An ultrasound-guided percutaneous electrical nerve stimulation regimen devised using finite element modeling promotes functional recovery after median nerve transection

Xiao-Lei Chu1,*, Xi-Zi Song2,*, Yu-Ru Li3, Zi-Ren Wu4, Qi Li5, Qing-Wen Li3, Xiao-Song Gu3,*, Dong Ming2,4,*

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Abstract

Percutaneous electrical nerve stimulation of an injured nerve can promote and accelerate peripheral nerve regeneration and improve function. When performing acupuncture and moxibustion, locating the injured nerve using ultrasound before percutaneous nerve stimulation can help prevent further injury to an already injured nerve. However, stimulation parameters have not been standardized. In this study, we constructed a multi-layer human forearm model using finite element modeling. Taking current density and activated function as optimization indicators, the optimal percutaneous nerve stimulation parameters were established. The optimal parameters were parallel placement located 3 cm apart with the injury site at the midpoint between the needles. To validate the efficacy of this regimen, we performed a randomized controlled trial in 23 patients with median nerve transection who underwent neurorrhaphy. Patients who received conventional rehabilitation combined with percutaneous electrical nerve stimulation experienced greater improvement in sensory function, motor function, and grip strength than those who received conventional rehabilitation combined with transcutaneous electrical nerve stimulation. These findings suggest that the percutaneous electrical nerve stimulation regimen established in this study can improve global median nerve function in patients with median nerve transection.

Key Words: finite element modeling; median nerve transection; nerve regeneration; neurorehabilitation; percutaneous electrical nerve stimulation; peripheral nerve injury; randomized controlled trial

Introduction

The median nerve, also known as the ‘eye of the hand,’ is a mixed nerve that plays a crucial role in hand function. If damaged, the ability to abduct and oppose the thumb may be lost because of thenar muscle paralysis, which can result in severe hand dysfunction and impairment of activities of daily living (Robinson, 2000; Wang et al., 2019). Neurotmesis of the median nerve is more common at the forearm or wrist because it is located superficially in these areas. Neurotmesis is characterized by complete nerve transection and complete loss of function. Recovery cannot occur without surgical intervention. Even when surgery is performed, outcomes are generally poor. Even when surgery is performed, outcomes are generally poor.

Electrical stimulation is effective for accelerating nerve regeneration and functional recovery. Recent studies have demonstrated that low-intensity electrical stimulation of the proximal nerve stump can promote nerve regeneration (Gordon, 2016; Gordon and English, 2016; Choi et al., 2021; Wang et al., 2021) by increasing the expression of brain-derived neurotrophic factor (Kimura et al., 2019). It also promotes proliferation of Schwann cells and myelin formation during regeneration (Wan et al., 2010; Zhang et al., 2013). Promoting expression of genes associated with growth factors (Geremia et al., 2007) and neurotrophin signaling pathways (English et al., 2007) may also be therapeutic mechanisms that underly electrical stimulation.

Electrical stimulation is categorized according to stimulation depth as transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and peripheral nerve stimulation. PENS is also known as subcutaneous electrical stimulation. In TENS, electrical stimulation electrodes are placed on the skin and electrical impulses are applied to stimulate nerve endings. PENS is performed by placing stimulation electrodes around peripheral nerves in the subcutaneous space. Low-frequency TENS immediately after injury improves peripheral nerve regeneration (Cavalcante Miranda de Assis et al., 2014). PENS has a greater therapeutic effect than TENS because of its higher precision and targeting; however, it is associated with higher incidence of complications and greater cost. PENS also provides stronger electrical stimulation than TENS but requires an operation for electrode implantation. In a study comparing four types of contacts in electrodes implanted in resected sciatic nerves, Yu et al. (2019) found that point contact had the same effect as whole-circle contact. We speculate that electroacupuncture, as a type of PENS, is a low-cost and valid therapy. Electroacupuncture is a widely studied therapy that combines the use of acupuncture points and needles that conduct electrical current to produce...
therapeutic effects. Peripheral nerve injury (PNI) can be treated using acupuncture (Fei et al., 2019; Zhang et al., 2019). However, electrical needles are often placed at points selected based on acupuncture meridians and collateral points. The reported effectiveness of acupuncture-induced nerve injury is 1.3%; therefore, the precision of needle placement can be improved (Melchart et al., 2004; Xu et al., 2013).

Ultrasoundography is a non-invasive imaging technique used to measure skeletal muscle and nerve architecture in the upper and lower limbs (Romero-Morales et al., 2020; Schreiber et al., 2020). We believe that ultrasound-guided identification and classification of nerve damage before PENS can help prevent acupuncture-induced nerve damage. Acquiring a consistent response to electrical needle stimulation can be difficult because differences in electrode placement, skin movement, and physiological variables produce different tissue conductance. Therefore, a feasible clinical regimen that can adapt to these differences is required to produce repeatable results. Gordon et al. (2010) reported that proximal nerve stimulation can promote nerve regeneration. Brook et al. (2002) found that the duration of 20 Hz electrical stimulation to the proximal nerve for 1 hour can temporarily compress staggered regeneration and that this stimulation synchronized distal stump reinnervation. Other studies (Koo et al., 2018; Zhang et al., 2018) have shown that stimulating electrodes placed both proximal and distal to the injury site can improve nerve regeneration and lead to better functional outcomes. At present, the optimal stimulation site in injured nerves is unknown. Moreover, previous electrical stimulation studies have focused on the number of early regenerated nerves and general morphology rather than basic electrical theory. Therefore, several computer models have been developed to explore the effects of these variations and avoid exhaustive human testing. In one, the human lower leg has been constructed using a finite element model to simulate the generation of an acutaneous nerve fibers during percutaneous tibial nerve stimulation and to test feasibility of peripheral nerve stimulation in a human model (Elder and Yoo, 2018; Roointan et al., 2020).

In this study, we established a finite element model based on existing models and validated it using experimental data. The model parameters were as follows: discontinuous wave, frequency 20 Hz, and width 0.2 ms. PENS was administered using the random number table method. Patient numbers were arranged in the order of inclusion and grouping was determined. Odd number cards and their corresponding patient names were put into the envelope of the experimental group, even number cards and their corresponding patient names were put into the envelope of the control group. The details of grouping were sealed in opaque envelopes by an independent researcher. This researcher was blinded to group allocation. Three patients in the experimental group and four in the control group voluntarily withdrew during the study. Finally, 23 participants (8 women and 15 men) were included in the analysis.

Interventions
Patients in the TENS group received conventional rehabilitation treatment and TENS; those in the PENS group received conventional rehabilitation treatment and PENS. Conventional rehabilitation treatment included: 1) movement training: passive and active extension/flexion of fingers, elbows, and shoulders (aiming to prevent joint ankylosis and muscle atrophy); 2) manipulative therapy (aiming to reduce muscle cramps, eliminate local swelling, promote adhesions, and relieve clinical symptoms); 3) occupational therapy; and 4) sensory training, including cold and hot sensory training, two-point discrimination training, and positioning training. Patients received conventional rehabilitation once a day for 1 hour, four times a week, for 5 consecutive weeks.

For patients in the TENS group, first, the site of median nerve recruitment was located and the distance from skin to nerve measured using ultrasonography (Sonosite S650; Shenzhen SonoScape Bio-Medical Technology Co., Ltd., Shenzhen, Guangdong Province, China) (Figure 3). Then two disposable sterilized stainless-steel acupuncture needles (0.3 mm × 40 mm; Beijing Keyuan Medical Device Manufactory, Beijing, China) were used to administer electrical stimulation with the SD-III acupuncture instrument (Hwato, Suzhou, China). Stimulation parameters were as follows: discontinuous wave, frequency 20 Hz, width 0.2 ms. Patients were put into the envelope of the experimental group; even number cards and their corresponding patient names were put into the envelope of the control group. The details of grouping were sealed in opaque envelopes by an independent researcher. This researcher was blinded to group allocation. Three patients in the experimental group and four in the control group voluntarily withdrew during the study. Finally, 23 participants (8 women and 15 men) were included in the analysis.

Table 1: Tissue material constants

| Material | Electrical conductivity (µS/m) | Electrical permittivity |
|----------|-------------------------------|------------------------|
| Skin     | 25                            | 8000                   |
| Fat      | 100                           | 20000                  |
| Blood    | 7000                          | 5197                   |
| Muscle   | 10000                         | 100000                 |
| Bone     | 830                           | 613                    |
| Nerve    | 6000                          | 100000                 |

PENS was modeled using two uninsulated stainless steel needle electrodes (cylinder, diameter = 0.3 mm, length = 40 mm). Simulations were run under conditions of constant current (0.3 V). The selected frequency was 20 Hz, which is thought to promote nerve regeneration (Gordon et al., 2009; Park et al., 2019). PENS was simulated by changing the position of the electrodes, leaving all other model parameters unchanged. Next, a finite element model was constructed to calculate current density and active function of the corresponding nerve fibers. The current density represents the current per unit section area. The second derivative of biological tissue’s electrical excitation function is negative. To calculate the best electrode location, we set three lines in the model: center line of nerve, forearm line of nerve, and line between two needles (Figure 2). The current density and active function values on the center line of nerve were calculated at different positions, distances, and angles. Finally, the optimal treatment regimen was determined by comparing the ratio of the current density and a active function on the line between two needles to the forearm line of nerve.

Clinical trial
This study was approved by the Human Research Ethics Committee of Tianjin Hospital (approval No. 2020-053) and registered in the Chinese Clinical Trial Registry (registration No. ChiCTR200003790) on August 12, 2020 (Additional file 1). All patients provided written informed consent (Additional file 2). Consolidated Standards of Reporting Trials guidelines were followed (Additional file 3).

Patients aged 10 to 70 years who were diagnosed with complete median nerve neurotmesis and underwent neuroorrhapy at Tianjin Hospital from September 1, 2020 to January 1, 2021 were eligible. Inclusion criteria were as follows: 1) complete median nerve transaction based on observation in surgery (the surgeon was a hand surgeon from Tianjin Hospital with rich experience in neurosurgery), 2) stable vital signs, 3) disease course < 2 months, 4) no previous electrical stimulation treatment, and 5) no metal allergy or intolerance to electroacupuncture stimulation. We excluded patients with heart disease, hypertension, tuberculosis, asthma, hepatitis, nephritis, serious metabolic disease (hyperthyroidism, hypothyroidism, scurvy or edema), and unstable upper extremity fracture. Patients taking drugs affecting muscle excitability and those with acute fever, diarrhea, or other acute disease were also excluded. Patients were able to voluntarily withdraw from the trial at any time. Based on published data (Gordon et al., 2010), a sample size of 20 patients was enough to prove a treatment effect. To account for patients lost to follow-up, we recruited 30 subjects and randomly assigned them to the PENS (n = 15) or TENS group (n = 15) using the random number table method. Patient numbers were arranged in the order of inclusion and grouping was determined. Odd number cards and their corresponding patient names were put into the envelope of the experimental group; even number cards and their corresponding patient names were put into the envelope of the control group. The details of grouping were sealed in opaque envelopes by an independent researcher. This researcher was blinded to group allocation. Three patients in the experimental group and four in the control group voluntarily withdrew during the study. Finally, 23 participants (8 women and 15 men) were included in the analysis.
Sensory function assessment

The median nerve provides sensory innervation to the radial portion of the palm, thumb and index finger, and half of the middle and ring fingers (Soldado et al., 2016). Sensory dysfunction is common in patients with PNI. Sensory function was assessed using the BMRC score, which grades from 0 to 5 (Shen and Zhu, 1996). Recovery above grade S2 was considered good. Grade was assigned to deep and superficial sensation and allodynia. Higher grade indicates higher level of functioning.

Global function

The functional median nerve subscore of the Chinese Society of Hand Surgery upper limb functional assessment was used to assess median nerve function (Pan et al., 2000). This scale does not require any special equipment, is easy to apply, and provides accurate and objective results. Four indicators are evaluated: strength of wrist and finger flexors and thumb opposition as well as sensory function. Each indicator is graded on a four-point scale; therefore, the minimum and maximum scores are 0 and 16, respectively. Higher score indicates better median nerve function.

The Disabilities of Arm, Shoulder, and Hand (DASH) score was also used to assess upper limb function and disability (Hudak et al., 1996). This score is based on a self-reported questionnaire and divided into two parts: activities of daily living and the effect of upper limb symptoms on sleep and self-satisfaction. Each item is rated on a five-point scale. 0 items in total. Total DASH score = (scale score – 30)/1.2. Higher scores indicate worse functioning. Patient functional assessment was performed before the first treatment (visit 1) and after the last treatment (visit 20) and the scores recorded. To avoid subjective errors, patients were examined by the same physiatrist (YRL or ZRW).

Statistical analysis

Statistical analyses were conducted using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Intergroup comparisons were performed using the independent-sample t-test. Intragroup comparisons were performed using the paired-sample t-test. Data are expressed as means ± standard deviation (SD). The Wilcoxon signed-rank test was used to compare categorical variables. BMRC score was compared using the Wilcoxon signed-rank test. P < 0.05 was considered significant.

Results

Finite element model results

Location of needles

Using the finite element model, we compared stimulation with both electrodes proximal to the injury site with stimulation using one electrode proximal to the injury site and the other electrode distal (Figure 6A and B). The latter caused a 131.54% increase in current density and higher nerve activation (Figure 6C); therefore, stimulation using one electrode proximal to the injury site and the other distal was considered superior.

Distance between needles

Next, we examined the optimal distance between needles (1–12 cm). Current density gradually declined with increased distance (Figure 6D). The current density increased considerably when the distance was 1 to 3 cm. Active function peaked at distances between 3 and 5 cm (Figure 6E). Current density distribution was then examined with the electrodes at different distances. As shown in Figure 7, a 3 cm distance resulted in a moderate current density. When considering the current density results alone, 3 cm was the better distance. To further validate these results, current distribution at different distances was simulated using the finite element model (Figure 8). We found that the current was parallel to the nerve when the distance was 3 cm. Combining the current density and active function data, we concluded that 3 cm was the optimal distance between needles and that the nerve injury site should be located at the midpoint between the needles.

Angle between the needles

Current density was relatively large when the angle between the needles was 0°, 15°, 30°, 45°, and 90° (Figure 9A). Nevertheless, active function was higher when the angle was 0°, 60°, 75°, and 90° (Figure 9B). 0° and 90° were considered the point of intersection of the two parameters. A current density distribution map is shown in Figure 10. Greater current flow parallel to the nerve resulted in stronger nerve activity. It was difficult to accept 90° because inserting needles at this angle would cause severe pain. Ultimately, 0° was considered the best angle.

Therefore, we concluded that the optimal needle parameters for PENS were parallel placement located 3 cm apart with the injury site at the midpoint between the needles. These parameters were used in the clinical trial portion of the study.

Results of clinical trial

Baseline characteristics

There were no significant differences in baseline data between the PENS and TENS groups (Table 2). The study flow chart is shown in Figure 11.

| Table 2 | Characteristics of patients with complete median nerve neurotmesis |
|---|---|
| Control group | Experimental group | P-value |
| Weight (kg) | 60.9±11.06 | 67.58±16.09 | 0.211 |
| Age (yr) | 35.55±13.06 | 36.83±12.95 | 0.815 |
| The time of injury (d) | 75.45±43.93 | 62.67±29.72 | 0.419 |
| Grip strength/weight | 0.0±0.00 | 0.01±0.08 | 0.302 |
| Before treatment | 0.02±0.03 | 0.08±0.10 | 0.048 |
| After treatment | 6.09±1.92 | 7.50±1.68 | 0.074 |
| Functional score of median nerve | 7.45±2.38 | 9.42±2.07 | 0.046 |
| Before treatment | 72.12±14.77 | 67.29±11.91 | 0.396 |
| After treatment | 66.36±20.41 | 47.99±13.54 | 0.022 |

Data are expressed as the mean ± SD. *P < 0.05, **P < 0.01, vs. before treatment (independent-sample t-test (intergroup)), paired-sample t-test (intragroup).
Figure 1 | Three-dimensional forearm model created using COMSOL Multiphysics® finite element software version 5.3 (COMSOL AB, Stockholm, Sweden).

Figure 2 | Geometry of the human forearm model. Cross-sectional (A) and three-dimensional (B) geometry of the human forearm. In (A), forearm tissues are represented as shown in the key. In (B), the nerve is blue. (C) The red line represents the center line of nerve. (D) The red line represents the forearm line of nerve and the blue line represents the line between two needles.

Figure 3 | An ultrasonographic image. The dotted green line is a cross-section of the median nerve. The dotted red line represents the distance from skin to nerve. An individualized depth plan was developed for each patient.

Figure 4 | Percutanous nerve stimulation.

Figure 5 | Transcutaneous electrical nerve stimulation.

Figure 6 | Locations and distance of the needles under finite element analysis. (A) Both electrical needles were placed proximal to the nerve injury site. The black arrows represent needle electrodes, the black segment represents the nerve, and the red segment represents the injury site. (B) One electrical needle is placed proximal to the injury site and the other distal. (C) Current density and action function ratios at different locations. (D) Current density ratio at different needle distances. (E) Active function ratio at different needle distances.

Figure 7 | Current density distribution with the electrodes at different distances. Current density distribution with interelectrode distances of 1 cm (A), 2 cm (B), 3 cm (C), and 4 cm (D). On the x-axis, the site of median nerve injury was plotted at 100. With distances of 1 cm and 2 cm, the current at the injury site was relatively high. With a 3 cm distance, current density was moderate. Current density was relatively low at 4 cm.

Figure 8 | Current distributions at 1 (A), 2 (B) and 3 (C) cm inter-needle distances. The curves represent the electric field lines at different needle distances in the forearm model; the arrows indicate the direction of current. The figure C shows that smaller arrows indicate decreased current density. However, arrow number and depth increase. Besides, it has more homogeneous distribution of current and more electric field lines parallel to the nerve compared with the A and B.

Figure 9 | Changes in current density and active function at different angles between the two needles. (A) The current density was relatively high when the angle between the two needles was 0°, 15°, 30°, 45°, and 90°. (B) The active function was relatively high when the angle was 0°, 60°, 75°, and 90°.
Our finite model indicated that a needle distance of 3 cm can achieve best therapeutic effect. Moreover, several studies have reported that a parallel field is more sensitive than an orthogonal field (Roth and Basser, 1990; Ju et al., 2020), which may be the reason a 0° angle between needles results in optimal active function. Finally, our finite model simulations suggested that the optimal needle parameters for PENS were parallel placement located 3 cm apart with the injury site at the midpoint between the needles.

In the clinical trial phase of the study, we compared treatment effects of PENS and TENS in patients who underwent neurography after median nerve transection. Compared with the TENS group, grip was significantly stronger in the PENS group after treatment. Therefore, PENS using stimulation parameters determined using a finite element model restored motor function to a greater degree than TENS. Both motor and sensory recovery as measured by their respective BMRC scores was also better in the PENS group. These results are similar to those reported in a previous study (Koetsier et al., 2020). However, BMRC assessments lack precision. The functional median nerve subscore was used to validate these results. The functional score includes measures of motor and sensory function as well as thumb and finger movement. The functional score findings were consistent with those obtained using the BMRC score: improvement was better in the PENS group.

We believe that PENS promotes not only medial nerve regeneration but also functional recovery. Outcome analysis after PNI in previous studies usually included only measures of nerve impairment such as sensory and motor function. Few studies have evaluated functional outcome or health-related quality of life. Therefore, we used the DASH score to evaluate upper limb function. The degree of improvement in upper limb function was greater in the PENS group than in the TENS group. These results are also consistent with those in previous studies (Gordon, 2016; Tang et al., 2016). Therefore, we believe that the PENS regimen used in this study can reduce disability and improve function of median nerve-innervated muscles in patients with median nerve injury. However, the degree of improvement of median nerve function was not significant after treatment compared with before treatment. We speculate that this may be related to weaker stimulation effects. Philip et al. (2020) found that patients with PNI report considerable disability and that pain is the strongest predictor of DASH score. A DASH score in patients with PNI can be predicted by higher pain and disability, we believe PENS can be used to alleviate neuropathic pain and reduce DASH score.

Previous studies were reported mainly from the viewpoint of physiology. Our study reported outcomes in the context of electrical stimulation. Our PENS regimen, in which electrical needles are parallel and located at both ends of the injured nerve at a distance of 3 cm, creates an electric field parallel to the nerve and maximizes current density and active function. Ultimately, this may help optimize treatment effects in patients with median nerve injury. Furthermore, PENS can transmit electricity subsequently through the skin and onward, is low-cost, and does not require electrode implantation.

In our future research, we plan to expand the sample size and observe long-term effects of the established percutaneous electrical nerve stimulation regimen. Additionally, we will investigate our PENS regimen in patients with other types of PNI. In conclusion, we have presented a PENS regimen for median nerve transection that was developed using element finite modeling and shown to be effective in a small clinical trial. We believe this regimen has potential for widespread clinical use pending confirmation in large-scale studies.

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Ethics Approval (Chinese).

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Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Additional files: Additional file 1: Ethics Approval (Chinese).

Additional file 2: Informed Consent Form (Chinese).
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