Author's response to reviews

Title: Ultrasonographic median nerve cross-section areas measured by 8-point "inching test" for idiopathic carpal tunnel syndrome: a correlation of nerve conduction study severity and duration of clinical symptoms

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Author's response to reviews: see over
To Editorial Board

Thank you for your insightful opinions. The contribution of ultrasonography (US) in CTS detection and confirmation is well defined and there are reports examining the correlation of CTS severity with US findings. In this study, we used different measurement methods to examine this correlation.

The reviewers expressed concern regarding the authors’ training backgrounds and experience in NCS and US. We want to explain the situation before replying to the particular reviewer. First, we are all senior neurologists (Dr. Chen SF has been a neurologist for more than 10 years and Prof Chang WN has been a neurologist for more than 25 years). Second, NCS is a basic training of neurologists in Taiwan. It is easy for a neurologist to perform NCS for a patient with clinical CTS using the techniques mentioned in the “Methods” section. Dr Chen SF, Prof Lu CH, Dr Huang CR and Dr Tsai NW belong to the Neuromuscular Division of the Neurology Department, while the others belong to the General Neurology Division. Third, soft tissue echo is one of the issues for neurologist training in Taiwan. Drs Chen SF and Tsai NW have more than three years of experience in performing US examination for patients with related disorders, especially for those with clinical CTS. They have also been trained by musculo-skeletal radiologists. Fourth, the clinical symptoms of each included individuals have all been recorded and the collected data are fully discussed by all of the authors.

Opinions from Einar Wilder-Smith

Major Compulsory Revisions

This is a potentially interesting study on correlating CTS with size of the median nerve at various points of the median nerve before, as it enters inside and as it exits the carpal tunnel.

1. The authors show what has been known for some time- that NCV and CSA correlate. In Visser’s comparison of NCV and US, this is clearly shown (This paper should be quoted by the authors) Visser L H et al. J Neurol Neurosurg Psychiatry 2008;79:63-67. The authors should clearly state which measurements they recommend in patients with no NCV abnormalities noted.

The important information of the study results of Visser et al. has been cited in the “Discussion” section of the revised manuscript as follows: “It is known that in patients with a clinical diagnosis of CTS, the accuracy of US is similar to that of EMG but is probably preferable because it is painless, easily accessible, and favored by patients [25].” We also offer the information suggesting which measurement should be chosen in CTS with a negative NCS as follows: “Therefore, US can be
recommended as a useful technique in diagnosing CTS patients when NCS results are not confirmatory in patients suspected of having median neuropathy.”

2. The authors need to offer an explanation towards why the NCS minimal group, does not correlate with CSA. This is particularly important since the argument of the usefulness of US in NCV negative patients depends on this!
For this question, we have made a statement in the “Discussion” section as follows: “As shown in Table 3 and Figure 2, CSAs measured at the 8-point of the NCS minimal group are all larger than those of the NCS negative group, but this difference is not statistically significant. This insignificance can be explained partly by the trivial difference in NCS and measured CSAs in these two groups of “CTS-hands”. However, this study does not offer enough evidence to sufficiently explain the difference. Further large-scale study is needed for better delineation of the US findings between the NCS negative and NCS minimal groups.”

3. There is a problem with correlating CSA with NCV in that the authors fail to mention that at entrapment (around i2) the nerve should be smaller and distal (as well as proximal) the nerve should be larger. This needs to be differentiated in the discussion and in the formulation of the recommendations!
Thank you for your suggestion. For this question, we added a short statement in the “Discussion” section as follows: “The present study (Tables 4-1 and 4-2) also reveal that most of the “positive sites” detected in the “inchling test” involve the distal part (i2-i4) of the inlet, and the CSA measured at i2 is the smallest. These show that the area around i2 is the most possible site of nerve entrapment in idiopathic CTS, which may provide additional guidance for a more precise location for treatment.”

4. As the study centres on CSA, the authors need to incorporate into their discussion the reasoning why certain areas enlarge and others do not.
Thank you for your opinion. We made a statement of this finding in the “Discussion” section of revised manuscript as follows: “Although some insignificant enlargements detected in CSA measurement are shown by inter-group comparison (Tables 2 and 3), the present study demonstrates that slower NCS means a larger CSA by US study.”

5. In the discussion the authors offer normal values for tunnel inlet and outlet but fail to define them in relation to the inching in the methods section.
Thank you for your reminder. In the “Methods” section, we added the following description: “Measurements were conducted from the tunnel inlet of the forearm (i4, i3, i2, i1) to the wrist crease (w) and to the tunnel outlet (o1, o2, o3) (Fig. 1).”
6. The authors do not mention the weaknesses of the study and need to do this! For instance; the limits of accuracy in inching, variation in wrist size affecting measurements, difficulty in accurately obtaining a chronology of the length of duration of symptoms, examine the summation of damage in a defined section of the median nerve across the CT. Here the median nerve changes are subdivided introducing the problem that the entrapped site which should be

We have added a section to talk about the limitation of this study in the revised manuscript as followings: “This study has several limitations. First, although 212 “CTS-hands” were included for examination, further large-scale study is warranted for a more even distribution of the case number in the different sub-groups of “CTS-hands”. Second, the limitations of accuracy in inching need to be taken into consideration. Third, the variation in wrist size may affect measurements. Fourth, there is difficulty in accurately obtaining a chronology of the length of symptom duration. Fifth, there is a lack of using magnetic resonance imaging study to test the accuracy of CSA measurement at varying levels. Sixth, Additional measurements of the median nerve with US, like the measurement of width and circumference of the wrist, is not performed for CSA correlation [28]. Lastly, there is a discrepancy of median nerve length between the conventional surface measurement and US measurement [29].”

**Minor Essential Revisions**

I find it hard to believe the strict clinical selection process described by the authors as in my clinical experience most patients with CTS (and indeed normal subjects!) will have a history of some neck pain history and thus a suspicion of cervical radiculopathy!

1. Unfortunately the authors did not compensate for the circumference of the wrist which is a known factor affecting the CSA and nerve conduction correlations previously done. [Usefulness of additional measurements of the median nerve with ultrasonography. Claes F, Meulstee J, Claessen-Oude Luttikhuis TT, Huygen PL, Verhagen WI. Neurol Sci. 2010 Dec;31(6):721-5.]

In this study, we did not do additional measurements of the median nerve with US. This has been cited as a study limitation in the “Discussion” section.

2. The authors may like to broaden the discussion by commenting on the finding that the sensory NCV using the nerve length measured by ultrasound is in fact slower than that using the surface distance. Arch Phys Med Rehabil. 2011 Jan;92(1):1-6. Median
nerve conduction study through the carpal tunnel using segmental nerve length measured by ultrasonographic and conventional tape methods. Rha DW, Im SH, Kim SK, Chang WH, Kim KJ, Lee SC.

Thank you for this information. The finding of this cadaveric study has been added in the study limitations cited in the “Discussion” section.

3. Where was skin temperature measured- before or after US measurement?
Skin temperature was checked before US measurement at the ulnar side of the ventral forearm, the area proximal to the wrist crease around five centimeters.

4. Sensory latencies need to be defined as peak or onset.
The distal sensory latency was defined as onset. We have modified this definition in the “Methods” section of the revised manuscript.

5. Correct the sentence at the end of the discussion: Nonetheless, US has been known to be reproducible in median nerve measurements [26].
This sentence has been corrected as: “Nonetheless, US provides reproducible median nerve measurements [27].” (The number of the reference has been changed in the revised manuscript).

6. Figure 3 demonstrates a flattened Median Nerve at i2 within the Carpal Tunnel and there is enlargement of the median nerve both distal and proximal to it. The authors state that at the site of flattening of the nerve there is a typical prolongation of latency in the antidromic sensory nerve conduction. This contradicts the results which state that the larger the nerve the more delayed the SNAP.
We apologize for our errors in describing the findings in Figure 3. We corrected this in the revised manuscript as follows: “An example of “positive-site” between i4 and i3 corresponding to the relatively smaller cross-section area (CSA) at i2. The peak latencies (arrowhead) at i4 and i3 are 1.9 ms and 2.9 ms, respectively, and the difference between them is 1.0 ms, i.e. >0.4 ms. The CSA measured at i2 (arrow) is smaller than those measured at nearby levels.”

Opinions from Ahmad Reza Ghasemi Esfe

Major Compulsory Revisions
1. It is not clear who has performed the ultrasound? One operator or more than one.
Did the same operator perform the tests, both NCT and ultrasound? Was the operator
blind to the patient and control groups? Did a musculoskeletal radiologist help the authors in applying ultrasound of median nerve?

In our situation, it is difficult for the doctors (operators) to be blind to the CTS patients. In this study, Drs. Chen SF and Tsai NW performed all of the tests of US and NCS. For a more precise correlation, NCS and US examination were all performed by the same operator and were all measured on the same day.

2. Because of the skill and operator dependency of ultrasound, performing ultrasound always needs some experience in this field. How many years have the performer of ultrasound had experience in the field (musculoskeletal, peripheral nerve imaging)? It’s better to mention this issue in the method section. In studies like this when the reference is clinical diagnosis of a disease, the examiners of para-clinic studies are better to be the experienced ones.

Drs CSF and TNW have more than three years of experience in performing US examination for patients with related disorders, especially for those with clinical CTS. Both of them also have also been trained by musculoskeletal radiologists. This information is added in the “Methods” section.

3. Also, it is not clear who has confirmed the clinical diagnosis of CTS? One or more than one clinicians? Was agreement determined between the clinicians if there were more than one?

The clinical symptoms of each included individual were all recorded and the data were fully discussed by all of the authors.

4. The authors need to define their study groups more clearly, why did they choose a different number of controls to patients? They did not mention age and sex matching of the control group, if they did not, why not?

There was difficulty gathering an even number of controls and different severity sub-groups of CTS patients. We added this difficulty as one of the limitations of this study in the “Discussion” section. The basic information of the controls was added in Table 1.

5. In the ultrasound section of the methods the authors need to detail, is the transducer placed directly on the patient’s skin or with the interposition of a gel pad? How many times did they measure CSA of median nerve to report the mean CSA of each level, especially for tracing method?

The transducer is placed directly on the patient’s skin with gel instead of the interposition of a gel pad. In the study, mean CSA refers to the averaged CSAs from a
group of patients, not from a single patient.

6. How were bifid median nerves and persistent median vessels diagnosed? Was this done prior to or during the sonographic study?
The bifid median nerve and the persistent median vessels were diagnosed as follows: First, the probe was placed perpendicular to the wrist crease at the midline. If bifurcation of median nerve was found, the ultrasonic mode was changed to Colored-Doppler to see if the persistent vessels existed. If the bifid median nerves or persistent vessels were diagnosed, then this data was excluded in this study.

7. The diagnosis of CTS was based on clinical symptoms, did some or all patients have other diagnostic confirmation, i.e., reduction of symptoms after surgery or positive results by other imaging techniques (MRI)?
Aside from clinical symptoms, NCS and US studies were the only methods used for diagnostic confirmation. Some of the patients received operative treatment and/or wrist MRI studies, but the operative results and/or MRI findings were not used for clinical confirmation of CTS.

8. Is any normality test done for the data? Why the authors have used both parametric and nonparametric statistical tests?
Skewness and kurtosis were used for testing normality before applying the statistical tests. If skewness or kurtosis was between -2 and +2, then the parametric test was applied. If not and far from the value, then the non-parametric test was applied.

9. Limitations of the work are not stated. Authors should explain about limitations of the study in discussion section.
The limitations of this work are added in the “Discussion” section of the revised manuscript.

**Minor Essential Revisions**
1. The results presentation and figures are well.

**Discretionary Revisions**
1. The title is rather hard to read. We suggest that the authors may modify it.
The title has been modified. “Ultrasonographic median nerve cross-section areas measured by 8-point “inching test” for idiopathic carpal tunnel syndrome: a correlation of nerve conduction study severity and duration of clinical symptoms”

2. 1-Abstract needs some modifications. One should understand the whole process of
study from your abstract without referring to the main text. The abstract does not have an integrated format and should be thoroughly revised. For example in the sentence: “The median nerve CSAs were measured at the 8-point marked as i4, i3, i2, i1, w, o1, o2 and 03” the name of points are useless to mention, because not repeated in the following sections of the abstract. Or in the results section, the “cut of values” for what? Or it is not clear from the abstract why the authors have used 8 points, and what is the significance of considering several points? Also in the results section it is better to focus on your positive correlations and major novel findings of this study rather than reporting the number of subjects with different durations.

Thank you for your opinion. The purpose of this study has been summarized in the “Background” part of Abstract. In “Methods” section, the marks “i4, i3, i2, i1, w, o1, o2, and 03” are needed because the term “8-point” has been used in the “Background” and “Results” parts. Therefore, we humbly request that the reviewer allow us to keep these terms. In the “Results” part, we correct the “cut-off values” to “The cut-off values of the CSAs of the negative NCS CTS group…”. The reason for using 8-point levels in CSA measurement has been mentioned in the “Background” part of Abstract. The main purpose is to have a correlation of CSA measurement with inching test. We also added the findings in the “Results” part as follows: “In inching test, segments i4-i3 and i3-i2 were the most common “positive-site”. The corresponding CSAs measured at i4 and i3, but not at i2, were significantly larger than those measured at points that were not “positive-site”.”

3. The conclusion of the abstract does not point to the methods used and the novel findings of this study. It is already well known that US is a useful tool for CTS diagnosis, and CSAs are associated with CTS severity.

Thanks for your suggestion. We enhanced this weak point in the revised manuscript as follows: “Using the 8-point measurement of the median nerve CSA from inlet to outlet similar to the “inching test” has positive correlations with NCS severity and duration of CTS clinical symptoms, and can provide more information on anatomic changes. Combined NCS and US studies using the 8-point measurement may have a higher positive rate than NCS alone for diagnosing CTS.”

4. Why were other ultrasound findings for carpal tunnel syndrome not recorded between CTS-hands and A-hands (abnormal hypoechogenicity, Ratio between proximal and distal parts, #CSA, etc.)?

During US examination, we did see the hypo-echogenicity but did not have the software for such measurement. We measured the flatten ratio of the median nerve and the ratio of wrist-to-forearm and inlet-to-forearm, but these data were not
5. The major novel findings of this study, with respect to considering 8 cut-points should be discussed with more stress and considered in the conclusion of this study. In fact after reading the article and in comparison with recent published articles it seems performing ultrasound in 8 points is rather time wasting without any superior advantages for diagnosing or confirming CTS.

Thank you for your opinion. We have revised the “Conclusions” section accordingly. We understand the time-wasting issue concern of the reviewer, but this CSA measurement method has not been used before. This 8-point CSA measurement may offer an opportunity to have a better correlation to findings of the “inching test”, which is an important NCS method for CTS study.