STUDY PROTOCOL with STATISTICS

Treatment for Ulnar Neuropathy at the Elbow - a Randomized Control Trial

NCT Number: NCT03651609

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Patients

From January 2019, consecutive patients with suspected UNE will be prospectively recruited in a single referral centre (Institute of Clinical Neurophysiology, University Medical Center Ljubljana, Slovenia). Inclusion criteria will be: (1) sensory loss in the 5th finger; (2) weakness of 2nd and 5th finger abduction; and (3) UNE confirmed and precisely localized by short-segment nerve conduction studies (NCSs) and US. Exclusion criteria will be: (1) previous elbow fracture or surgery; (2) sensory loss outside of the ulnar innervation area; (3) an ulnar nerve conduction block of > 20% in the elbow segment; (4) C8 radiculopathy, lower brachial plexopathy, or ulnar neuropathy at the wrist; (5) polyneuropathy or multiple mononeuropathy; (6) spinal cord anterior horn cell disorders (e.g., monomelic amyotrophy, amyotrophic lateral sclerosis).

The trial protocol will conform to CONSORT guidelines. Written informed consent will be obtained from all patients before their inclusion into the study. The trial was approved by the National Ethics Committee of Slovenia (Nr. 0120-497/2018/5) and was registered on the 27th of August 2018 at ClinicalTrials.gov (NCT03651609).

History and Clinical Neurologic Examination

The first examiner will collect demographic and clinical data using a standard questionnaire for assessment of UNE severity (UNEQ).[1] The UNEQ considers the patient's numbness and tingling of the last two fingers, elbow pain, and changes in these symptoms with elbow

position. It also evaluates hand weakness. Questionnaire items are graded as: 1 – absent, 2 – mild, 3 – moderate, 4 – severe, or 5 – very severe. The final UNEQ score is calculated as the mean of the nine items.[1] Patients will also report whether UNE symptoms: 1 – improved, 2 – remained unchanged, or 3 – worsened. The first examiner will also perform a focused neurological examination and graded: (1) muscle wasting of the first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles (0 – absent, 1 – mild, 2 – moderate or 3 – severe); (2) muscle strength of FDI, ADM, and four indicator forearm muscles using the modified MRC scale;[2] and (3) light touch and pin-prick sensation on the tip of the 5th and 2nd finger, ulnar sides of the 4th finger, palm, and hand dorsum as well as the forearm (0 – normal, 1 – moderately reduced, 2 – severely reduced or 3 – absent). For statistical analyses, the modified MRC scale will be transformed as follows: MRC grade 0 = 0, 1 = 1, 2 = 2, 3 = 3, 4– = 4, 4 = 5, 4+ = 6, and 5 = 7. Clinical UNE severity was graded: (1) *Mild* UNE – reduced sensation in the ulnar-innervated areas; (2) *Moderate* UNE – + ulnar hand muscle weakness, and (3) *Severe* UNE – + at least moderate ulnar hand muscle atrophy.

Electrodiagnostic Examination (EDx)

The second examiner (clinical neurophysiologist > 25 years) will also perform motor and sensory NCSs of the ulnar and median nerve in the affected arms using a standard EMG system (Nicolet Synergy, Natus Medical Incorporated, San Carlos, USA). Compound muscle action potentials (CMAPs) will be recorded from the ADM and abductor pollicis brevis (APB) muscles using disposable adhesive surface electrodes. With the elbow flexed at 90º, the ulnar nerve will be stimulated at the wrist, ME, 2 and 4 cm distal (D2, D4), and 2 and 4 cm proximal (P2, P4) to ME (i.e., short-segment NCSs). The median nerve will be stimulated at the wrist and the elbow. Ulnar and median antidromic sensory nerve action potentials

(SNAPs) will be recorded from the 5th and 2nd fingers on stimulation 14 cm proximally at the wrist.

Using short-segment NCSs, UNE will be diagnosed and localized to a 2-cm ulnar nerve segment with either motor nerve conduction velocity (MNCV) < 31 m/s (the lower reference limit) or a CMAP amplitude drop > 12% (the upper reference limit) (Fig. 1).[3]

Ultrasonography (US)

The third examiner (US technician >10 years) will measure the ulnar and median nerve CSAs in the affected arm using a standard US device (ProSound Alpha 7, Hitachi Aloka Medical, Ltd., Tokyo, Japan) with a 13 MHz linear array transducer (UST-5412, Hitachi Aloka Medical, Ltd., Tokyo, Japan). During the US examination, the probe will be positioned perpendicular to the nerve, and minimal pressure will be applied. A trace method will be used for CSA measurements, and the nerve hyperechoic rim will be excluded. Ulnar nerve CSA will be measured at the wrist, D4, D2, ME, P2, and P4. In addition, ulnar nerve CSA will be measured at the site of maximal CSA (CSAmax) and minimal CSA (CSAmin). Median nerve CSA will be measured at the wrist and 10 cm proximally.

Using the US, UNE will be diagnosed and localized as follows: (1) if a clear constriction (i.e., a focal narrowing of at least 2 mm^2 relative to the nerve size proximally and distally) will be seen distal to the ME then the case will be classified as CTE; (2) if a focal enlargement > 10 mm^2 at or proximal to the ME will be seen then the case will be classified as RCC; (3) in cases where CSAmax (> 10 mm^2) will be found distal to the ME, but nerve constriction will not be seen, then the entrapment site will be taken to be located just distal to the nerve enlargement and the case will be classified as CTE.[3] In arms with discordant EDx and US localisation, US will be given preference.

Randomization and Masking

The study will have a parallel trial design with a 1:1 allocation ratio, and a trial CONSORT diagram will be drawn. CTE and RCC patients will be separately randomized by one of the authors (SP), throwing dice as follows: (1) even number – surgical release, and (2) odd number – conservative treatment. In patients with bilateral UNE, the more affected arm will be randomized. Patients randomized to the surgical arm will be referred to a plastic surgeon. All included CTE and RCC patients (also those randomized to surgical release) will be given illustrated instructions showing arm positions they should avoid to prevent further ulnar nerve damage due to external compression.

The examiners will be blinded to the patient's study arm and the findings of other parts of the patient evaluation. During follow-up, examiners performing EDx and US examinations will be able to see a post-operative scar, but will be unaware of the patient group (i.e., CTE vs. RCC). Patients will not be blinded to treatment.

Treatment

The surgeon will perform division of the HUA 2-3 cm distal to ME in CTE and RCC patients.[4]

To prevent potential harm due to the delay of surgery, CTE patients randomized to a conservative arm will also be seen at 3 and 6 months. In case of clear clinical progression, they will be referred for immediate surgery. After 12 months of follow-up, these patients will be advised to proceed to surgery. CTE patients randomized to a surgery arm will be seen at 6 months for calculation of the sample size.

Sample Size Calculation

The required number of patients in the treatment arms will be determined after the first 20 patients in both CTE treatment arms have completed 6 months of follow-up. We will calculate the proportions of patients perceiving symptom improvement in both treatment arms and a standardized difference. For 80% power, the necessary sample size will be determined using a nomogram for calculating sample size.[5]

Primary and Secondary Outcome Measures

At 12-month follow-up (after surgery or the start of conservative treatment), all patients will be evaluated using the same protocol as during the initial evaluation. The primary outcome measure of the study will be the change in UNEQ score from baseline at inclusion of patients into the study and at 12-month follow-up.

The secondary outcome measures will be changes in: (1) clinical UNE severity; (2) atrophy of the ADM and FDI muscles; (3) strength of the ADM and FDI muscles using the modified MRC scale; (4) light touch sensation on the tip of the 5th finger; (5) ulnar MNCVmin across the elbow; (6) the amplitude of the ulnar CMAP on stimulation at D4; (7) the amplitude of the ulnar SNAP; (8) ulnar nerve CSAmax in the elbow segment; (9) ulnar nerve CSAmin in the elbow segment.

Statistics

All data will be transferred into a Microsoft Excel (Microsoft Corp., Redmond, Washington, USA) spreadsheet and analysed using Statistics Kingdom,[6] an internet-based statistical package. Distribution of numerical variables will be established by the Shapiro-Wilk test. In case of non-normal distribution, non-parametric descriptive statistics (i.e., median (25th–75th percentile)) and a non-parametric comparison test (Mann-Whitney U) will be used. In case of normal distribution, parametric descriptive statistics (i.e., mean (SD – standard deviation))

and a parametric comparison test (a two-sample t-test) will be used. Categorical variables will be presented as frequencies and percentages. A two-sample Z-test will be used to calculate the difference between the two proportions. All tests will be performed at a significance level of $\alpha = 0.05$ (two-sided).

Changes to the protocol

Patients

No changes.

History and Clinical Neurologic Examination

Dynamometer results are not presented because they duplicate manual testing without added value.

Electrodiagnostic Examination (EDx)

No changes.

Ultrasonography (US)

The ulnar hand muscle CSA results are not presented because they duplicate clinical testing without added value.

Randomization and Masking

No changes.

Treatment

No changes.

Sample Size Calculation

The sample size was calculated using the initial primary outcome measure because we do not know the minimal clinically important difference for UNEQ.

Primary and Secondary Outcome Measures

The initial primary outcome measure was the percentage of patients with: (1) no UNE symptoms or (2) symptoms markedly improved – only minor symptoms persist at 12 months follow-up. However, due to the inclusion of only patients with moderate or severe UNE in the present trial, and follow-up of only 12 months, the trial outcomes were much worse than expected based on our previous study results. That study also included patients with mild UNE and had a much longer follow-up of 2-3 years.[7] Only 8 patients (13%) in the CTE arms of the present trial reached the primary outcome. Patients also often reported inability to reliably compare their current hand symptoms with symptoms one year ago. Therefore, as the primary outcome, we reported a comparison of patients' responses to standard UNEQ at the baseline and at 12-month follow-up. This outcome measure was also recommended by the authors of a recent Cochrane review.[8]

As explained, we deleted instrumental measurements of the FDI muscle CSA using US and ADM/FDI muscle strength using a dynamometer, due to duplication of clinical gradings without added value, and a large number of secondary outcomes.

Statistics

The large majority of numerical variables were distributed non-normally, and therefore, non-parametric descriptive statistics (i.e., median (25th–75th percentile)) and a non-parametric comparison test (Mann-Whitney U) were used.

References:

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4. Adkinson JM, Chung KC. Minimal-incision in situ ulnar nerve decompression at the elbow. *Hand Clin* 2014; **30**(1): 63-70.

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8. Caliandro P, La Torre G, Padua R, Giannini F, Reale G, Padua L. Treatment for ulnar neuropathy at the elbow. *Cochrane Database Syst Rev* 2025; **4**(4): Cd006839.