Neurosurgical Forum

LETTERS TO THE EDITOR

Short-term ϵ -aminocaproic acid treatment and endovascular coil embolization

TO THE EDITOR: We read with interest the article by Malekpour and colleagues⁶ (Malekpour M, Kulwin C, Bohnstedt BN, et al: Effect of short-term ϵ -aminocaproic acid treatment on patients undergoing endovascular coil embolization following aneurysmal subarachnoid hemorrhage. *J Neurosurg* [epub ahead of print June 17, 2016; DOI: 10.3171/2016.4.JNS152951]), describing short-term treatment with ϵ -aminocaproic acid (EACA) in a consecutive case-control cohort undergoing endovascular treatment. The authors found no reduction in the risk of pretreatment recurrent bleeding in the EACA treatment group. Furthermore, short-term treatment showed no increase in pulmonary embolism and deep venous thrombosis (DVT), either in the risk of vasospasm, clinical stroke, or radiological infarction.

This article is important: it is one of the few reports describing short-term EACA treatment before endovascular aneurysm occlusion. Interestingly, the authors found no increase in the risk of DVT, which is in contrast to the findings of Foreman et al.² and Starke et al.⁷ This is especially remarkable because the authors continued EACA treatment until the start of the endovascular procedure, which is in contrast with previous reports in which EACA treatment was discontinued several hours before endovascular aneurysm treatment^{5,7} because of the potential risk of more thromboembolic complications during aneurysm treatment. Some points that might have strengthened the study are data on the total average dose of administered EACA, the mean duration of administration of EACA, and whether EACA treatment led to more risk of thromboembolic complications during aneurysm treatment.

Furthermore, the authors report that short-term treatment resulted in no increase in the risk of vasospasm, clinical stroke, or radiological infarction. However, a clear definition of vasospasm and clinical stroke was not provided, nor were how and when radiological infarction was defined and which modality was used. Hence, interpretation of these results remains difficult.

It is remarkable that the recurrent bleeding percentage was low when compared to findings reported in the litera-

ture: 3.1% versus 4.1% in the no treatment versus EACA treatment group, respectively. The authors report some factors that might have led to these low percentages: first, a decrease in the time interval between aneurysm rupture and treatment over the years; and second, interhospital transfers of some patients. A recent study by Germans et al.³ did indeed show that early recurrent bleeding occurs in 12% of individuals, with an additional 4% of patients having possible recurrent bleeding. Also, Germans et al.³ found that up to 40% of patients had recurrent bleeding before reaching a treatment center. Therefore it might be possible that out-of-hospital recurrent bleeding and that occurring during interhospital transfer was underreported. Nevertheless, Germans et al.³ found that the median time from onset of hemorrhage to recurrent bleeding was only 3 hours, precluding a positive effect of even more expeditious treatment.

Therefore, it appears that the start of antifibrinolytic treatment as early as possible is warranted, preferably as soon as the diagnosis of subarachnoid hemorrhage (SAH) is made, and only for a very short period of time, up until the causative aneurysm is treated. In this way the beneficial effects on recurrent bleeding are maximized, and the side effects of long-term treatment are minimized, as proposed in the recent update on the use of tranexamic acid in patients with SAH.¹

An ongoing, randomized, controlled trial (the Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage [ULTRA] trial) is currently enrolling patients in the Netherlands,⁴ and is registered at the Dutch Trial Registry (NTR3272) and clinicaltrials.gov (NCT02684812). This study should provide an answer to the question of whether ultraearly (as soon as possible after diagnosis) and short-term (until aneurysm treatment—with a maximum of 24 hours) tranexamic acid treatment leads to a better functional outcome. The final results are expected in 2019.

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Disclosures

The authors report no conflict of interest.

Response

We sincerely appreciate the comments by Dr. Post and colleagues. The current lack of prospective, randomized data regarding short-term antifibrinolysis in the setting of aneurysmal SAH leaves important clinical questions unanswered; their upcoming randomized controlled trial (i.e., the ULTRA trial) should assist in answering these clinical questions.

In our study, the data points for the incidence of vasospasm, clinical stroke, and radiological infarction were collected from the medical records prospectively during the course of the patient's hospitalization, based on clinical documentation. Vasospasm and clinical stroke (the latter defined as transient vs permanent focal neurological findings that could not otherwise be attributed to another source) were determined based on the clinical judgment of the neurosurgical team.

We agree that our findings differ from those reported in other similar series regarding DVT rates. Both cited studies,^{3,4} however, included microsurgically and endovascularly treated patients, whereas our study included only endovascularly treated patients, thus representing different patient populations.

More aggressive DVT screening protocols would have found more thromboses that otherwise would have been clinically silent and never required treatment. The control versus study group in Foreman et al.'s study³ was screened at a similar rate (35.1% vs 39.4%, respectively), suggesting that some of the DVTs in the antifibrinolytic group

potentially were clinically silent and that these were thus incidental findings. Finally, differences in DVT prophylaxis protocols between institutions may contribute to the different rates of DVT detection.

The rehemorrhage rate in our study may have been lower than expected. This finding is probably due to limitations of our study design. Rehemorrhages prior to admission or in transit were unlikely to be captured; our hospital is the primary aneurysm referral site for a large geographic area. We agree that the optimum strategy to maximize benefit from antifibrinolysis is to initiate it as early as possible and to combine its use with early aneurysm treatment to avoid the negative effects of long-term antifibrinolysis administration.

The antifibrinolytic agent of choice remains elusive, yet tranexamic acid may carry advantages over EACA because it is 10 times more potent, does not affect the blood coagulation parameters, and more readily crosses the blood-brain barrier.^{1,2} We appreciate the authors' insights, especially given their ongoing work in this area, and also eagerly await the results of the ULTRA trial to see if such an application of antifibrinolysis does indeed provide clinical benefit.

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Maxillary nerve schwannoma

TO THE EDITOR: We read with interest the article by Wallace et al.¹⁷ (Wallace SA, Meyer RM, Cirivello MJ, et al: Lateral orbitotomy for a maxillary nerve schwannoma: case report. **J Neurosurg** **125**:869–876, October 2016). The authors have discussed the effectiveness of lateral orbitotomy without resorting to craniotomy for resection of the tumor. As the subject is directly related to our clinical interest, we wish to make some comments.

As in the presented case, trigeminal neurinoma can generally be diagnosed on the basis of presented clinical symptoms and related signs, and characteristic radiological features. Our articles on the subject discuss the issue of characteristic “interdural” presence of the tumor when it is in relationship to the lateral wall of the cavernous sinus, and even when it has an extracranial extension.^{6,9,11,15} Although the interdural nature of trigeminal neurinoma is well understood by present-day neurosurgeons, such was not the case 25 years ago. We recently identified that even the posterior cranial fossa component of the tumor can be entirely interdural in nature.¹⁵ On the basis of this observation, in the year 1995 we reported that trigeminal neurinomas located within the cranial cavity and in relationship to the cavernous sinus, and also those having a posterior cranial fossa extension, could be resected by an infratemporal fossa approach.⁷ This operation involved widening of the foramen ovale and exploiting the anatomical character of the interdural presence. The tumor was resected, and no craniotomy was performed. As per our information, our report was the first in the literature wherein a relatively challenging intracranial tumor (at least at the time of the report) was resected without opening the skull. It is surprising that the authors could not locate this article in their literature search. In our subsequent article, we reported a series of 28 cases of trigeminal neurinomas having extracranial extensions.¹⁵ We identified that the extracranial portion of the tumor also had a well-defined “dural” cover that separated it from adjoining critical neural and vascular structures. Although in larger tumors this dural membranous divide may be thinned out, understanding its presence during surgery provides a remarkable surgical safety zone and a well-defined surgical plane of dissection. This understanding also provides an opportunity to reduce surgical exposure. By exploiting the relatively soft and avascular consistency of the tumor and working within the dural confines, the tumor resection can be performed and the traversing neural fibers can be saved. As in trigeminal neurinomas, C-2 neurinomas also have characteristic dural relationships.⁸ The nature of the dural relation of C-2 neurinomas has been previously described by our group and published with a cover page illustration in the *Journal of Neurosurgery* (February 2008). On the basis of understanding dural relations, we resected selected C-2 neurinomas, including those having spinal canal extensions, by working within the dural limitation and avoiding all types of bone resection. We believe that our article was the first in the literature wherein a spinal canal tumor was resected without any bone work.⁸ We have also discussed the issue of dural relationship of oculomotor neurinomas, chordomas, pituitary tumors, nasopharyngeal angiofibromas, cavernous hemangiomas, epidermoid tumors, dermoid tumors, and teratomas.^{1-5,7,10,12-14,16}

For trigeminal neurinomas having large extracranial extensions, we have described the reverse skull base approach.¹⁵ This technique involved a craniotomy and extradural retraction of brain to expose the extracranial tumor. This policy of retraction of brain to expose extracranial tumor is a reversal of tenants of skull base surgery, in which bone is resected to avoid brain retraction to expose the tumor.

Although the authors were able to reduce surgical ex-

posure, it is surprising that they did not elaborate on the dural characteristics of the tumor.¹⁷ We believe that if anatomical concepts about the location of the tumor are well understood, intraoperative imaging and navigation tools can safely be avoided. Particularly for a tumor of the described nature and size, use of the endoscope appears to be superfluous. Moreover, the need for neurophysiological monitoring of motor evoked potentials and somatosensory evoked potentials of cranial nerves appears to be more than necessary. The proposed technological orchestra seems to be an attempt to introduce the noise of metallic clutter and complicate an otherwise straightforward surgical problem. There is no discussion about the status of trigeminal nerve fibers at the end of tumor resection. The authors mention that the maxillary root was not involved in their case. This observation does not seem to be correct, as there was sensory loss in the maxillary division of the nerve before the operation and the sensations worsened after the operation. The authors could have discussed the anatomical relationship of the tumor with the foramen rotundum and the superior orbital fissure. We had earlier identified that in trigeminal neurinomas with large extracranial extensions, frequently it may not even be possible to identify the exact nerve division of the origin of the tumor. The authors report that the sensations of the maxillary division of the nerve were “mildly” diminished following surgery. Although a decrease in sensations of the involved division of the nerve is a frequent result, a successful outcome in such cases is when the sensations recover following surgery, at least to some extent. I am wondering if the sensations would have diminished or been lost in the first division of the trigeminal nerve, the patient would have had a severe visual problem or there even could have been a threat to the survival of his eye. For a similar tumor, we would have only performed a lateral orbitotomy and avoided manipulation of the zygomatic bone. As the authors have alluded to in the article, we prefer removal of the anterior part of the temporal squamous bone to achieve the exposure of the extracranial component of the tumor (particularly in larger tumors) rather than removal of the frontal process of zygomatic bone, which is not only time consuming and unnecessary but also can have negative cosmetic consequences.

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Response

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

Disclosures

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Ultrasound in peripheral nerve injuries: the challenge

TO THE EDITOR: We read with great interest the article by Toia et al.⁴ (Toia F, Gagliardo A, D’Arpa S, et al: Preoperative evaluation of peripheral nerve injuries: What is the place for ultrasound? *J Neurosurg* **125**:603–614, September 2016). A series of 108 patients with 119 injuries was presented: 69 were affected by nerve entrapment syndromes, 36 by posttraumatic or postsurgical nerve injuries, and only 3 by tumors.

We agree with the authors that high-definition ultrasound is a tremendous tool for studying damaged nerves. In fact, it is commonly used in presurgical evaluations, as demonstrated by the numerous clinical articles cited by the authors. The surgical study by Toia et al.⁴ is noteworthy

and prompted some considerations. First, we truthfully think that in entrapment syndromes, ultrasound can be exceptionally useful for planning surgeries, making surgery faster and easier and improving discussions with the patient. But a bifid nerve in a carpal tunnel, for example, does not alter the procedure, and the same can be said for other entrapment syndromes. At the present time, we think that the most important discussion on the role of ultrasound as regards entrapment syndromes is if this tool would, in the future, almost completely replace the more uncomfortable electrophysiological examination: diagnosis of the most common entrapment syndromes could then be based on clinical symptoms and ultrasound findings only.

Second, we agree with the authors that the main contribution of ultrasound is its ability to visualize nerve continuity. Ultrasound can distinguish between interrupted fascicles and those in continuity, allowing early differentiation of neurotmetic from axonotmetic injury. For this reason, we consider ultrasound to be mostly useful in post-traumatic and postsurgical nerve injury. Before surgery, ultrasound can even be revolutionary because it allows us to overcome one of the most important problems in the field of peripheral nerve repair—that is, surgical timing. In fact, it is not rare in traumatic peripheral nerve injuries for the surgeon to have difficulty distinguishing between neurotmesis and axonotmesis.¹ In these cases, waiting 6 months for an eventual spontaneous functional recovery before performing exploratory surgery is an old rule. In fact, ultrasound actually makes a difference not only in the assessment of posttraumatic nerve injuries, avoiding any delay in treatment, but also in the surgical planning, making surgery faster and easier. In fact, the nerve route is followed with the ultrasound probe until the neuroma and beyond it: taking into account the cross-sectional area and the echoic features of the injured nerve, the gap requiring graft placement can be precisely measured. In this way, tailored skin incisions are drawn over the injury site as well as the donor nerve site, and surgery is more thorough and less time consuming.² We also want to emphasize the role of ultrasound after reconstructive surgery. In fact, during follow-up, the graft shape can be easily checked, and the eventual scar tissue as well as its misplacement can be detected early.²

The third consideration is related to the role of ultrasound in peripheral nerve tumors, most of which are schwannomas. In this field, we think that the most important diagnostic “tool” in the majority of cases is the clinical examination together with the survey for tumefaction and a Tinel sign: ultrasound and/or other radiological examinations such as MRI and/or CT support the surgeon in confirming the suspected diagnosis. Then, standard microsurgery allows selective and safe tumor removal, after recognizing and dissecting most of the nerve fascicles not involved by the tumor.³

In conclusion, we think that ultrasound can be really useful for improving surgical planning, decision making, and clinical follow-up and that in the near future, with the finest techniques, ultrasound could replace the use of neurophysiological studies in peripheral nerve injuries.

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Disclosures

The authors report no conflict of interest.

Response

We read with interest the letter by Lauretti et al. in response to our article.

The authors agree with us on the relevant contribution of ultrasound in the preoperative evaluation of nerve injuries but comment on 3 points that we would like to discuss further.

Their first point is that ultrasound is of little help in entrapment syndromes and could replace neurophysiological examinations in the future. We disagree with their point of view. First, although ultrasound is not essential to the diagnosis and surgical planning of entrapment syndromes, we believe that it does contribute to a more refined surgical approach. For instance, it can reveal the need for neurolysis, contraindicating an endoscopic decompression technique, or visualize an unexpected compressive mass to be removed. Moreover, we think that ultrasound can never replace neurophysiological examination as a means of wide exploration of the neuromuscular system, which is not feasible by ultrasound and is necessary to identify surgical candidates and discriminate systemic neuropathies or neurodegenerative diseases. Further, the study of bioelectrical tissues cannot be compared to the morphological study of electrically inactive tissues, such as the tendons. A nerve is indeed an anatomical conductive structure that works by bioelectrochemical potentials, and the functioning fibers must be characterized and quantified. Thus, a morphological study of the nerve by ultrasound can only be used for anatomical correlation of functional findings and can only enrich those findings, not replace them. This specific information on preoperative nerve function can be compared with the postoperative data to follow up the outcome of surgery. In addition, ultrasound is not always reliable in the postoperative follow-up of entrapment syndromes; after the surgical release of a nerve, there is often an increase in the nerve cross-sectional area, which could be classified as a worsening. In contrast, electrodiagnostic studies do

correctly show the functional improvement. These considerations have both a clinical and medico-legal value too.

Second, as mentioned by the authors and in our paper, ultrasound's major contribution lies in posttraumatic and postsurgical nerve injuries, and we thank the authors for emphasizing its role in the follow-up.

Third, Lauretti et al. state that in nerve tumors, the presence of a mass and a positive Tinel sign provides the most important diagnostic "tool" and that imaging is only useful for confirmation. We disagree with them. In tumors, we need the anatomical information for surgical planning. Although diagnosis of a nerve tumor, if palpable, can be clinical, we need information on the size and the relationships with the fascicles to adequately plan surgery and to correctly inform the patient preoperatively. Ultrasound gives adequate information and can replace the more time-consuming, expensive, and less patient-friendly MRI.

In our opinion, ultrasound can help to achieve a comprehensive diagnostic and therapeutic plan, bridging the gap between the pathophysiology and morphological anatomy of nerve injuries. We believe that imaging should be performed in each case of a nerve lesion, adding detailed anatomical information that is not otherwise possible to provide after neurophysiological evaluation and before surgery. The diagnostic challenge is providing all the functional and anatomical information, showing subclinical alterations without ignoring the specific role of the nervous conduction potentials.

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Threshold criterion in transcranial motor evoked potentials

TO THE EDITOR: We read with deep interest and anticipation the article by Abboud et al. (Abboud T, Schaper M, Dührsen L, et al: A novel threshold criterion in transcranial motor evoked potentials during surgery for gliomas close to the motor pathway. *J Neurosurg* 125:795–802, October 2016)¹ regarding the use of a novel threshold criterion in motor evoked potentials (MEPs) elicited by transcranial electrical stimulation (TES) to predict patients' postoperative motor deficits after glioma surgery.

The authors applied their personalized protocol to 93 patients harboring a glioma close to the motor pathway, who were thus at risk of developing postoperative neurological deficits, but excluding those with motor cortex

involvement. No data were available about preoperative approximate distance from the motor pathway, nor apparently was preoperative diffusion tensor imaging assessment performed.

The first and main flaw we find in their work lies in a conceptual error that derives directly from a major drawback in their applied method. To our understanding, the use of MEPs recorded by TES is not a reliable, safe, or appealing intraoperative method to assess the integrity of the motor pathway during surgery of brain tumors located in close relation to the corticospinal tract (CST) at the supratentorial space.

As a basic principle, TES creates an arch-shaped electric current that passes between a selected anode and cathode, with pre-established current intensity. This arch-shaped current grossly stimulates the CST deep in the brain, generating the propagated stimulation that allows the MEP recording.⁴ Note that the higher the preselected current intensity, the bigger the arch, and thus deeper structures or functional bundles are stimulated until reaching the brainstem fibers.⁶ Therefore, if the CST is damaged during the resection of the tumor, added to the fact that no previous warning signal will be recorded, an increase in the intensity of the stimulus will increase the size of the current's arch, and therefore the stimulus will bypass the lesion and stimulate fibers distal to the working area.⁸ In this way, MEPs recorded from TES—even though it is an extraordinarily valuable technique for intraoperative functional assessment in posterior fossa, brainstem, and spine surgeries—do not guarantee the integrity of the CST during supratentorial tumor resections.

Although direct subcortical stimulation would have provided the surgeon with information regarding the distance to reach the motor pathway and permitted the practitioner to stop the resection in a safe distance, allowing a real-time assessment of the CST during the surgical procedure, the authors in their work did not perform real-time monitoring. In our opinion the authors only performed an intraoperative neurophysiological electrical recording of a possible postoperative neurological deficit.

Finally, the authors reported a remarkably low rate of postoperative neurological deficits (in 13 of 93 patients), but taking into account the fact that they were dealing with gliomas near eloquent areas, these results could be related to their high rate of subtotal resection (40% of patients). Furthermore, among the patients who presented with a postoperative neurological worsening, a notably high percentage (almost 40%) presented with a permanent neurological deficit.

It has been widely demonstrated that the extent of resection in low-grade and high-grade gliomas has a major impact in overall patient survival,^{2,7} and also that direct brain stimulation techniques and brain mapping could improve the quality of resection in gliomas located in eloquent areas.^{3,5}

For these reasons, surgical procedures treating both low- and high-grade gliomas near eloquent areas should be performed with the aid of intraoperative real-time functional assessment. An individualized functional approach combining direct cortical and subcortical stimulation with intraoperative neurophysiological monitoring is nowadays the most accurate, safe, and reliable technique for per-

forming an intraoperative functional approach in gliomas near eloquent areas, allowing maximization of the resection and avoiding permanent neurological deficits.

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Disclosures

The authors report no conflict of interest.

Response

We would like to thank Dr. Sanmillan et al. for the interesting discussion regarding our article, and we greatly appreciate the opportunity to respond to their comments.

Monitoring of MEPs after TES during surgery for supratentorial lesions is a well-established method, and we were not the first to use it; it has been described by Neu- loh et al.,⁵ Szelényi et al.,¹⁰ and Krammer et al.⁴ The use of threshold level itself to predict neurological deficit has been reported before, also in the context of direct cortical stimulation (DCS).⁸ What we introduced in our article is a new interpretation of the threshold criterion during cranial surgery for unilateral supratentorial lesions, taking into consideration the affected and unaffected sides. The unaffected hemisphere should be understood as a reference to the affected one, thus allowing us to detect changes in threshold level resulting from other factors than damage to

the CST. We showed that the threshold level can increase on the affected and unaffected sides without damaging the motor pathway, and elaborated on these changes in a further study,¹ in which we performed a comprehensive analysis of factors that might influence intraoperative MEP and lead to a change in threshold level.

Regarding the extent of tumor resection, we agree that it is an important predictor of overall survival, and according to the postoperative MRI scans in our series, gross-total resection was achieved in 56 of 82 patients (68%) in whom complete tumor resection was attainable. This rate is comparable to the rate of gross-total resection (65%) reported by Stummer et al. in their randomized controlled study conducted to validate the use of 5-aminolevulinic acid for resection of malignant glioma,⁹ and is higher than rates of gross-total resection reported in other series.^{2,7}

The understanding of Sanmillan et al. that TES and MEP monitoring is not a reliable or safe method to assess integrity of the motor pathway during surgery for supratentorial lesions located close to the CST, as they argued, was not based on clinical series that would compare TES with DCS (which would be an interesting comparison), and we do not know if it was based on their clinical experience with TES. The postulation that TES with a high stimulus intensity may produce a stimulus that can depolarize deeper subcortical structures was first discussed by Rothwell et al. in the context of spine surgery and D-wave latency measurements.⁶ They used a TES system with an anode located at the vertex and a cathode located 7 cm laterally, a stimulation intensity up to 1500 V, and recorded epidural evoked volleys.

In our series we performed a completely different setting, because first we used a more selective stimulation (C4/C3 to Cz), and second we defined the threshold level as the minimum voltage needed to elicit a motor response from the muscle being monitored, allowing the depolarization to occur at the level of cortex or subcortex.³ The starting values of threshold level had a median of 118 V in patients without preoperative paresis and a median of 126 V in patients with preoperative paresis. We performed the intraoperative MEP monitoring while always assessing both affected and unaffected sides, and the stimulus intensity was always raised in relation to the unaffected side until a difference of 20% between sides was exceeded, which then was considered a significant alteration requiring an adequate reaction from the surgeon. In addition, if the electrical stimulus bypasses the lesion, a false-negative result should be expected, which was not the case in our series.

Subcortical stimulation, which we also apply in daily practice, is not a functional assessment but a mapping tool to estimate the distance to the CST, and this tool does not allow us to detect direct vascular damage, critical end-artery blood supply, or ischemia due to brain retraction.⁸ Therefore, a functional assessment performed using intraoperative MEPs is mandatory to predict the postoperative motor function.

Finally, we would encourage these colleagues to apply the TES MEP and perhaps to compare it with the DCS. A wider use of the novel threshold criterion would be interesting, and would enable a discussion of more specific concerns than those regarding TES MEP in general.

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