Letters to the editor

Subarachnoid hemorrhage


Ruptured aneurysm–related subarachnoid hemorrhage (SAH) is an emergent neurosurgical condition requiring clipping or embolization of the aneurysm. Moreover, SAH-induced vasospasm often leads to cerebral infarction and morbidity, or death. Kuo et al. conducted a laboratory investigation to evaluate the effect of baicalin reduction of neurological injury in the early stage after SAH. They found that baicalin significantly decreased mortality and neuronal injury. Moreover, treatment with baicalin was associated with a decrease in reactive oxygen species (ROS) and better neurological scores.

Their study provided an important potential application of baicalin in the improvement of SAH-induced neuronal injury and cerebral vasospasm, and aroused the curiosity of readers to ask whether the effect of baicalin is through direct passage through the blood-brain barrier to regulate the cerebral inflammation and ROS, or indirectly regulates the peripheral blood inflammation to improve the outcome of SAH-induced vasospasm.

TSUNG-YING YU
CHAO-HUNG CHEN
MAN-WEI HUA
CHIAO-CHIN LEE
DUENG-YUAN HUANG, M.D., Ph.D.
Tri-Service General Hospital
National Defense Medical Center
Taipei, Taiwan, R.O.C.

Disclosure

The authors report no conflict of interest.

Reference


Radiographic resolution

TO THE EDITOR: We found the report by Takagi et al.4 in the Journal of Neurosurgery of considerable interest (Takagi I, Shakur SF, Lukas RV, et al: Spontaneous radiographic resolution and subsequent redemonstration of an untreated glioblastoma. Case report. J Neurosurg 115:24–29, July 2011). In this paper the authors offered two explanations for why this patient’s untreated glioblastoma no longer enhanced on MRI. We believe that there is a third explanation that was not fully explored but warrants our attention whenever using MRI for tumor follow-up. While

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the authors did not describe the details of imaging in their report, we have reasons to suspect that the second study, in which the tumor did not appear to enhance, was performed on a 3-T scanner using a gradient echo T1-weighted technique.

There are a number of factors that contribute to the magnitude of tumor enhancement on MRI. These include time elapsed from injection, the contrast agent selected and its dose, the specific scan technique, and field strength. It has long been an accepted fact that gradient echo T1-weighted techniques offer less sensitivity to gadolinium contrast compared to spin echo T1 imaging techniques. Nevertheless, it is not uncommon to see gradient echo T1-weighted techniques used on 3-T scanners for both pre- and postcontrast imaging. This technique is commonly used at 3 T both to circumvent the inherently lower T1 tissue contrast encountered at high field strength and to limit power deposition, since this may be an issue at high field strengths. The known limitations of the gradient echo technique for postcontrast imaging seems to be tacitly accepted for 3 T, however, perhaps with the hope that 3-T scanners may be inherently more sensitive to gadolinium. The latter is widely accepted but without substantial experimental proof at concentrations comparable to those encountered in brain tumors.

We think it is important to consider the possibility that the apparent lack of enhancement described in this report could be an artifact of technique. While just conjecture on our part, since the scan details were not included, that explanation seems much more likely and better fits the principle of Occam’s razor than the concept of spontaneous regression of a glioblastoma. While much to be desired, that theory runs counter to decades of imaging experience with this tumor. The famous physician-writer Dr. Arthur Conan Doyle had his character Sherlock Holmes use this reasoning in such circumstances, “Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth.” In this particular case the possibility of an MR artifact certainly seems in the realm of the possible. We also have experimental evidence that indicates that diminished contrast sensitivity should be expected on 3D gradient echo imaging at 3 T, and this limitation of 3-T MR has also been described in at least one previous report. Our interest in this pitfall was stimulated by our own experience with a case of metastatic disease to the brain that demonstrated resolution of enhancement in a fashion remarkably similar to that noted in this Journal of brain that demonstrated resolution of enhancement in a

whether or not field strength and scan technique alone explain the findings in this particular case, we believe it is important for radiologists and neurosurgeons alike to consider carefully the effect of technique and field strength on postcontrast MRI. Standardizing and optimizing the factors that contribute to apparent contrast—field strength, agent, dose, time from injection, and scan technique—will minimize the effects of technique on the postcontrast tumor enhancement qualities.

Francis Cloran, M.D.
Jimmy S. Lee, M.D., Ph.D.
Alexander Mamourian, M.D.
Hospital of the University of Pennsylvania
Philadelphia, PA

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Disclosure

The authors report no conflict of interest.


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

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RESPONSE: We greatly appreciate the comments offered by Dr. Ramesh. Psychosurgery has a long history of controversy, mostly due to its indiscriminate use, the lack of clear criteria for the selection of patients, and the paucity of objective outcome measures. However, it has also had notable successes regarding severe problems such as refractory aggressiveness, providing quality of life to patients who otherwise were destined to social exclusion and would have required restraining by physical means. The large series reported by professors B. Ramamurthi, V. Balasubramaniam, and T.S. Kanaka yielded successful outcomes in as many as 76% of patients, with a mortality rate of 4%, all during a period in which MRI and other technical advances had not yet been developed.1–6 The rationale for selecting the lesion site was solid, and as was the case for many of the current DBS procedures (which have been based on previous lesioning experiences), was the basis for the selection of our target for the treatment of refractory aggressiveness with DBS.

Compared to lesioning, DBS is a reversible and safer form of treatment. However, it is fundamental that DBS treatments are performed in highly specialized centers equipped with adequate technology, and that patients are selected by multidisciplinary teams following strict criteria. Also, objective methods of assessment must be utilized and all procedures must adhere to the highest ethical criteria. It is likely that DBS indications will grow and a larger number of patients will benefit from this procedure over the next years. We believe that lesioning procedures, however, may continue to have a role in certain cases in which DBS is contraindicated or cannot be implemented, always safeguarding the same ethical standards and approach to the work.

Cristina V. Torres, M.D., Ph.D.
Rafael G. Sola, M.D., Ph.D.
Jesús Pastor, M.D., Ph.D.
Manuel Pedrosa, M.D., Ph.D.
Marta Navas, M.D.
Eduardo García-Navarrete, M.D., Ph.D.
Elena Esquigá, M.D., Ph.D.
Eduardo García-Cambr, M.D., Ph.D.
University Hospital La Princesa
Madrid, Spain

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**Thyroid and meningioma**

**To The Editor:** I read with great interest this article by Sughrue et al.1 (Sughrue ME, Kane AJ, Shangari G, et al: Prevalence of previous extracranial malignancies in a series of 1228 patients presenting with meningioma. Clinical article. *J Neurosurg* **113**:1115–1121, November 2010). The authors reported an epidemiological link between papillary thyroid carcinoma and meningioma. They encourage further studies to detect the common pathogenetic cause between the two diseases.

Regarding other benign diseases associated with meningiomas, I reviewed the records for meningiomas that have been surgically treated since 1978 at Di Venere Hospital in Bari and the Neurosurgical Clinic of University of Rome Tor Vergata. I’ve also noticed in women the nearly constant coexistence of meningiomas with various types of thyroid disease. In our series the thyroid disease most frequently associated with meningiomas is benign multinodular goiter. Very often the patients were receiving thyroid replacement therapy after thyroideectomy.

I also noticed that women with meningiomas and thyroid disease were frequently affected by other benign diseases, such as uterine fibroadenoma and fibrocystic mastopathy.

In my opinion this survey, which is based on our experience, deserves a further thorough genetic and epidemiological study.

**Filiberto Contratti, M.D.**

University of Rome

Rome, Italy

**Disclosure**

The author reports no conflict of interest.

**Reference**


**Response:** No response was received from the authors of the original article.

**Trigeminal neuralgia**


We would like to discuss some aspects and know the authors’ opinions about some observations.

Percutaneous balloon compression and retrograde glycerolization are only 2 of numerous therapeutic procedures that can be performed for trigeminal neuralgia; other treatments include microvascular decompression in the posterior cranial fossa, stereotactic radiosurgery, radiofrequency thermocoagulation, and peripheral alcohol injections.

Regarding the results reported by the authors with the 2 procedures, with particular attention to the rate of pain recurrence, it should be noted that these therapeutic tools can be considered temporary therapeutic choices for a large percentage of patients.

Because of the high rate of recurrence in our previous experience,1 we have not performed glycerolization for the treatment of trigeminal neuralgia for many years, preferring other methods which we select according to the individual characteristics of our patients (age and general condition) and their specific case of trigeminal neuralgia (the branch of the nerve involved, the severity of symptoms).

We would like to know why the authors didn’t consider, in the Discussion (under “The Therapeutic Spectrum for TN”), the peripheral alcohol injection, which is very effective in our experience, especially in older patients with trigeminal neuralgia involving the V2 (instillation of 2 ml of absolute alcohol through the infraorbital foramen). This simple procedure has allowed us to provide patients with a pain-free period ranging from 2 to 6 years.

Regarding balloon compression, we would like to know why the authors perform the procedure under general anesthesia with endotracheal intubation. We perform the same procedure under sedation with propofol, as the authors described for glycerolization. In contrast to the authors, we don’t consider hemifacial hypesthesia a complication of balloon compression (which is a harmful procedure) but its aim in order to achieve a satisfactory result regarding pain control. Accordingly, we think that the problem with general anesthesia is that it is not possible to test the produced hemifacial hypesthesia during the procedure and decide to stop the procedure itself, or to continue inflating the balloon or change its position if hemifacial hypesthesia has not been produced.

In our experience, the patients in whom we did not achieve a marked hemifacial hypesthesia experienced

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**Disclosure**

The author reports no conflict of interest.

**Reference**


**Response:** No response was received from the authors of the original article.
early pain recurrence; in other words, in order to achieve a durable good result with this procedure, a marked hypesthesia has to be provoked to the entire hemifacial area because it is not possible to select only the involved branch of the trigeminal nerve. For this reason, we propose this therapeutic solution only when other procedures have failed. We would like to know if in the reported experience the authors observed absence of pain recurrence in patients in whom no hemifacial hypesthesia was produced after the procedure; we would also like to know, if possible, if pain recurrence occurred at the same time with recovery of facial sensitivity.

MARIO FRANCESCO FraIoli, M.D.
DAMIANO Lisciani, M.D.
University of Rome “Tor Vergata”
Rome, Italy
CHIARA FraIoli, M.D.
CIRAD Villa Benedetta
Rome, Italy

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References

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Blood-brain barrier

To The Editor: We are interested in the experimental investigation by Nduom et al.1 (Nduom EK, Yang C, Merrill MJ, et al: Characterization of the blood-brain barrier of metastatic and primary malignant neoplasms. Laboratory investigation. J Neurosurg 119:427–433, August 2013). The blood-brain barrier (BBB) plays important roles in the physiological barrier to pathogen attack. Breakdown of the BBB has been proposed when astrocytomas grow or malignant metastases lead to severe brain edema and neurological compromise. Nduom et al.1 investigated the integrity of the BBB using immunofluorescence to demonstrate the continuity of glial fibrillary acidic protein (GFAP; astrocyte marker), CD31 (endothelial marker), and aquaporin 4 (AQ4) among specimens of astrocytoma, glioma, and metastatic cervical cancer. They concluded that contrast-enhanced lesions in patients with metastatic or primary malignancies match to regions of collapse of the astrocyte–endothelial cell association of the BBB, including defect of normal perivascular astrocytic construction on AQ4 and GFAP immunohistochemistry. Nonenhancing lesions on MRI are related to maintenance of the common astrocyte–endothelial cell connection of the undamaged BBB.

There is one minor concern that they did not address, that is, whether cases enrolled in their study received osmotic diuretic (such as mannitol) treatment or not. Mannitol altering the BBB has been reported in metastases patients who received osmotic diuretic treatment for brain edema.2 Therefore, treatment with osmotic diuretics may become a confounding factor for breakdown of the BBB and must be claimed in their study.

Dueng-Yuan Hueng, M.D., Ph.D.
Huey-Kang Sytwu, M.D., Ph.D.
Tri-Service General Hospital
National Defense Medical Center
Taipei, Taiwan

Disclosure

The authors report no conflict of interest.

References

RESPONSE: We appreciate the interest that Drs. Hueng and Sytwu expressed in our recent report. To gain insight into the mechanisms of the astrocytic component of the BBB in metastatic and primary brain tumors, we analyzed postcontrast MRI and compared with the corresponding immunohistochemical and histological features of the astrocytic component of the neoplastic vasculature. We found that there was breakdown of the normal astrocyte–endothelial cell relationship of the BBB in areas of contrast extravasation on postcontrast MRI. Alternatively, in neoplastic regions without enhancement on postcontrast MRI, the normal physiological astrocyte–endothelial BBB relationship was maintained.

In their letter, Drs. Hueng and Sytwu indicate mannitol can be used to open the BBB and, if used, could affect the study results. To support their assertion, they cite a study by Palma and colleagues.3 Nevertheless, that study did not indicate that intravenous mannitol opened the BBB but rather demonstrated that “mannitol may leak through the altered BBB near gliomas” into adjacent white matter, which is consistent with the BBB disruption associated with contrast-enhancing gliomas examined in our study. Moreover, the same study found that there was minimal to no leakage of mannitol into the immediately surrounding white matter associated with meningiomas or metastases. The authors concluded that “in brain tissue surrounding extrinsic tumors like meningiomas and metastases, the BBB is largely normal or undisrupted, and edema builds up from leaking neoplastic vessels by bulk flow,” which is consistent with our study findings and previous analyses of neoplastic vascular permeability and edema.

There are therapeutic situations in which mannitol can be used to purposely disrupt the BBB. Specifically, BBB disruption can occur when high doses of intraarterial (intracarotid or intravertebral artery) mannitol (200–300 ml) are given as a bolus over 30 seconds, which is performed in association with intraarterial chemotherapeutic delivery for treatment of intracranial neoplastic processes.1,4 Consequently, while in specific circumstances mannitol delivered rapidly and intraarterially can open the BBB, we are confident that the findings of our study are consistent with previous data/findings and that intravenous infusions of perioperative mannitol would not impact the results.

EDJAH K. NDUOM, M.D.1,2 ZHENGPING ZHUANG, M.D., PH.D.2
RUSSELL R. LONSER, M.D.2,3
1Emory University
Atlanta, GA
2National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD
3The Ohio State University Wexner Medical Center
Columbus, OH

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Transcranial electrical stimulation and monitoring

To the Editor: We read the article written by Ito et al.3 (Ito E, Ichikawa M, Itakura T, et al: Motor evoked potential monitoring of the vagus nerve with transcranial electrical stimulation during skull base surgeries. Clinical article. J Neurosurg 118:195–201, January 2013). We agree with the idea of monitoring corticobulbar responses from laryngeal muscles after transcranial electrical stimulation (TES) during skull base surgery, but unfortunately we have major objections to the applied methodology in their article.

Recording of laryngeal muscle responses using an endotracheal tube with recording electrode embedded within is an appropriate method when stimulating (mapping) the vagus nerve at the neck (superior or inferior laryngeal nerve). This method is mostly used during thyroidectomy. In these settings one can map a single nerve (laryngeal superior or inferior nerve) and no other muscles are involved in recorded responses than laryngeal muscles.

If the method of recording laryngeal activity (corticobulbar response) is applied with an endotracheal tube after TES of the lateral part of the primary motor cortex, many muscles of the neck get activated in addition to the laryngeal muscles. Large surface electrodes of the endotracheal tube can easily detect this activity. This can bring a false negative response (and laryngeal nerves could get damaged), but activity of surrounding muscle picked up by large surface electrodes of the endotracheal tube might mimic laryngeal responses.1

As an example, we show in Fig. 1 how TES activates tongue muscle innervated by the hypoglossal nerve and contaminates the corticobulbar responses recorded from mentalis muscle innervated by the facial nerve. This might occur if the recording is performed using large recording surfaces of electroencephalography (EEG) needle electrodes, but not by very small recording surfaces of hook wire electrodes. The patient in Fig. 1 woke up with facial palsy, but still had response recorded with EEG needle electrodes. In this patient, far-field response from tongue muscle contributed to the amplitude of facial corticobulbar motor evoked potentials (MEPs) recorded in mentalis muscle.

Dong et al.2 previously published a study showing that the methodology for eliciting corticobulbar responses

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in patients under general anesthesia includes delivering a short train of stimuli and comparing the response with the result after delivering a single TES (Fig. 1). This method allows one to distinguish between corticobulbar and peripheral responses. The peripheral responses elicited by a single stimulus are due to the activation of the peripheral part of the cranial nerves by the spreading of current delivered through the scalp.

If the current spreads to the peripheral part of cranial nerves, the response should be present after a single TES as well as after a train of TES. When the corticobulbar tract is exclusively activated by a train of stimuli, a single stimulus applied transcranially will not elicit a response. Unfortunately, Ito and his colleagues did not follow this recommendation; therefore they cannot be sure about the origin of their recorded responses.

RESPONSE: We would like to thank Dr. Fernandez-Conejero and Dr. Deletis for their interest in and comments regarding our article. As Dr. Fernandez-Conejero has mentioned in the letter, the methodology used for monitoring cranial nerves is important and should be reproducible. During TES, the stimulation is not restricted to the primary motor cortex because a relatively high-intensity stimulus is necessary to overcome skin and skull impedance, and this leads to current spread.

In TES, many muscle groups are simultaneously activated because the motor cortex is widely stimulated. Therefore, if the target muscle is not appropriately selected at the recording site, a far-field response may produce a false-negative result. We agree that recording using a hook wire instead of an EEG needle is theoretically a more preferable way of eliminating the far-field response at a recording site on the target muscle. According to the paper by Bigelow et al., recordings obtained from the endotracheal tube by using bipolar hook wire electrodes compare the vagus nerve.

References


Disclosure

The authors report no conflict of interest.
are useful in surgery, because these recordings have maximum sensitivity. Therefore, recordings obtained using endotracheal tube electrodes may contain the far-field response evoked by the laryngeal response. Although we do not believe that neck muscles surrounding the vocal cord are activated in our method, we would need to conduct further studies to verify this.

The onset latency by current spread to the peripheral part of cranial nerves is shorter than the onset latency by TES by approximately 4–5 msec. The onset latency observed in our study (12.4 ± 1.8 msec) was longer than the onset latency observed with direct nerve stimulation, and was similar to the onset latency observed with direct cortical stimulation (13.97 ± 1.11 msec). On the basis of these data, we have performed intraoperative monitoring. Depending on the duration of onset latency, we can confirm the presence or absence of current spread. In patients with short-onset latency, we have always performed single TES and have ensured the absence of current spread.

In addition, high-frequency multiple TES may directly stimulate the extracranial segment of cranial nerves because of current spread, without conduction through the corticobulbar tract (CBT). Reduced electrical intensity can reduce the problems associated with current spread. In the present study, the motor cortex was stimulated at 20% above the threshold level, and this may have helped reduce current spread. Therefore, our method for CBT monitoring was effective and did not lead to current spread.

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by Tseng et al. (Tseng MY, Hutchinson PJ, Richards HK, et al: Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a Phase II randomized, double-blind, placebo-controlled trial. *Clinical article. J Neurosurg* III:171–180, July 2009). In the study of Tseng et al., erythropoietin (EPO) was considered to be beneficial in the early phase of treatment for patients with aneurysmal subarachnoid hemorrhage (aSAH), which was indicated by the p value 0.039 comparing the favorable Glasgow Outcome Scale (GOS) score with the unfavorable GOS score, using the Pearson chi-square test. But by using a more accurate method (the Fisher’s exact test), one can calculate that the p value is 0.066 above 0.05. So the improvement in GOS score in the EPO group was not significant compared with that in the placebo group.

Subarachnoid hemorrhage is one of the neurosurgical emergencies with high rates of deaths and complications, and aSAH accounts for 80% of SAH. Until now, cerebral vasospasm, which can lead to delayed cerebral ischemia or even cerebral infarction, has been considered the primary cause of morbidity and death following SAH. Although today’s technology, such as aneurysm clipping and endovascular treatment, can effectively control bleeding and prevent rebleeding, delayed cerebral vasospasm—usually occurring approximately 4–9 days after aSAH—still has a serious impact on the prognosis of patients.

Recently, whether or not EPO has neuroprotective effects has become a hot topic of research. In experimental research, EPO has been shown to play a protective role in ischemic vascular injury by activating the EPO receptor, Akt1, and mitochondrial modulation, or by avoiding the neuronal death mediated by nitric oxide and cathepsin. Moreover, a meta-analysis and a systemic review have confirmed the efficacy of EPO in an animal model of ischemia. However, the effect of EPO on patients with delayed cerebral vasospasm or cerebral infarction following aSAH has not been clear.

There are 3 possible main reasons that EPO treatment was not superior to placebo, which are also supported by the study of Tseng et al. One reason could be the dose of the EPO. The reported maximum dose of EPO providing the neuroprotective effect in animal experiments was 450 IU/kg during each 48-hour period, but in clinical trials the dose of EPO was not confirmed in a small range but in a wide range. So we conjecture that the dose of EPO would affect the prognosis of clinical patients, which has been reported in animal experiments. Another possible reason is that, to remit the delayed cerebral vasospasm and cerebral infarction, the time window of EPO intervention should be limited. As mentioned previously, delayed cerebral vasospasm usually occurs approximately 4–9 days after aSAH, but the early studies reported that the time until EPO took effect was more than 3 days, so the earlier or later treatment might be ineffective. The final possible reason is that the neuroprotective effect of EPO could be hindered by calcium channel blockers. Ifmodipine, a common calcium antagonist, must be used in patients with aSAH to alleviate cerebral vasospasm, based on the treatment guidelines of SAH, because it is
the only confirmed effective drug, as a result, the role of EPO in neuroprotection may be interfered with.

YING-LI GU, PH.D.1,2
ZHONG-XIN ZHAO, PH.D.2
1The Fourth Affiliated Hospital of Harbin Medical University
Harbin, China
2West China Hospital
Chengdu, Sichuan Province, China

Disclosure
The authors report no conflict of interest.

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