Neurosurgical Forum

LETTERS TO THE EDITOR

Magnetic resonance–guided focused ultrasound thalamotomy for Parkinson’s disease

TO THE EDITOR: We wish to thank Zaaroor et al.² for their report on MR-guided focused ultrasound (MRgFUS) for the treatment of Parkinson’s disease (PD) and essential tremor (ET) (Zaaroor M, Sinai A, Goldsher D, et al: Magnetic resonance–guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson’s disease and essential tremor cases. *J Neurosurg* [epub ahead of print February 24, 2017. DOI: 10.3171/2016.10.JNS16758]). The authors described their experience with 9 patients with PD, 18 with ET, and 3 with both. The clinical efficacy was monitored using a rating scale (Clinical Rating Scale for Tremor), the scores of which improved significantly at both 1 and 6 months following the treatment. The authors reported the adverse events, which included those that were transient and related to the sonication (headache, vertigo, nausea, and vomiting) and more long-term effects (ataxia and numbness). Of note, more than one-third of the patients experienced headache, although there is no comment on the severity. Also, almost half experienced vertigo, although only 10% experienced nausea. Of concern, 2 patients vomited around the time of the sonication. There is no mention of claustrophobia or positional discomfort, both of which we have seen at our center. Apart from local anesthetic administration for placement of the stereotactic frame, there is no mention of any other analgesia, sedation, or antiemetic.

In a series reported by Elias et al.,¹ there was a 60% incidence of head pain during sonication, and a 33% incidence of nausea with a 20% incidence of vomiting. In our experience with more than 50 patients with ET, we have seen the following. 1) Pain. The headache experienced can be severe enough to limit the power used. This can necessitate intravenous analgesia or risk aborting the procedure. 2) Nausea and vomiting. The vertigo is a relatively consistent experience for ET patients and may contribute to the nausea. Vomiting while secured to the MRI table and helmet poses a safety threat to the patient. 3) Claustrophobia is usually mild, but we observed severe symptoms requiring moderate to heavy sedation to complete the procedure. 4) Positional discomfort is a relatively common experience for these lengthy procedures (3–4 hours) and is effectively managed with sedation.

Therefore, we contend that the comment in the authors’ conclusions that there is no need for anesthesia is premature. While general anesthesia may not be required, we believe that the presence of personnel able to provide intravenous sedation and analgesia is essential for the safety of the patients and a more comfortable experience throughout the procedure.

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Disclosures

Dr. Chapman states that, although he has participated in trials funded by Insightec, Inc., he has received no personal benefit.

Response

We wish to thank Drs. Chapman and Tarshis for their important comments on our report of MRgFUS for tremor. In our cohort, forehead pain was encountered in 11 patients. Forehead pain occurred during sonication, although patients were treated with preoperative 1000 mg paracetamol. Patients usually complained of pain toward the end of the procedure, when the treatment energy was high, with a temperature above 50°C. Most patients tolerated the pain or responded to intravenous paracetamol. One patient in this series asked to stop the procedure prematurely because of pain but was convinced to undergo additional sonications while holding a staff member’s hand until a target temperature above 55°C was reached.

As for vertigo, we encountered short-lasting, self-limited vertigo during the sonication in 14 patients. Vertigo was rarely reported spontaneously by patients and was noted only when patients were specifically questioned about this symptom. In our patients, it was not a limiting factor for treatment. Vomiting was rare in our series, but, as the patients are secured with the stereotactic frame to

the MRI table during the procedure, it is indeed a great concern. In most cases an antiemetic was given preoperatively (8 mg ondansetron) and was administered again, during sonications, when needed. Because of the seriousness of vomiting while secured to the MRI table, our team includes an anesthesiologist for all treatments. We agree with Chapman and Tarshis that this treatment should not be performed without an anesthesiologist present during the procedure. We want to clarify that general anesthesia is not needed for MRgFUS, but an experienced anesthesiologist is required.

We did not encounter claustrophobia in our present series, probably because we questioned patients before the procedure regarding this condition. None of our patients complained of positional discomfort since special attention was given to a padded and warm patient environment with flexed legs and pads under the knees. Furthermore, between sonications, when examining the patients, we encouraged them to exercise their legs.

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Postcranioplasty changes in cerebral blood perfusion and its impact on neurological and clinical outcomes

TO THE EDITOR: We studied with keen interest the article by Shahid et al.² regarding their experience of the effects of cranioplasty on neurological and clinical outcomes and its relationship with cerebral blood flow (Shahid AH, Mohanty M, Singla N, et al: The effect of cranioplasty following decompressive craniectomy on cerebral blood perfusion, neurological, and cognitive outcome. *J Neurosurg* [epub ahead of print March 3, 2017. DOI: 10.3171/2016.10.JNS16678]). We commend the authors for undertaking an evaluation of this commonly performed neurosurgical procedure beyond the cosmesis and mechanical protection it provides.

The authors found that all tests of cognition showed statistically significant improvement after cranioplasty, but the effect was limited regarding improvement in hemodynamic parameters. There was a significant increase in blood flow only to the occipital lobe, while the frontal lobe showed only a nonsignificant increase. It is difficult to explain the improvement in the cognitive parameters based on these findings, as most of the neuropsychological tests that were administered are of functions executed by the frontal lobe. Even the immediate and delayed recall showed improvement while SPECT revealed a decrease in blood flow to the temporal lobe, although not significant, which is opposite to the obvious expectation. Also, we sus-

pect that there might be an indirect relationship between the decrease in blood flow to the basal ganglia and improvement in motor functions of all 10 of the 34 patients who had weakness before cranioplasty. It would have been useful if the authors had discussed the possible explanations for these counterintuitive findings. We also note that in this study an arbitrary time interval of 3 months was chosen to evaluate the effect of cranioplasty on all outcome variables, but there was no biologically plausible rationale or reference provided for this choice.

It has been noted that 2 patients had to undergo titanium mesh cranioplasty due to autologous bone infection. It would have been very interesting for the readers to know the outcomes of these 2 patients in particular. It would have helped in gaining insights regarding the differences different materials may make in the blood flow changes, and finally in the outcomes across various parameters.

Another very important aspect of cranioplasty that was not mentioned in the article was in regard to the postcranioplasty complications. It has been found by different studies that there is significant risk of resorption of the bone used for cranioplasty, sometimes as high as 20%.³ The effect that such resorption has on the cerebral hemodynamics and consequently its effect on clinical and neurological outcome variables should have been evaluated and discussed, considering its significant rate. For this, a longer follow-up duration is needed with blood flow measurements and neuropsychological testing repeated at well-defined intervals.

The initial indication for performing decompressive craniectomy was not mentioned anywhere in the article. We suspect that the initial diagnosis may have a major bearing on the final outcome of the patients. It must be mentioned whether patients with frontal lobe injury or contusion, infarct involving frontotemporal region, etc., were included without any selection bias. If not, then it will be erroneous to extrapolate the findings of this study to all patients with traumatic brain injury.

It is appreciable that the authors have compared the early (less than 6 months) and the late cranioplasty groups separately with matching. Although they found greater improvement in the neurological outcomes in the early group, they have noted that this may be confounded by the greater rate of spontaneous recovery early in the postcraniectomy phase as noted by Di Stefano et al.¹ The question of long-term impact of early cranioplasty thus goes unanswered in spite of the prima facie advantage. The improvement attributable to cranioplasty over and above the expected spontaneous recovery has not been evaluated for either group. Although ideally a control group not undergoing cranioplasty must be considered, if the outcomes of the late cranioplasty group are also measured around the time of early cranioplasty, these may serve as controls for the early cranioplasty group.

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Disclosures

The authors report no conflict of interest.

Response

We have read with interest the comments by Sharma et al. In our study, all 34 patients who had undergone cranioplasty following decompressive craniectomy had head injuries of different grades. Patients who had undergone decompression following vascular insult such as infarct were not included in the study.

The postoperative course in all 34 patients was uneventful. There were no reported surgical-related complications, such as CSF leaks, wound infection, wound bulge, etc. However, postoperative details of 3 patients who dropped out were not available. Different studies have reported a high percentage of bone resorption, but in the present study we did not specifically measure the degree of bone resorption and surgical-related complications. In a previous study conducted in our department by Singla et al.,³ the measured rate of bone resorption was found to be about 14%.

Two patients underwent titanium mesh cranioplasty due to autologous bone infection. Neurological, neuropsychological, and SPECT outcomes of these patients were not much different from others, suggesting that maintaining cranial continuity would be more important for maintaining CSF hemodynamics than choice of material used for cranioplasty.

We agree with the comment that there was some discordance between the improvements in cognition related to different lobar functions as compared with SPECT findings for assessing cerebral blood flow. This asymmetry could be due to redistribution of blood over the cerebral convexity in the frontal, temporal, and occipital lobes over the basal ganglion. Other demographic and clinical variables such as age, education, injury status, and time interval between injury and hospital admission are important factors that could have influenced the outcome and have not been explored in the present study.

The patients were assessed after 3 months following cranioplasty as spontaneous recovery is usually faster in the first 3 months. The time elapsed between cranioplasty and cognitive assessment would have controlled the effect of spontaneous recovery on cognitive functions to a certain extent. Various other studies have also evaluated their findings at 6 weeks to 6 months postcranioplasty.^{1,2} But a

definitive conclusion cannot be drawn because there was no control group for comparison. In the current scenario, it is unethical to deprive any patient of available treatment options. Hence, the control group was not included in our study. In this study, each patient served as his or her own control, as the same patients were assessed at two different time points.

Despite a few limitations, this is an important study that paves the way for further research. Hence, there is a need to replicate the study using a larger sample and controlling confounding factors.

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Methodological issues with the development of a prediction rule for diagnosing postoperative meningitis

TO THE EDITOR: We have enthusiastically read the article by Hernández Ortiz and colleagues² (Hernández Ortiz OH, García García HI, Muñoz Ramírez F, et al: Development of a prediction rule for diagnosing postoperative meningitis: a cross-sectional study. *J Neurosurg* [pub ahead of print March 10, 2017. DOI: 10.3171/2016.10.JNS16379]). The authors endeavored to construct a diagnostic prediction model for postoperative meningitis using laboratory, clinical, and CSF variables and risk factors for CNS infection. They developed the model in a cross-sectional study and concluded that their prediction model for nosocomial meningitis improves diagnostic accuracy in neurosurgical patients suspected of infection. It should be noted that the study they conducted is engaging and fruit-

ful; however, it seems that some points regarding methodological issues should have been taken into account.

First, the authors constructed a prediction model for nosocomial meningitis in a cross-sectional study, which is problematic per se. The major assumption in prediction models is that these types of models should be applied to longitudinal data.⁵ In other words, it should be ensured that exposure variables have occurred before outcome and that the temporality assumption is not violated.⁵ However, in cross-sectional studies, exposure and outcome are assessed simultaneously, whereby the temporality assumption may be violated.⁴ To put it another way, as Steyerberg states, clinical prediction models should be constructed in longitudinal studies; otherwise, the yielded results may be misleading.⁵ Given this point, the prediction model developed by Hernández Ortiz et al. should be interpreted with caution as it employed a cross-sectional study.

Second, in addition to its construction, any model should be validated internally or externally through appropriate methods. Hence, when the model has not been validated, the results must be interpreted with caution.⁵ Hernández Ortiz and colleagues neither internally nor externally validated their prediction model; thus, it should be considered with caution.

Third, the authors conducted a cross-sectional study in which the adequate sample size was not calculated. But it is an established fact that the adequate sample size of any study should be calculated before conducting that study in order to not only gain predetermined precision for the estimated parameters, but also to consider the minimum acceptable power (0.8) for statistical tests.¹ However, the minimum power of statistical tests and sample size were not considered in the study conducted by Hernández Ortiz et al., in which some significant associations may be presented as nonsignificant due to the lack of minimum acceptable power for a statistical test.

Finally, scientists usually add 10 observations to the calculated sample size for each independent variable added to the multivariate model to avoid any over-parameterization. Hernández Ortiz and colleagues not only did not calculate the sample size, but neither did they consider additional observations for the multivariate model.³

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Response

We appreciate the comments by Drs. Safiri and Ayubi about our research. They raised several interesting issues that deserve special attention: “The authors constructed a prediction model for nosocomial meningitis in a cross-sectional study, which is problematic per se. The major assumption in prediction models is that these types of models should be applied to longitudinal data.” From a clinical and methodological point of view, the concept behind prediction applies to both prognosis and diagnosis processes.¹ Certainly, in a prognostic prediction, a longitudinal relationship with a clear temporal relationship between predictors before the outcome is required. In a diagnostic prediction, on the other hand, the interest is, in principle, a cross-sectional relationship between the index test and the reference standard.¹ Indeed, according to Steyerberg on the issue of studies for diagnosis,³ “the study may therefore be labeled cross-sectional, since the predictor-outcome relationships are studied at a single point in time. Several characteristics may be predictive of the underlying diagnosis. For a model, we should start with considering simple characteristics such as demographics, and symptoms and signs obtained from patient history. Next, we may consider simple diagnostic tests, and finally invasive and/or costly tests. The diagnosis (presence or absence of the target disease) should be established by a reference test or standard. This test used to be called “gold standard.” In the same way, our model selected simple clinical and laboratory variables to improve the accuracy of diagnosis in CNS infection, as cultures yield positive results in just 20% of cases.

On the other hand, we absolutely agree that any prediction model should be validated both internally and externally. As a matter of fact, we explained under *Sensitivity Analysis* that “internal validation was performed using bootstrapping with 200 repetitions.” Moreover, the results of this bootstrapping are shown in the supplemental material available on the journal’s website. Additionally, we acknowledged in the abstract’s *Conclusions* that “an independent validation of the rule in a different group of patients is warranted.”

Finally, Safiri and Ayubi affirmed that we conducted a cross-sectional study in which the sample size was not calculated. Needless to say, the issue of sample size is a developing process in predictive models. Indeed, according to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement, “although there is a consensus on the importance of having an adequate sample size for developing a prediction model, how to determine what counts as ‘adequate’ is not clear.”¹ In our research, we considered not only the concepts of sample size and power, but also the historical records in our institutions. Under *Data Collec-*

tion and Predictors, we wrote, “According to hospital records from prior years, the total number of patients with confirmed/probable NM [nosocomial meningitis] was calculated to be approximately 150. With this value, up to 15 independent variables might be included in the multivariate model, following the guide of 10 outcomes for each predictor.”² Our final study population was composed of 154 patients (48.1%) with confirmed/probable NM and 166 (51.9%) with NM ruled out. Although 40 variables were initially considered, after bivariate analysis just 15 variables had statistical associations with the outcome. The final multivariate analysis fitted a model with 6 variables for the prediction rule. Accordingly, we do follow the classic rule for sample size according to outcomes/predictors.

Currently, we are planning and establishing the settings for external and multicenter validation of the prediction rule. Thus, this research into CNS infections is in continuous development and improvement.

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Intraoperative brain relaxation using mannitol

TO THE EDITOR: We read with great interest the article by Seo et al.³ (Seo H, Kim E, Jung H, et al: A prospective randomized trial of the optimal dose of mannitol for intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection. *J Neurosurg* 126:1839–1846, June 2017). We commend the authors for trying to answer a clinically pertinent question.

Many other authors have also published the results of their research to find the appropriate dose of mannitol to achieve adequate intraoperative brain relaxation or control of intracranial pressure.^{1,4,5} Seo and colleagues have tried to balance many known variables among the groups receiving the different doses of mannitol, which the previous

studies did not do. We would like to direct the readers' attention toward a few points that will impact the conclusion of the study.

Patients with supratentorial tumors who are drowsy or have a low Glasgow Coma Scale score are usually started on steroids (oral or intravenous) and/or hyperosmolar therapy (oral or intravenous) preoperatively. As patients with Glasgow Coma Scale scores ≥ 12 were included in the current study, it is likely that many of the patients would be on steroids (oral or intravenous) and/or hyperosmolar therapy (oral or intravenous) before surgery. Patients who received mannitol in the preoperative period were excluded from the study, but there is no accounting of the patients who received steroids or hypertonic saline or glycerol in the preoperative period. These drugs will have an effect on the condition of the brain intraoperatively. We think that it is important to study this variable as well, since it may have acted as a confounding variable.

The patients included in the study showed a midline shift > 3 mm on brain MRI. The mean midline shift varied from 8.4 to 10 mm among the different dose groups, with no statistically significant difference. The authors concluded that a 1.0-g/kg dose of mannitol led to satisfactory brain relaxation with the least number of adverse effects in their patients. We think that it is not right to generalize the adequate dose of mannitol to all the patients with supratentorial tumors with different degrees of brain edema and midline shift. For patients with less midline shift, a smaller dose might be adequate. We think that the conclusion of this study should mention that 1.0 g/kg of intraoperative mannitol achieves adequate brain relaxation for patients with supratentorial tumors with midline shift ranging from 8.4 to 10 mm. The higher doses of mannitol provide better brain relaxation, but at the cost of adverse effects. Hence, an optimal dose of mannitol should be used.^{2,3}

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Disclosures

The authors report no conflicts of interest.

Response

First, we thank Dr. Garg and coworkers for their great interest in our recent article. They were concerned that preoperative steroids and hypertonic saline, which are generally used for peritumoral edema control in patients with supratentorial brain tumors, affect the intraoperative brain condition and thus acted as a confounding variable in our interpretation of our results. We fundamentally agree with their opinion. However, most patients in the study, except one, received intravenous dexamethasone preoperatively. In addition, no patient had hyperosmolar therapy such as hypertonic saline administration before the surgery. Therefore, in our study, there is no possibility that preoperative steroids and hypertonic saline acted as confounding variables in determining the optimal dose of mannitol for intraoperative brain relaxation.

With respect to the effect of the extent of midline shift and peritumoral edema on the mannitol dose, we agree with their opinion that the optimal mannitol dose for producing satisfactory brain relaxation may be different in patients with supratentorial brain tumors because of the different degrees of brain edema and midline shift. In our study, the extent of midline shift and peritumoral edema was not initially considered because group assignment was based on the dose of mannitol. However, our subgroup analysis showed that in patients ($n = 43$) who had midline shift of more than 10 mm, but not in those with midline shift less than 10 mm, there was a positive linear relationship between the administered dose of mannitol and the proportion of satisfactory brain relaxation ($p = 0.012$). In addition, only in the patients ($n = 101$) who had peritumoral edema of more than 10 mm was there a significant positive linear relationship between the intraoperative mannitol dose and the proportion of satisfactory brain relaxation ($p = 0.004$). Such findings suggest that at least in patients with midline shift or peritumoral edema more than 10 mm, the greater doses of mannitol yield better brain relaxation. As mentioned by Dr. Garg and coauthors, for patients with less midline shift and peritumoral edema, a smaller dose of mannitol might be adequate to provide satisfactory brain relaxation. In our study, we suggested 1.0 g/kg of mannitol as an optimal dose in patients with supratentorial brain tumor because there was no statistically significant difference in the preoperative brain conditions among the 4 groups with the different mannitol doses. However, our subgroup analysis suggests that the optimal dose of mannitol may be different in patients with supratentorial brain tumor because there is a significant difference in preoperative brain conditions among patients.

In conclusion, we believe that the dose of mannitol should be individualized based on preoperative brain conditions such as the extent of midline shift and peritumoral edema in consideration of the balance between the beneficial and adverse effects of mannitol.

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Delayed parent vessel occlusion in Pipeline embolization

TO THE EDITOR: We read with interest the article by Potts et al.³ regarding parent vessel occlusion (PVO) caused by the Pipeline Embolization Device (PED) (Potts MB, Shapiro M, Zumofen DW, et al: Parent vessel occlusion after Pipeline embolization of cerebral aneurysms of the anterior circulation. *J Neurosurg* [pub ahead of print January 6, 2017. DOI: 10.3171/2016.9.JNS152638]). The authors presented a retrospective review of 256 patients with anterior circulation aneurysms treated with PED, identifying those who subsequently experienced PVO either acutely or in a delayed fashion. The clinical details and aneurysm characteristics of the patients who did and did not develop PVO are well presented. Overall, 6 patients had asymptomatic PVO, which was delayed in 3 patients. The other 3 cases were not documented as delayed, and the time course of the occlusion remains unknown. Two patients had acute PVO with associated symptoms. Thus, the incidence of delayed PVO was 1.2%. Just prior to publication of the article by Potts et al., the 5-year results of the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial¹ were also published, noting 6 cases of PVO among 109 treated vessels, 5 cases being asymptomatic. Fusiform morphology accounted for 5 of the 6 cases of PVO.

Interestingly, at the time the article was published online, our own article on the same phenomenon was under review and has recently been published in the *Journal of NeuroInterventional Surgery*.⁴ Given these recent reports, we would like to briefly highlight some of the shared findings and propose areas for further investigation.

We and Potts et al. both noted several cases (2 and 3, respectively) that had clear documentation of the progression of delayed PVO, with an intermediate state of nonocclusive stenosis prior to full occlusion. Potts et al. reported occlusion occurring between 6 months and 3 years, in line with our findings, which ranged from 3 months to 2 years. We additionally noted its occurrence in smaller aneurysms (especially in distal aneurysms with smaller parent vessels), beyond the large or giant aneurysms seen by Potts et al. We also noted the occurrence of PVO in cases of overlapping PEDs and suspect that this may be a contributing factor. While the use of multiple PEDs was once more common,² we now use multiple PEDs mostly in cases of large or giant aneurysms.

All the patients in our series and the delayed occlusions described by Potts et al. were asymptomatic despite the PVO. We both noted the development of pial-pial collater-

als, and Potts et al. additionally described the presence of collateral flow via the external carotid artery circulation. We hypothesize that the PED may act as a “smart” device wherein delayed PVO occurs only in patients with sufficient collateral flow to the territory, due to a change in the normal anterograde flow dynamics.

We agree with their hypotheses regarding the pathophysiology underlying PVO based on neointimal hyperplasia. While our multicenter experience and the New York University experience are the first few that have focused on the occurrence of delayed PVO, we are hardly the first to notice this phenomenon, as shown in Table 1 by Potts et al. However, given the relative rarity of PVO, neither we nor Potts et al. could determine any risk factors for PVO or, if any, the potential maneuvers or medications to avoid any symptomatic occlusions.

We hope that other investigators with extensive experience in flow diversion continue to collaborate and explore this phenomenon to optimize our care of aneurysm patients.

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Disclosures

Dr. Kan has been a consultant for Stryker Neurovascular and Medtronic Covidien.

Response

No response was received from the authors of the original article.

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