Challenges and solutions to optimize stroke recovery trial enrollment and execution

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Transcranial direct current stimulation (tDCS) has emerged as a promising adjunctive tool for post-stroke upper extremity motor recovery owing to its portability, easy-to-use and safety profile. Although there have been flourish of publications in tDCS and post-stroke motor recovery in the last decade, large multi-center well-powered clinical trials are still lacking to formally establish the clinical evidence of tDCS.[1,2]

In this issue of *The Lancet Regional Health-Europe*, the NETS Trial Collaboration Group published their results of the NETS trial, an investigator-initiated, 11-center, randomized, double-blinded, sham-controlled tDCS post-ischemic-stroke recovery trial.[3] It took the consortium almost 10 years to enroll and follow up 123 study participants to complete this trial. The trial aimed to test the hypothesis that tDCS 20-min stimulation at 1 mA level along with 45-min standardized UE function rehabilitative training for 10 sessions over a 2-week period would lead to a better impairment reduction with upper extremity (measured by Upper Extremity Fugl–Meyer Scale) in patients with ischemic stroke. Not surprisingly, the trial turned to be against the hypothesis with a neutral result, i.e., there is no sign of separation between the two groups immediately after intervention (The mean changes in group differences: –0.31; 95% confidence interval: –2.97 to 2.35, p = 0.82). While positive trials can be exciting, the stroke recovery field can chew, think and learn from a negative trial. Indeed, there are several things we can learn from this NETS trial that can be informative to the field.

First, mismatch and dilemma between fast science advancement and slow trial enrollment. NETS trial is not the only stroke recovery trial with struggles with slow enrollment.[4] With 11 enrolling centers with experience in stroke research or rehabilitation, only 1 patient was enrolled per month or 1 patient was enrolled per center per year. When the trial was initiated in 2009, the stimulation dose was decided at 1 mA, however, many studies challenged that low dose is likely not adequate,[1,5,6] as a matter of fact, a phase I study with dose/current escalation to 4 mA was proven to be safe and tolerable in stroke patients.[7] With a traditional study design and slow enrollment, the NETS trial is not designed to incorporate new science during trial enrollment. Trials with an adaptive design can be more flexible, efficient and informative than trials with a conventional design since they often make better use of resources such as time and money with fewer participants which is highly implicated in stroke recovery study.[8] Other option is to implement decentralized clinical trials and to gather evidence through real-world data to mitigate challenges in patient recruitments.

Second, there is a lack of funding resources to build the fundamental research infrastructure that can expedite and catalyze the translation of future stroke recovery efforts. Researchers, as a group, need to advocate and request stakeholders at various levels to invest infrastructure for stroke recovery studies which involves many resources—therapist both personnel and time, equipment both for therapeutic and assessment purpose, outcome assessor, study coordinator for patient visits and transportation, etc. A good example is that the National Institute of Health poured investment to establish a "Strokenet"–a centrally coordinated network with over two dozen regional coordination centers that are linked to 300+ stroke hospitals across the United States to conduct stroke trials in acute treatment, prevention and recovery.[9] Two large stroke recovery studies are currently ongoing now including one tDCS stroke upper extremity recovery study (https://classic.clinicaltrials.gov/ct2/show/NCT03826030) that is testing whether there is an overall treatment effect among three dose groups—sham stimulation group vs. low dose group (at 2 mA) and high dose group (at 4 mA).

Finally, we need to train the next generation of research force for stroke rehabilitation and recovery. As stroke mortality decreased over the time in several regions and it became a leading cause of long-term disability demanding more effective and accessible rehabilitation modality based on a recent published WHO-Lancet Neurology Commision.[10] Professional society such as the World Federation of Neurorehabilitation, can bear the responsibility to utilize conference platform to train and standardize outcome

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assessments and other common study procedures, clinical trial methodology, publication which are all critical factors towards sucess of future stroke recovery trials.

Contributors

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Declaration of interests

None.

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