Author's response to reviews

Title: The Impact of Extended Electrodiagnostic studies in Ulnar Neuropathy at the Elbow

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Author's response to reviews:

To

BMC Neurology

Dear Andrea Bucceri PhD
Scientific Editor
BMC-series journals
BioMed Central

Thank you very much for finding so many competent reviewers for our manuscript.

Please find enclosed the revised manuscript MS: 1309534307263980 entitled “The Impact of Extended Electrodiagnostic studies in Ulnar Neuropathy at the Elbow”

We would like to thank all the reviewers for valuable comments and suggestions.

Our response to the reviewers concerns are as follows:

Reviewer Peter Dioszeghy

“7. It should be important to compare more detailed the advantages and drawback of the new protocol opposite to the other common methods, like inching”

In the discussion page 11 is added: The advantages of the new protocol are that it can be performed as a screening test by the neurophysiology technicians and take less time than inching. There is also less risk of electrical spreading due to longer distances between the nerve stimulation points (six and four cm), while the segment steps in the inching technique is one or two cm. The inching
technique need a high level of accuracy and is superb in experienced hands.

"8. The writing is acceptable. In a the use of brackets are not correct"

Years in brackets were removed from the Introduction

"Table 3.
Dorsal branch amplitude – Not recorded in three patients
SCV dorsal branch – The potential was unobtainable in 18 patients
Contradictory data? In how many patients were the sensory potentials unelicitable?"

The data are not contradictory. Unfortunately data were not complete in some cases, and in three patients the dorsal branch nerve was not examined. Of the remaining 124 patients the sensory potentials were unelicitable in 18 patients. We have changed the word unobtainable to unelicitable in Table 3.

"What is the explanation that orthodromic method was used to study the dorsal sensory ulnar branch? The antidromic method is commonly used and is more reliable."

In our lab we decided some years ago to examine this nerve with the orthodromic method because we expected that this method would yield a larger sensory potential. We agree that the antidromic method may have some advantages, but we did not change our protocol for the present study.

Reviewer: Jia Zhi-rong

"But I think that the describing of the result are too confusion. It may be revised. In this paper, so many numbers are incompatible compared to these in the table. eg, in page 8, "…reduced ulnar sensitivity occurred in 98 of 121 patients (81%)", but "is 86.3% (107/124)" in table 1. " 53%(64/120) is reported reduced muscle strength", but is” 47.6% in table 1”. Please let the author check the mistakes carefully."

The first text under Results on page 8 represent the patient’s symptoms, and the clinical findings are presented in Table 1. Symptoms and clinical findings may be different; we have changed the text to avoid misunderstandings.

Some numbers were given in “percent” directly, not to note the abnormal numbers. I think that it may be clearly to write the abnormal numbers first then note the abnormal percent in the text and in the table.

The first paragraph under Results, page 8 has been changed accordingly

Please let the authors to revise it. It is essential that this manuscript be seen by
an expert statistician

One of the authors has a University degree in mathematics and statistics.

Reviewer: Zsuzsanna Arányi

“2. Minor Essential Revisions
There are very few typographical or grammatical errors (e.g. „standards protocol”, instead of 'standard protocol'; „departments” instead of 'department’s'; „p-values <0.05 was considered” instead of 'p-values <0.05 were considered'; etc.)”

These grammatical errors have been corrected

“3. Discretionary Revisions
• One of the conclusions of the authors is that electrodiagnostic work-up is needed for the diagnosis of ulnar nerve lesion at the elbow. This statement is too obvious as to make it a major conclusion.”

This statement is moved to the end in the Conclusions. We agree with the reviewer that the statement is obvious, but it is not obvious to many surgeons who prefer to operate without electrodiagnosis for UNE.

• Another conclusion is that the use of a motor nerve conduction study with three stimulation sites at the elbow is more sensitive than with two stimulation sites in the diagnosis of ulnar nerve lesion at the elbow. This method is an intermediate between the standard ulnar nerve conduction study and the segmental (' inching') nerve conduction study, which is widely used in many laboratories as part of the routine assessment of the ulnar nerve. With its help, ulnar nerve lesion can be very precisely localised to for example the retroepicondylar region. I miss the comparison of the method advocated by the authors and to the inching method, and the discussion of the possible advantages of their method.”

Almost the same as Peter Dioszeghy. This aspect is commented on in the first paragraph page 11.

• From the data provided it is seen that conduction velocity is reduced on the forearm in about 20% of patients. In the authors’ opinion, is this mainly observed in patients with already pronounced axonal lesion, or is it explained by other factors?”

Yes, we believe it is explained by pronounced axonal degeneration. A sentence is added in the Discussion, page 10.
“Are there anatomical data supporting that a stimulation point 4 cm distal to the midpoint of the sulcus is below the cubital tunnel in most patients?”

According to Dawson DM (Entrapment neuropathies of the upper extremities. N Eng J Med 1993;329:2013-8) the site of constriction is 1.5-3.5 cm distal to the epicondyle.

Our choice of stimulating 4 cm below the midpoint of the sulcus is based on recommendations from reference books. In “Essentials of Electrodiagnostic Medicine” by William W. Campbell is written on page 265; “surface stimulation much more than 3-4 cm beyond the elbow, especially in large arms, runs a substantial risk of being submaximal. In our experience it is difficult to stimulate the ulnar nerve more than 4 cm below sulcus, strongly indicating that the nerve at more distal points are covered by the flexor muscles (i.a. distal to the aponeurosis that constitute the roof of the cubital tunnel.)”

In “Electrodiagnostic Medicine” by D. Dumitru, AA Amato and MJ Zwarts, page 1080 is written that “the nerve should be stimulated 4 cm distal to the medial epicondyle and 4 – 8 cm proximal to the medial epicondyle.”

• The authors have done an orthodromic ulnar sensory nerve conduction study with recording at the wrist, and have found a relatively low proportion of abnormality. With this method, only axonal sensory nerve fiber damage can be assessed, whereas the widely used antidromic method with three stimulation points (wrist, below and above the elbow) may also detect demyelinative lesion in the sulcus. Do the authors have experience with it? Why was the orthodromic method chosen?

We do not normally do the antidromic method with three stimulation points, and used our ordinary orthodromic method. The advantage of the orthodromic method is the selective stimulation of sensory fibers. We agree, however, that a sensory method capable of determining SCV across sulcus would have been appropriate in these patients.

Reviewer: Pietro Caliandro

“1. Major Compulsory Revisions
The present study aim is to evaluate the most sensitive and least time-consuming neurophysiological approach to diagnose UNE. The matter is relevant but some important considerations are necessary. The main concern is the used inclusion criteria. Indeed to measure sensibility the authors evaluated a sample of patients with clinical and electrodiagnostic findings of UNE and exclude “subjects with normal neurophysiological results……regardless of their symptoms and neurological findings”. That is an important methodological
problem because it is not possible to study sensitivity of electrodiagnosis in patients with electrodiagnostic evidence of UNE, you need a gold standard different than the element you are evaluating. According to me it is not useful to extend neurophysiolocal examination if the diagnosis is already reached with a standard neurophysiological approach. On the other hand that inclusion criteria introduces a bias selection because it excludes all patients with symptoms suggestive of UNE but without electrodiagnostic evidence.

Another problem is the absence of a control group composed by patients with other pathologies. Speaking about diagnostic approach, it is necessary to evaluate specificity too.

I suggest: 1) studying also patients without neurophysiological evidence of UNE but with clear symptoms and signs of UNE and without possibility of other diagnosis (radiculopathy for example), 2) introduce a control group to evaluate specificity, 3) defining a clinical gold standard although it may be difficult.

We agree that the results from such a broad study would have been very interesting and would have been necessary to also study specificity. Our aim was, however, to study only the sensitivity of the neurophysiological methods. We used clinical inclusion criteria for these patients as recommended by The American Academy of Electrodiagnostic Medicine, ref. 11, page 16, and for the control group was used our department’s reference values, described in page 5.

“2. Minor Essential Revisions

line 1 of “Results”. The authors describe the clinical findings and they say that 117 patients of 122 had paresthesias but previously they have described that 127 patients were evaluated in one arm. The same mistake is in line two of the same section they speak about 121 patients and not about 127. Probably it is a typing mistake.”

Unfortunately, the data set was not complete for all patients, and in only 122 of the 127 patients were paresthesias evaluated. In all cases of incomplete data sets for different variables the total number of examined patients are given.

“3. Discretionary Revisions

I think that the idea to study ulnar nerve in two small segments across the elbow is very interesting because it could allow a better localization of the damage. I suggest to evaluate this aspect in a sample of patients with clinical and electrophysiological evidence of UNE. Of course a similar approach cannot have the aim to improve diagnostic sensitivity but it could be a good method to better localize the damage. It is necessary to discuss the technical problems due to the
evaluation of CV in short segments."

From the start of this study were examined patients with symptoms and neurological findings indicative of ulnar nerve entrapment at the elbow according to our standards protocol. We agree that three stimulation sites will localize the damage of the nerve either in proximity to the cubital tunnel or more rostral over the elbow. Technical problems due to evaluation of MCV in short segments are discussed in page 10.

Reviewer: Eszter Hidasi

“There was a little bit confused for me to understand the number of the examined patients, because they mentioned sometimes 127, sometimes 122, or 121, or 120 patients. If there were 127 person in the study, why did they check the paraesthesias just in 122 cases, the reduced ulnar sensitivity in 121 cases, and the muscle strength in 120 cases?”

The same as Pietro Caliandro. Unfortunately, the data set was not complete for all patients, and in only 122 of the 127 patients were paresthesias evaluated. In all cases of incomplete data sets for different variables the total number of examined patients are given. To clarify this problem we have added a sentence at the beginning of the Result paragraph.

The evaluation of the pain in different regions is also confused. Did they check it at the hand, elbow and forearm, or at the hand, elbow and shoulder?

Pain was checked for in the hand, forearm and elbow and is reported in the first paragraph in the Results.

“What did it mean: reduced muscle strength? What kind of movements did they examined?

These questions are answerable and the datas are correctable.”

All kinds of muscular strength in the hand were tested. In Table 1 can be seen that these patients had no weakness in muscles innervated from the median and radial nerves, only the ulnar nerve. 47.6% had weakness in finger spreading, abduction of the fifth finger and flexion of the fourth and fifth fingers. An additional sentence is added at the bottom of Table 1.

“I have two basic problems with this study.

1. In my opinion the inclusion criteria were unadvised. If they excluded the patients with clinical signs of ulnar nerve lesion, but without the electrophysiological evidence of this lesion using just the standard ENG method, then they could lose patients potential electrophysiological abnormalities detectable just with the extended ENG method.”
We agree to this statement concerning handling of the initial pool of patients. Patients with normal electrodiagnostic results according to the old protocol also had extra stimulations done. They were, however, not be included in the present study because our intention was to compare the abnormal results in the old and new protocol.

“There could be useful to examine a group of this type of patients with the extended ENG method. The real clinical advantage of this new method could be to find the most patients with ulnar nerve lesion (compression) for surgical, or conservative therapies.”

We fully agree and we intend to perform such a study in the future

“2. Nowadays there is a very sensitive, and not time-consuming method to diagnose precisely the ulnar nerve entrapment. This is the inching stimulation technique. With this method the precise localisation of the nerve compression could be performed. Using the inching technique the nerve is stimulated in 1 or 2 cm long segment steps, and the site of the nerve compression is clear for the clinician and the surgeon. To use just one more stimulation point (in the mid-sulcus) is not enough for the precise diagnosis”

This topic is also discussed by two other reviewers and is addressed in the revised manuscript in page 11.

Reviewer: Ali Shakir

“Major Compulsory Revisions:
1. There is a significant flaw in the study’s design. By the authors choosing to only look at using extended motor nerve conduction studies to increase sensitivity in the identification of UNE, they lose sight of the impact on specificity. If the repercussions of increasing sensitivity is the loss of specificity then there would be little clinical benefit from pursuing extended nerve conduction studies if the results were increasing false positive rate. Therefore without knowing the impact on specificity, their conclusion that three stimulation sites in the elbow is most effective is not supported. By determining the impact of specificity a better judgment of the value of three stimulation sites can be achieved. This would require adding an asymptomatic control group.”

The same concerns as Peter Caliandro and answered above.

“2. Also when evaluating sensitivity and specificity of a test, ideally one would want to use a gold standard that is separate from the test being studied to identify populations with and without disease. The lack of a diagnostic criterion
for UNE based on clinical criterion independent of the electrodiagnostic variables under evaluation is a significant study limitation in regards to evaluating sensitivity as this could lead to a falsely elevated sensitivity for motor nerve conduction studies. This limitation should be brought up and discussed in the discussion section."

We agree with this general comment, but the situation in entrapment diagnostics is more complex because there is no useful clinical gold standard for the diagnosis, and because nerve conduction methods, used for more than 50 years, have proved to be reliable supplementary diagnostic methods. Attempts to define standards based on operative success will also fail because peroperative complications, placebo effects and spontaneous remissions will interfere. Thus, most experts consider a combination of clinical and electroneurographic signs as a “gold standard” for entrapments. If this is accepted, sensitivity of new ENeG methods should be assessed in such a group, as in the present study. It should also be noted that in this design we mainly compare sensitivities of subtests and combination of subtests. These points have been added to the discussion on page 14.

“3. In the results section of the abstract it is mentioned that sensitivity for use of a third stimulation site increased from 80% to 96% but no where else in the paper is this mentioned. Only in the discussion section does it briefly state that sensitivity was increased by 16% by using a third stimulation site, but it is not clearly presented in the results section of the paper. There should be clarification in the results section of the paper stating this finding."

This is now written in the neurophysiology results section in page 8 and 9.

“Minor essential revisions:
1. Did the authors mean amplitude (<2µV) rather than amplitude (>2µV), in the patient section of methods on page 5, regarding sensory amplitude criteria.
2. On page 12, 6th line from the top, unspecific is misspelled.
3. On page 13, 3rd line from the top, literature is misspelled."

1 < 2µV
2 and 3; The errors have been corrected

“Discretionary revisions:
1. Consider changing title to: The Impact of Extended Electrodiagnostic studies in Ulnar Neuropathy at the Elbow.”

OK, thank you.
Thanks for your consideration.

St.Olavs Hospital, Trondheim, July 5, 2009

With best regards,

Kari Todnem