ELECTRICAL IMPEDANCE MYOGRAPHY IN A SAFETY STUDY OF FETAL STEM CELL IMPLANTATION IN ALS

Seward B. Rutkove MD[1], Meraida Polak[2], Crystal Kelly[2], Eva Feldman MD PhD[3], Nicholas Boulis MD[2] and Jonathan Glass MD[2]

From the Departments of Neurology, [1]Beth Israel Deaconess Medical Center, Boston MA, [2]Emory University, Atlanta GA, and the [3]University of Michigan, Ann Arbor MI

INTRODUCTION

Electrical impedance myography (EIM) is a non-invasive technique that relies on the localized application of high-frequency, low-intensity electrical current to an area of muscle and the measurement of the consequent surface voltages. From these voltages, the impedance characteristics of the muscle can be obtained. Unlike standard electrophysiogical measures, EIM does not rely directly on the electrical activity of the muscle tissues, but rather on the changes in surface voltage patterns as energy is introduced into the muscle. These impedance measures can serve as a sensitive index of muscle status and thus make a potentially useful tool for monitoring disease status and rate of progression in amyotrophic lateral sclerosis (ALS) and other neuromusuclar disorders in clinical trials.

One advantage of EIM over other approaches for evaluating disease status is that it can be applied to specific muscles of interest. For this reason it was incorporated as a potential outcome measure in a safety study in which human fetal stem cells are injected directly into restricted regions of the spinal cord (cervical and lumbar) via laminectomy.

OBJECTIVE

To establish the usability and reproducibility of electrical impedance myography as an outcome measure in a safety study (Neuralstem, Inc) of fetal stem cell implantation in ALS.

METHODS

A total of 12 patients have been enrolled to date. In the first 7 only single measurements were made prior to cell implantation. However, in the last 5 of these patients, multiple measurements were made prior to implantation and only that data is presented here.

EIM measurements were made on bilateral medial gastrocnemius, tibialis anterior, and quadriceps using predefined electrode positioning. To help ensure accurate electrode placement on repeat visits, small pinpoint tattoos were placed in the locations where the electrodes were to be positioned. In patients with substantial hair, the skin was gently shaved to remove as much as possible prior to each measurement session.

EIM was performed with an impedance device (the SFB7 from Impedimed, Inc) on bilateral medial gastrocnemius, bilateral tibialis anterior, and bilateral quadriceps taking care to position patients identically at each visit. Two individuals (MP and CK) performed all measurements after an initial training session with Dr. Rutkove. Two early measurement sessions were also viewed by Dr. Rutkove via Skype, but from that point onward all measurements were performed without Dr. Rutkove's supervision.

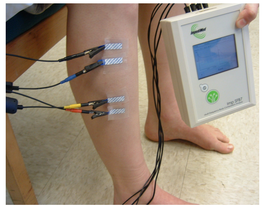
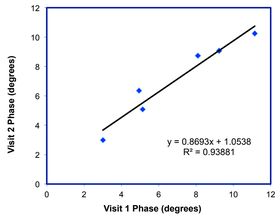
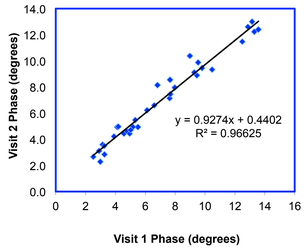


Figure 1. EIM being performed on the right tibialis anterior using the Impedimed SFB7. Improved, dedicated EIM devices are currently in development.

RESULTS

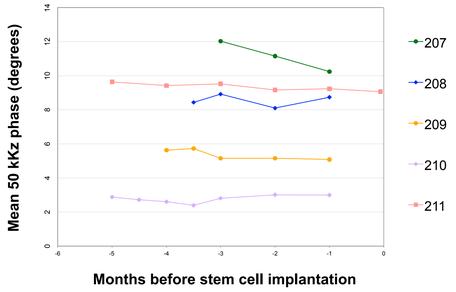
Reproducibility. We assessed reproducibility by plotting the EIM phase data at the last two visits prior to stem cell implantation for each of the 6 muscles in the 5 patients. The data were plotted both as individual muscle data for all the patients and as a mean measure for all 5 subjects (see Figures 2 and 3). Note that the slope of the fitted line is less than one for both plots





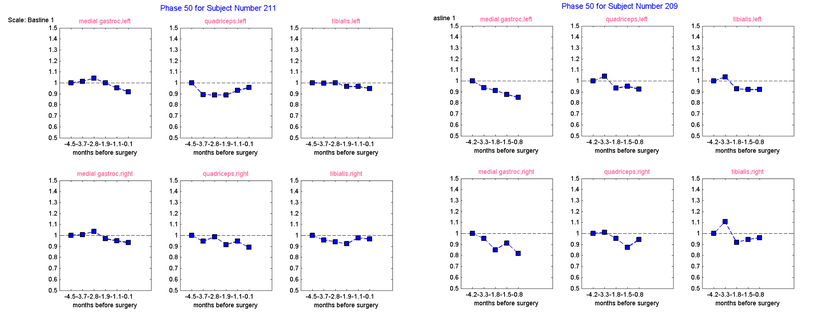
Figures 2 and 3. Test-retest reproducibility across all the individual muscles (Figure 2) and for the data from each individual patient (Figure 3).

Detection of disease progression over time—average values. Figure 4 shows the mean value for the 50 kHz phase over time for all 5 subjects. Patient 210 with 7 visits already shows very low values, consistent with advanced disease. The other 4 patients all show more preserrved values.



Figures 4. Mean 50 kHz EIM values for the 5 subjects over time. Patient 211 already has advanced disease whereas the others show values either within or only slightly below the normal range.

Detection of disease progression over time—individual muscles. Figures 5 and 6 show examples of the individual muscle values for Patients 209 and 211, plotted as relative values normalized to the data obtained on the first visit. Note the reproducibility of these measurements, especially given that most are obtained nearly one month apart. In addition, in both cases, for both muscles slight declines are apparent as are also identified in the average value shown in Figure 4).



Figures 5 and 6. Single muscle EIM data from Patients 209 and Patient 211, normalized to the first visit to show alterations over time prior to stem cell implantation. Note the consistency of measurements and the subtle downward trends in most muscles.

CONCLUSIONS

1. Electrical impedance myography (EIM) can be performed accurately and reproducibly with limited training but considerable practice.

2. EIM can detect subtle alterations in ALS disease status over time periods of just 2-3 months, offering the potential of greatly improved power to detect drug effect in clinical therapeutic trials over standard approaches.

3. EIM can potentially provide useful longitudinal data from even single muscles rather than relying upon average, whole-body data, making it possible to follow those regions that are most rapidly deteriorating during a clinical trial or judging the effect of a localized treatment, such as stem cell implantation.

4. Although the impedance device used in this study has worked well, it is no longer available for purchase in the United States. Future studies using EIM as an outcome measure will likely await the arrival of dedicated EIM systems, now in development. Such systems will offer increased ease-of-use, the ability to survey multiple muscles rapidly, and additional parameters for the identification of disease progression.

This research is supported by Neuralstem, Inc.

Abstract P07.076

Disclosures; Dr. Rutkove holds equity interest and receives consulting income from Convergence Medical Devices, Inc