Letters to the Editor

NEUROSURGICAL FORUM

Stereotactic injection of nondiffusible dyes

TO THE EDITOR: We read with interest the paper by Margetis et al.³ (Margetis K, Rajappa P, Tsiouris AJ, et al: Intraoperative stereotactic injection of Indigo Carmine dye to mark ill-defined tumor margins: a prospective Phase I–II study. *J Neurosurg* 122:40–48, January 2015). Our group in Treviso used a very similar technique and published the results about 25 years ago.^{1,2} We similarly used nonspreading dyes to highlight the tumor borders before performing the craniotomy and consequently before brain shift could occur. Methylene blue was injected to label the tumor boundaries. The only differences were the use of a stereotactic frame, because the frameless navigation system was not available at that time, and the injection of the dye through a single bur hole. With this technique, the mass is encompassed in a cone, with its apex at the entry point and its base at the deepest face of the tumor. The colored tracks can be also helpful to reach the tumor, minimizing the damage to the normal brain tissue. Our series included 25 patients harboring not only WHO I–IV gliomas (19 cases), but also cavernomas and metastasis.

Of course, nowadays we would not recommend such a method to resect cavernomas, which are much better localized using neuronavigation. However, we agree with Margetis et al. when they say that stereotactic injection of nondiffusible dyes can be useful to better visualize tumor margins for improving the extent of removal, reducing damage to normal brain tissue, and avoiding inaccuracies due to brain shift. Moreover, this technique has very limited costs, which is of great interest for the large number of neurosurgical departments that cannot afford the expenses related to more updated and technologically advanced techniques to localize and intraoperatively outline brain tumors.

After the publication of our first 25 patients in 1990, we have been using dye injection until recent years in selected cases. The injection of nondiffusible dyes should be considered as a possible tool especially for deep-seated tumors and for low-grade gliomas, whose limits are often difficult to guess intraoperatively. Coupling this technique with cortical and subcortical neurophysiological mapping is likely to maximize the resection and better preserve functionally eloquent areas.

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DISCLOSURE

The authors report no conflict of interest.

References

1. Longatti P, Carteri A: Stereotactic location and delimitation of brain tumors in children. Technical note. *Childs Nerv Syst* 5:250–251, 1989
2. Longatti P, Di Paola F, Baratto V, Zanata R, Trincia G, Carteri A: Stereotactic support in the excision of brain tumors. Technical note. *J Neurosurg Sci* 34:315–318, 1990
3. Margetis K, Rajappa P, Tsiouris AJ, Greenfield JP, Schwartz TH: Intraoperative stereotactic injection of Indigo Carmine dye to mark ill-defined tumor margins: a prospective Phase I–II study. *J Neurosurg* 122:40–48, 2015

Response

We thank Drs. Feletti and Longatti for bringing to our attention their work on the stereotactic injection of methylene blue for delineating the border of brain tumors prior to surgery.^{3,4} Their work predates our paper and clearly represents the first stereotactic injection of dye in the brain for these purposes. As such, they should be credited for proof of concept. The differences in the techniques (e.g., framed vs frameless stereotaxy, single vs multiple bur holes for dye injection, the use of preoperative CT vs MRI, and the use of brain cannula vs spinal needle) are not based on different fundamental concepts, but rather they represent technological advances that occurred between the two studies.

However, we wish to point out another key difference, which is that our study required approval from the FDA for an investigational new drug study emphasizing the safety of the pharmaceutical compound used. The use of methylene blue by the Treviso group hinders the generalizability of their method. Several reports^{1,2,5,6}—with the first one being published 66 years ago⁷—have established the toxicity of methylene blue after intrathecal injection. In the light of these reports it would be problematic to use methylene blue for this technique. The use of methylene blue was eliminated from consideration very early in the

planning phase of our study, which may explain why the Treviso study eluded our literature review. Ultimately, we are pleased to reiterate and confirm the utility of stereotactic injection of dyes for tumor delineation as a helpful adjunct in neuro-oncological surgery even in the age of intraoperative MRI scans.

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References

1. Arieff AJ, Pyzik SW: Quadriplegia after intrathecal injection of methylene blue. *JAMA* **173**:794–796, 1960
2. Evans JP, Keegan HR: Danger in the use of intrathecal methylene blue. *JAMA* **174**:856–859, 1960
3. Longatti P, Carteri A: Stereotactic location and delimitation of brain tumors in children. *Childs Nerv Syst* **5**:250–251, 1989
4. Longatti PL, Di Paola F, Baratto V, Zanata R, Trincia G, Carteri A: Stereotactic support in the excision of brain tumors. Technical note. *J Neurosurg Sci* **34**:315–318, 1990
5. Schultz P, Schwarz GA: Radiculomyelopathy following intrathecal instillation of methylene blue. A hazard reaffirmed. *Arch Neurol* **22**:240–244, 1970
6. Sharr MM, Weller RO, Brice JG: Spinal cord necrosis after intrathecal injection of methylene blue. *J Neurol Neurosurg Psychiatry* **41**:384–386, 1978
7. Walker AE: Spontaneous ventricular rhinorrhea and otorrhea. *J Neuropathol Exp Neurol* **8**:171–183, 1949

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Published online May 29, 2015; DOI: 10.3171/2014.12.JNS142909.

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Early noninvasive brain stimulation after severe TBI

TO THE EDITOR: We read with interest the review by Shin et al.⁷ (Shin SS, Dixon CE, Okonkwo DO, et al: Neurostimulation for traumatic brain injury. *J Neurosurg* **121**:1219–1231, November 2014), which addressed the potential of noninvasive stimulation for treating posttraumatic cognitive impairment, but also pointed out the possible risk of functional impairment depends on the stimulation site and parameters.

One of the most prevalent neuropsychiatric outcomes of traumatic brain injury (TBI), particularly severe TBI, is personality change.^{5,6} These changes, as reported by Tate et al. (1999), can more precisely be defined as behavioral manifestations of cognitive deficits acquired after the TBI.⁸ Most likely, this intimate relationship between cognitive deficits and personality changes explains the latter as a highly independent factor that is associated with not returning to work in survivors of severe TBI.⁴

Noninvasive cerebral stimulation is a promising intervention for the treatment of cognitive impairment after TBI.¹ According to Villamar et al.,⁹ the acute recovery of

cerebral functions after brain injury includes the activation of cellular repairs, which occurs in the earlier weeks following injury, cellular plasticity, and anatomical plasticity, including the formation of new connections. After the acute phase, remyelization and plasticity are the main processes that occur—particularly during the 3 months following the trauma. Certain methods of cerebral stimulation are able to suppress some of the pathological events and to reinforce other favorable processes, inducing cognitive and motor function recovery, which in turn help to minimize incapacitating sequelae.⁹ Accordingly, the theoretical use of adequate noninvasive cerebral stimulation early after TBI could result in a neuroprotective action that may help to reduce the incidence and severity of long-term neuropsychiatric complications of TBI. Nevertheless, the risks of transcranial magnetic stimulation (TMS)–induced seizures and skull conductance modifications, for example, especially in severe TBI victims, could limit the use of such interventions in the period immediately after the trauma; indeed, the potential for neuropsychological damage may even be intensified with their application.¹ Still, the identification of biomarkers with sufficient accuracy to discriminate among those individuals with a higher chance of a worse prognosis could help to evaluate a risk/benefit relationship linked to early interventions, such as noninvasive cerebral stimulation.

In a recent study, we demonstrated that the duration of posttraumatic amnesia (PTA) was independently associated with personality changes, a clinical entity that is deeply connected with global cognitive deficits.³ An important limitation of that study, the retrospective evaluation of PTA, could be eliminated with prospective data collection, permitting the identification of the cutoff for the risk of personality changes as well as predicting specific cognitive deficits that are associated with both behavioral disorders and impaired activities of daily living, including the ability to return to work. These issues are being investigated by an ongoing multicenter study.

Noninvasive cerebral stimulation for enhancing cognition in neuropsychiatric disorders is undoubtedly a promising method.² Compared to other brain diseases, such as Alzheimer's disease, schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder, TBI has the benefit of the exact time of onset of the pathophysiological process being known. This advantage facilitates the completion of studies using noninvasive techniques as a neuroprotective method for individuals with higher risks of cognitive sequelae.

The possibility of mitigating the cognitive deficits associated with TBI using noninvasive brain stimulation in an early phase after trauma based on the duration of PTA in higher-risk individuals could have a positive impact on reducing the social burden associated with TBI. In particular, this treatment strategy could minimize the personal and familial suffering that accompanies severe TBI for a significant portion of survivors.

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DISCLOSURE

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References

1. Demirtas-Tatlıdide A, Vahabzadeh-Hagh AM, Bernabeu M, Tormos JM, Pascual-Leone A: Noninvasive brain stimulation in traumatic brain injury. **J Head Trauma Rehabil** 27:274–292, 2012
2. Demirtas-Tatlıdide A, Vahabzadeh-Hagh AM, Pascual-Leone A: Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? **Neuropharmacology** 64:566–578, 2013
3. Diaz AP, Schwarzbald ML, Guarnieri R, de Oliveira Thais ME, Hohl A, Nunes JC, et al: Posttraumatic amnesia and personality changes after severe traumatic brain injury: preliminary findings. **CNS Neurosci Ther** 20:479–482, 2014
4. Diaz AP, Schwarzbald ML, Thais ME, Cavallazzi GG, Schmoeller R, Nunes JC, et al: Personality changes and return to work after severe traumatic brain injury: a prospective study. **Rev Bras Psiquiatr** 36:213–219, 2014
5. Diaz AP, Schwarzbald ML, Thais ME, Hohl A, More M, Schmoeller R, et al: Psychiatric disorders and health-related quality of life after severe traumatic brain injury: a prospective study. **J Neurotrauma** 29:1029–1037, 2012
6. Rao V, Spiro JR, Handel S, Onyike CU: Clinical correlates of personality changes associated with traumatic brain injury. **J Neuropsychiatry Clin Neurosci** 20:118–119, 2008 (Letter)
7. Shin SS, Dixon CE, Okonkwo DO, Richardson RM: Neurostimulation for traumatic brain injury. **J Neurosurg** 121:1219–1231, 2014
8. Tate RL: Executive dysfunction and characterological changes after traumatic brain injury: two sides of the same coin? **Cortex** 35:39–55, 1999
9. Villamar MF, Santos Portilla A, Fregni F, Zafonte R: Non-invasive brain stimulation to modulate neuroplasticity in traumatic brain injury. **Neuromodulation** 15:326–338, 2012

Response

We appreciate the interest of Diaz et al. in our recent review of brain stimulation strategies for the treatment of TBI. These authors specifically comment on the potential use of noninvasive brain stimulation in the more acute period following TBI. They suggest that the duration of PTA is a potential criterion for the use of brain stimulation because it can possibly identify those individuals at most risk for post-TBI personality changes. This is an interesting idea, and it highlights the complexity of TBI and the difficulty inherent in selecting appropriate patients and time frames after injury in which to initiate experimental therapies. Clearly, no single parameter will be sufficient for this purpose. The identification of structural imaging, functional imaging, and electrophysiological biomarkers that, in combination with clinical characteristics such as PTA, may predict the potential for therapeutic modulation by neurostimulation, remains a primary goal for research in this field.

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Published online June 5, 2015; DOI: 10.3171/2014.12.JNS142425.

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