
- The improvement of pain scores in VAS prior to the intervention, at 3 months and at 6 months
- The improvement of quality of life score SF 36 prior to the intervention, at 3 months and at 6 months

Data collection

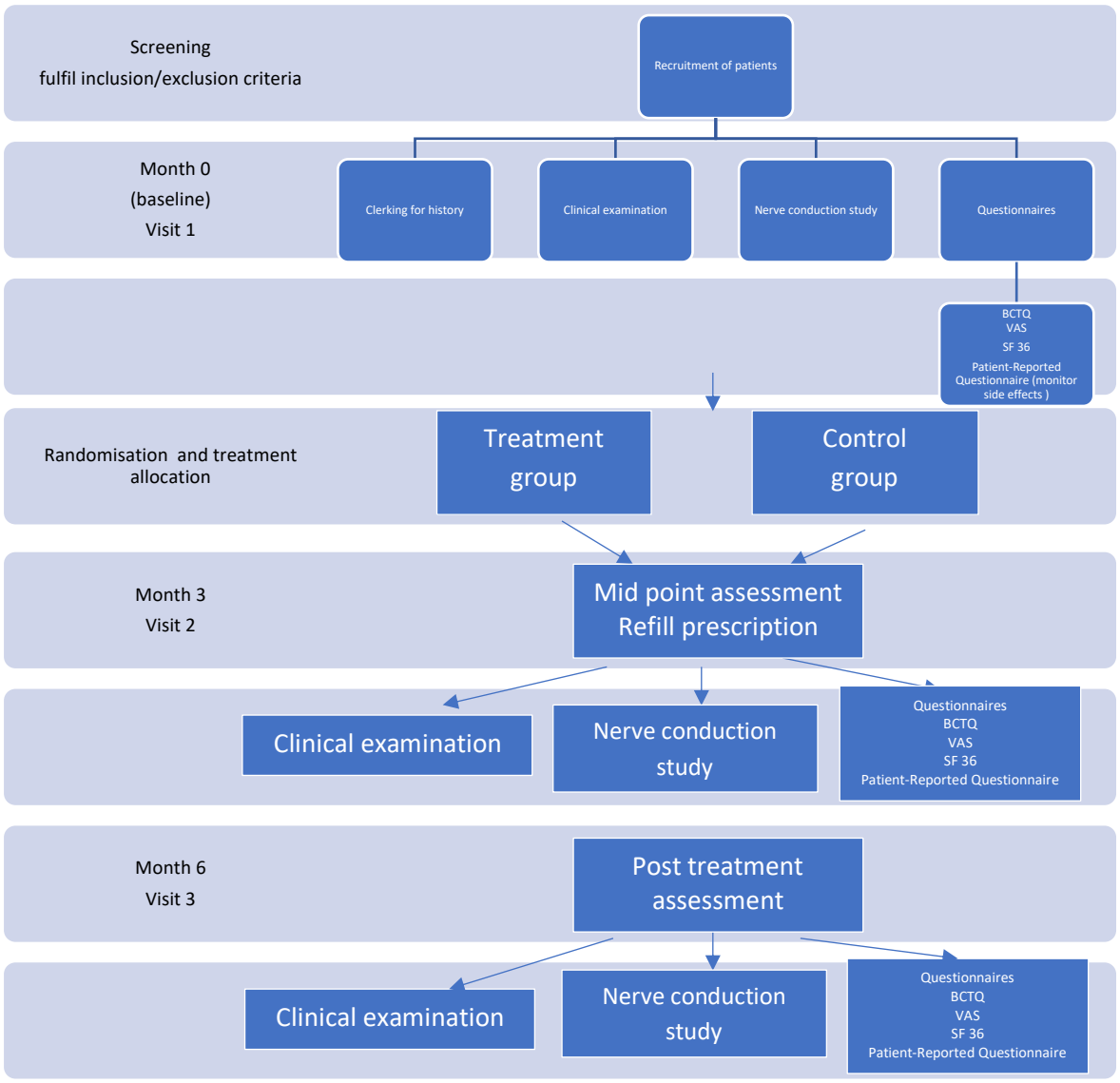
Protection of human rights is the utmost priority for researchers. We obtain informed consent from all participants in this research. The consent process included giving full and comprehensible information about the research and clear assurance of their voluntary

participation. Beneficence is the essence of concern for the well-being of the participants whereby the risk of harm was the least possible.

Privacy of patients are obtained in a respectful manner whereby every patient is given the confidence to directly disclose information to the researcher in a peaceful and non-threatening manner. Data collection sheets and questionnaires will not contain patients identification such as name, IC number, phone number, address or RN. Specific ID was used on the data collection sheet to ensure patient privacy.

All information obtained in this study will be kept and handled in confidential manner, in accordance to applicable laws and regulations of the country. Data management will be conducted using appropriate database and validation programmes, with standard practice to secure information for all computer based data storage (i.e encryption and password protection). Data collected may be retained for re-use in further studies. The standard duration of three to five years with strict security of research records will be adhered and destroyed after this period of time. Relevant bodies such as JKEUPM will have access to the study data.

Study flowchart



10. Data analysis

Analyses sets

All randomised subjects will be included in the analysis.

Baseline Comparability

True randomisation, concealed location and adequate sample size planned for this study will ensure enough baseline comparability between groups (treatment and control group). Additionally, a table of baseline characteristics of participants in each group, without between-group statistical comparisons will be included. This data will be analysed to determine whether any characteristics were imbalanced enough to have influenced the outcomes of the study

Efficacy Analysis

Analyses were performed on an intention-to-treat basis. The primary treatment comparisons of benefit include all eligible patients. Both eligible and ineligible patients are included in the analyses and compared by treatment assignment when an intent-to-treat analysis is specifically indicated.

Safety Analysis

The summaries of tolerability include all patients who received any study treatment; those who did not receive study treatment are not included in these summaries. The safety population comprised all randomized patients who received at least one treatment dose and was based on the actual treatment received.

11. Ethical consideration

The study was performed in accordance with the Declaration of Helsinki and has received ethical approval from Ethics Committee for Research Involving Human Subjects in University Putra Malaysia (Ref: JKEUPM-2022-984).

12. Declaration of conflict of interest

The investigators declare no conflict of interest.

The sponsor of this study (Brego Life Sciences Sdn. Bhd.) is sponsoring the study including the placebo treatment and insurance coverage. The company is aware of the randomized, blinded and controlled nature of the study, thus understands that the results may be neutral and adverse events may occur. However, this should not hinder research and publication process of evidence based medicine.

13. References

1. Ostergaard PJ, Meyer MA, Earp BE, Meyer MA. Non-operative Treatment of Carpal Tunnel Syndrome. 2020;
2. Keith MW, Masear V, Amadio PC, Andary M, Barth RW, Graham B, et al. Treatment of carpal tunnel syndrome. J Am Acad Orthop Surg. 2009;17(6):397–405.
3. Jiménez del Barrio S, Bueno Gracia E, Hidalgo García C, Estébanez de Miguel E, Tricás Moreno JM, Rodríguez Marco S, et al. Conservative treatment in patients with mild to moderate carpal tunnel syndrome: A systematic review. Neurol (English Ed [Internet]. 2018;33(9):590–601. Available from:

http://dx.doi.org/10.1016/j.nrleng.2016.05.015

4. Pajardi G, Bortot P, Ponti V, Novelli C. Clinical usefulness of oral supplementation with alpha-lipoic acid, curcumin phytosome, and B-group vitamins in patients with carpal tunnel syndrome undergoing surgical treatment. Evidence-based Complement Altern Med. 2014;2014.
5. Monroy Guízar EA, García Benavides L, Ambriz Plascencia AR, Pascoe González S, Totsuka Sutto SE, Cardona Muñoz EG, et al. Effect of Alpha-Lipoic Acid on Clinical and Neurophysiologic Recovery of Carpal Tunnel Syndrome: A Double-Blind, Randomized Clinical Trial. J Med Food. 2018;21(5):521–6.
6. Hernández-Secorún M, Montaña-Cortés R, Hidalgo-García C, Rodríguez-Sanz J, Corral-De-toro J, Monti-Ballano S, et al. Effectiveness of conservative treatment according to severity and systemic disease in carpal tunnel syndrome: A systematic review. Int J Environ Res Public Health. 2021;18(5):1–34.
7. Sonoo M, Menkes DL, Bland JDP, Burke D. Nerve conduction studies and EMG in carpal tunnel syndrome: Do they add value? Clin Neurophysiol Pract [Internet]. 2018;3:78–88. Available from: https://doi.org/10.1016/j.cnp.2018.02.005
8. Bahar-Moni AS, Abdullah S, Fauzi H, Chee-Yuen SY, Abdul-Razak FZ, Sapuan J. Demographics of patients undergoing carpal tunnel release in an urban tertiary hospital in Malaysia. Malaysian Orthop J. 2019;13(3):53–9.
9. Hui ACF, Wong SM, Leung HW, Man BL, Yu E, Wong LKS. Gabapentin for the treatment of carpal tunnel syndrome: A randomized controlled trial. Eur J Neurol. 2011;18(5):726–30.
10. Talebi M, Andalib S, Bakhti S, Ayromlou H, Aghili A, Talebi A. Effect of vitamin B6 on clinical symptoms and electrodiagnostic results of patients with carpal tunnel syndrome. Adv Pharm Bull. 2013;3(2):283–8.
11. Di Geronimo G, Caccese AF, Caruso L, Soldati A, Passaretti U. Treatment of carpal tunnel syndrome with alpha-lipoic acid. Eur Rev Med Pharmacol Sci. 2009;13(2):133–9.
12. Passiatore M, Perna A, De-Vitis R, Taccardo G. The use of alfa-lipoic acid-r (Ala-r) in patients with mild-moderate carpal tunnel syndrome: A randomised controlled open label prospective study. Malaysian Orthop J. 2020;14(1):1–6.
13. Choi KH, Park MS, Kim HS, et al. Alpha-lipoic acid treatment is neurorestorative and promotes functional recovery after stroke in rats. Mol Brain. 2015;8:9.

14. Li DW, Wang YD, Zhou SY and Sun WP. α-lipoic acid exerts neuroprotective effects o n neuronal cells by upregulating the expression of PCNA via the P53 pathway in neuro degenerative conditions. Mol Med Rep. 2016;14: 4360-4366.

15. Keith MW, Masear V, Chung K, Maupin K, Andary M, Amadio PC, et al. Diagnosis of carpal tunnel syndrome. J Am Acad Orthop Surg. 2009;17(6):389–96.

16. Padua L, LoMonaco M, Gregori B, Valente EM, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurol Scand. 1997;96(4):211–7.

17. Abdullah A, Che Daud AZ, Dahlan A, Muhammad Nawawi RF. Cross-Cultural Adaptation, Validity and Reliability of Malay Version Boston Carpal Tunnel Questionnaire. Environ Proc J [Internet]. 2019;4(12):149. Available from: http://dx.doi.org/10.21834/e-bpj.v4i12.1936

18. Lue YJ, Lu YM, Lin GT, Liu YF. Validation of the Chinese version of the boston carpal tunnel questionnaire. J Occup Rehabil. 2014;24(1):139–45.

19. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain [Internet]. 2016; 13:67–75. Available from: http://dx.doi.org/10.1016/j.sjpain.2016.06.012

20. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res. 2008;31(2):165–9

21. Sow WT, Wee HL, Wu Y, Tai ES, Gandek B, Lee J, et. Al. Normative data for the Singapore English and Chinese SF-36 version 2 health survey. Amm Aced Med Singapore. 2014;43(1); 15-23.

22. Musa AF, Yasin MSM, Smith J, Yakub MA, Nordin R Bin. The Malay version of SF-36 health survey instrument: testing data quality, scaling assumptions, reliability and validity in post-coronary artery bypass grafting (CABG) surgery patients at the National Heart Institute (Institut Jantung Negara—IJN), Kuala Lumpur. Health Qual Life Outcomes [Internet]. 2021;19(1):1–11. Available from: https://doi.org/10.1186/s12955-020-01658-9

17. Leite JCDC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskelet Disord. 2006;7.

18. Abdullah A, Che Daud AZ, Dahlan A, Muhammad Nawawi RF. Cross-Cultural Adaptation, Validity and Reliability of Malay Version Boston Carpal Tunnel

Questionnaire. Environ Proc J [Internet]. 2019;4(12):149. Available from: http://dx.doi.org/10.21834/e-bpj.v4i12.1936

19. Lue YJ, Lu YM, Lin GT, Liu YF. Validation of the Chinese version of the boston carpal tunnel questionnaire. J Occup Rehabil. 2014;24(1):139–45.
20. Mody GN, Anderson GA, Thomas BP, Pallapati SCR, Santoshi JA, Antonisamy B. Carpal tunnel syndrome in Indian patients: Use of modified questionnaires for assessment. J Hand Surg Eur Vol. 2009;34(5):671–8.
21. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain [Internet]. 2016;13:67–75. Available from: http://dx.doi.org/10.1016/j.sjpain.2016.06.012
22. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res. 2008;31(2):165–9.