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EDITORIAL

Unlocking consciousness through right median nerve stimulation. Has a potential cure arrived at our doorstep?

Mathieu van der Jagt[1*], Chiara Robba[2,3] and Markus B. Skrifvars[4]

Although traumatic brain injury (TBI) represents a major public health issue, there has been a dearth of clinical trials providing evidence on effective therapies [1]. Concurrently, more research is warranted to find evidence on treatments to improve emergence from traumatic coma. Peripheral electrical nerve stimulation to enhance central nervous system neuroplasticity and thereby arousal and emergence from coma has shown clear potential. For instance, transcutaneous auricular vagal nerve stimulation is currently being explored as one such therapy [2]. Its purported benefit has been linked to enhanced arousal in disorders of consciousness, such as minimal conscious state (MCS) and unresponsive wakefulness syndrome (UWS), with improved connectivity of thalamo-cortical and -prefrontal brain circuits. The mechanism appears to be via stimulation of excitatory norepinephrin and serotonergic neurotransmitter circuits with a subsequent decrease of the thalamo-inhibitory pathway through the striatum and globus pallidum interna [3]. Right median nerve electrical stimulation (RMNS; applying repeated electrical currents to the median nerve) is another example. It has been explored in observational studies and small clinical trials showing promising results and an excitatory N-methyl-D-aspartate (NMDA) receptor-mediated pathway has been reported in an animal model [4–7]. However, to date, sufficiently powered clinical trials testing peripheral electrical nerve stimulation are lacking.

In this issue of the Journal, Wu et al. report a randomized controlled clinical trial on the use of RMNS in comatose TBI patients aimed at improving emergence from coma [8]. This study randomized adult TBI patients with acute coma at 7 to 14 days to RMNS or sham intervention. From a total of 329 participants, at 6 months, a higher proportion of patients treated with RMNS regained consciousness compared with controls (72.5 vs. 56.8%, $p = 0.004$). Additional post hoc analyses for other outcomes such as Glasgow Coma Scale (GCS) supported the signal of effectiveness. This therapy did not seem to have any clinically relevant side effects. These results are nothing short of revolutionary with a clinical effect that, if real and replicated, would transform the management of patients with prolonged traumatic coma given the number needed to treat for RMNS of only 6.

Strengths of this randomized clinical trial are its multicenter setting and independent outcome assessment. However, at face value, the results are intuitively hard to accept, given that the pathophysiological underpinning of the intervention is not very firmly established and the impressive effect size on the primary outcome of regaining consciousness has only rarely been paralleled in past trials [9].

However, there are notable methodological weaknesses, that should be considered. These pertain to the inclusion criteria, the incomplete blinding, the outcome assessment, and the lack of data regarding withdrawal of life sustaining measures (WLSM). First, the inclusion criterion of a GCS 4–8 and a GCS motor (M) score of < 5 at 7–14 days after trauma is not clearly defined: how was the coma assessed exactly? Was residual sedation taken into account and how? This criterion would have been more robust when failure to awaken from coma was used as an

*Correspondence: m.vanderjagt@erasmusmc.nl
[1] Department of Intensive Care Adults, Erasmus MC–University Medical Centre, Rotterdam, The Netherlands
Full author information is available at the end of the article

entry criterion, including a well-defined 'wake-up call' protocol and strict criteria to assess residual sedation. The manuscript is not entirely clear on how this inclusion criterion should be interpreted, slightly hampering the understanding of which patients exactly qualified for inclusion. Of note, the GCS evaluation for inclusion in the trial report states to use GCS upon enrolment, whereas the published protocol mentions GCS on admission [10]. Nonetheless, the authors do show that intervention and control groups were well matched, based on the baseline variables and the fact that the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic scores were similar in both groups.

Second, in spite of the attempt to blind the intervention by sham-application of the electrodes in the control group, without electrical currents being administered, the authors found that (partial) unblinding occurred because muscle twitches could be observed in some patients in the intervention group.

Third, the primary outcome was a non-validated outcome measure for regaining consciousness, introducing possible variability due to subjectivity in its assessment. The definition from the published protocol [10] included "complete wakefulness and awareness of self and environment, precise comprehension and interaction, correct orientation of figures, time and location, the ability to obey commands and intact light and deep reflexes". This rather lengthy definition bears the risk of variable interpretation: indeed, why did not the authors just use GCS M6 score as endpoint? Were intact deep reflexes indeed necessary for consciousness evaluation and what then if they were not present in an otherwise awake patient?

Fourth, no details were provided on WLSM and together with the unblinding and the fact that the authors had been engaged in a previous large non-randomized study with similarly impressive results [11], there was a potential for biases in clinical management: the results would have been more convincing when clear reluctance was stimulated towards WLSM, given that this has been reported in large prospective studies as both frequent and variable [12, 13], but data are absent.

Other notable issues worth considering were the fact that the trial was primarily halted due to coronavirus disease 2019 at 85% of the power; incomplete follow-up and the lack of data on clinical management in intervention versus control group, hampering assessment of possible treatment bias.

We agree with the authors when they state that "the subjectivity of the primary outcome in an unblinded, and underpowered trial setting warrants a cautious interpretation." Therefore, we suggest that confirmation of the reported effects is warranted before implementation. Such a trial should ideally be multicentric, with blind intervention (authors mention a possible solution for blinding: covering the right forearm to hide muscle twitches from observers) and including detailed data on WLSM as well as long-term outcome by a validated metric informing on functional independence.

In spite of its methodological shortcomings, this trial is important and if the results are replicated, this will improve the prospects for patients in prolonged traumatic coma and their families.

Author details
[1] Department of Intensive Care Adults, Erasmus MC–University Medical Centre, Rotterdam, The Netherlands. [2] IRCCS Policlinico San Martino, Genoa, Italy. [3] Dipartimento di Scienze Chirurgiche Diagnostiche Integrate, University of Genoa, Genoa, Italy. [4] Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland.

Declarations

Conflicts of interest
MS has received speakers fees from BARD Medical (Ireland).

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