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Safety, Science, and Sales: A Request for Valid Clinical Trials to Assess New Devices for Endovascular Treatment of Intracranial Aneurysms

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Synergy of a Combined Near-Infrared Spectroscopy and Blood Oxygenation Level-Dependent Functional Activation Study

Early functional neuroanatomic studies by Broca described the association of the left cerebral hemisphere with language function. More recent investigations have included invasive optical techniques applied in conjunction with neurosurgery and, to a lesser degree, noninvasive optical techniques based on near-infrared spectroscopy (NIRS). Functional MR (fMR) imaging studies with blood oxygenation level-dependent (BOLD) contrast provide the advantage of high spatial resolution and association of the functional data with anatomic structure. These techniques have elicited widespread interest and found application in the investigation of normal brain function as well as a range of disease processes and are increasingly employed in the clinical setting for surgical planning. The case report by Murata et al published in this issue of the *AJNR* combines BOLD fMR imaging with noninvasive optical imaging and reports unexpected findings that may motivate further investigation into the assumptions that underlie these techniques.

To understand the potentially synergistic combination of NIRS and fMR imaging, it is useful to recall that the basic couplings between neuronal and vascular responses to stimulation are not well understood. In light of the fact that hemodynamic responses can be precisely and statistically correlated with functional stimuli, however, the connection can be studied. NIRS is designed to detect changes in cerebral perfusion produced by functional stimulation through measurement of changes in the concentrations of total hemoglobin (Hb), oxyhemoglobin (oxy-Hb), and deoxyhemoglobin (deoxy-Hb). An increase in regional cerebral blood flow, induced by stimulation and detected by NIRS, is reflected in an increase in the concentration of oxygenated hemoglobin and a decrease in the concentration of deoxygenated hemoglobin. Total hemoglobin also increases because of the increased cerebral blood flow. As noted by Obrig and others (1), NIRS is quite specific to hemoglobin and offers good temporal resolution with a simple and patient-friendly experimental setup. fMR imaging, on the other hand, provides exquisite anatomic detail to overlay the areas of detected activation. The signal intensity in fMR images reflects the concentration of (paramagnetic) deoxygenated hemoglobin but does not respond to the other two parameters obtained by NIRS. Thus, activation in fMR imaging is typically described as a decrease in paramagnetic deoxyhemoglobin, an increase in T2*, and an increase in the BOLD signal intensity.

In the case report, the classic BOLD response accompanied a physiologically consistent evoked cerebral blood oxygenation (CBO) change as a re-

sponse to stimulation presurgery. That is, with functional activation of the brain through motor activity, there was a decrease in concentration of deoxyhemoglobin accompanied by an increase of oxyhemoglobin and total hemoglobin concentrations. Postsurgery, an apparent atypical response occurred manifested by an increased regional cerebral blood flow and a negative BOLD signal intensity. Analysis of the NIRS data revealed that the deoxy-Hb concentration increased along with the oxy-Hb and total Hb concentrations instead of decreasing as expected with stimulation. The measured BOLD signal intensity was decreased (negative activation), consistent with the deoxy-Hb change.

The authors previously demonstrated similar evoked CBO changes associated with cerebral ischemia, and they suggest in the report that surgical injury could produce a relative ischemia due to decreased oxygen delivery in the surgical bed. This could result from a disproportionately large regional blood flow increase required to compensate for the reduced ability to deliver oxygen in the surgical bed postoperatively. That would produce a relative ischemia and increased deoxy-Hb concentration consistent with the observation. Other possibilities that could produce this atypical response are an increased oxygen extraction ratio (OER), recirculation, and variable production of deoxy-Hb. The OER can increase as a result of capillary dilatation. If this occurred, one would expect an increase in total Hb and an increase in deoxy-Hb, and there might be an associated increase in oxy-Hb concentration. Further, the NIRS volume measures total Hb and rCBF in an area much larger than the fMR imaging voxel, and this might overshadow small rCBF changes actually occurring in the voxel of brain depicted by BOLD MR imaging. This, however, is considered a less likely possibility than the increased OER and other physiologic changes previously described.

Despite the fact that this report describes a single patient, the study illuminates the potential benefit of obtaining NIRS studies with their physiologic hemoglobin measures to complement our understanding of the functional brain activation depicted by fMR imaging. The challenge of relating two techniques with different spatial resolutions should be not underestimated and may actually be a contributor to the present data. The increasing role of fMR imaging in surgical planning in particular motivates interest in characterizing the hemodynamic responses to surgical procedures. This interest may extend to intraoperative (invasive) NIRS measurements supporting the interpretation of the postsur-

gical NIRS. Studies that relate these evoked CBO changes to the fMR imaging signal intensity may provide surgical guidance in specific cases as well as further insight into brain organization and reorganization and may help in management of nonsurgical disease processes that affect cerebral blood flow. Interpretation of changes in BOLD contrast should include consideration of the potential for regional cerebral blood flow to increase in conjunction with either an increase or a decrease in deoxy-hemoglobin concentration. Experimental animal studies with more invasive physiologic monitoring may help to further refine and define these tech-

niques and their application to human brain evaluation and treatment.

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Safety, Science, and Sales: A Request for Valid Clinical Trials to Assess New Devices for Endovascular Treatment of Intracranial Aneurysms

Many advances in neurointerventional procedures depend on the development of new devices. Endovascular approaches to neurovascular diseases are still young. They do not attract the same level of financial support as other fields. They should nevertheless be developed along rigorous, scientific steps, from valid laboratory and animal studies to well-designed randomized clinical trials. Ideally, valid trials should address important clinical dilemmas, such as the preventive treatment of unruptured aneurysms, as well as precede the widespread use of new devices.

Patients with ruptured intracranial aneurysms benefit from a better clinical outcome when treated by coil embolization than by surgical clipping. The benefit shown by International Subarachnoid Aneurysm Trial (ISAT) is an absolute decrease in poor outcomes of 7% (1). Although this gain is obtained at the cost of more frequent incomplete occlusions and angiographic recurrences, the clinical consequences of these angiographic recurrences are modest: a bleeding risk of 0.1-1% per year (1-3). The impact of endovascular approaches on the management of patients with intracranial aneurysms will continue to increase to the extent that long-term efficacy will be improved, without significant compromise regarding safety. We cannot afford an absolute increase in complication rates of a few percent without jeopardizing the benefits of endovascular treatment. The safety of adjunct methods or of new devices to treat aneurysms has not been compared with standard platinum coils. This comparison may not be possible with tools that permit treatment of lesions that would otherwise not be favorable for coiling, such as intracranial stents and aneurysmal neck-bridge devices (4), and selection bias forbids direct or historical comparisons. Thus, these tools should be reserved for lesions that cannot be treated otherwise, because favorable results shown by ISAT may not apply to treatment with tools that have unknown long-term effects when permanently implanted in cerebral arteries.

Coils with surface modifications have recently been introduced (5-7). Unfortunately, the regulatory pathway chosen to introduce new coils is one of equivalence with standard platinum coils and clinical studies have not been planned to test for safety nor efficacy. Now are we dealing with new embolic agents that do not bring any benefit to the immediate care of patients. They may even jeopardize initial success of the procedure if they involve added complications.

The introduction of a new device on the market is not justification of its clinical use. Regulatory agencies are not meant to control the medical practice, and their actions are no substitute to the clinicians' responsibility for the safety of their patients. Regulatory agencies rely on companies to supply preclinical safety data, which may be biased or selected in favor of the new material or device (8). No matter how favorable the results of the preclinical safety data may be, the evaluation of the potential risks associated with the new technology as compared with standard tools should always be included in the design of clinical trials.

Endovascular approaches to neurovascular diseases have matured in the past decades. From expert acrobatic tricks reserved to the management of impossible clinical challenges, they have become standardized procedures for routine applications in specialized centers. Nevertheless, clinical trials in this field are frequently limited to uncontrolled, nonrandomized "pilot studies," case series, or registries. Although this type of study may be all that can be done in the evaluation of devices designed to assist the treatment of rare or previously untreatable cases, pilot studies are insufficient to propose the substitution of the standard device used in everyday cases. Without a control group, it is impossible to interpret long-term results that are so intimately related to case selection (2, 5). Furthermore, artifacts that could falsely suggest a new "biologic effect" are more difficult to detect. For example, the friction encountered

with "coated" coils have led to an increased incidence of suboptimal initial results, giving the impression that the "biologic effects" of the new device leads to unusually frequent thrombosis of aneurysms at 3 months (7, 9, 10). If incomplete initial occlusions were more frequently accepted, the incidence of progressive obliteration would rise, as recently shown in 60% of lesions incompletely treated with standard coils (9). Because pilot studies may be all that is required to introduce a device to the market, and postmarketing studies are too often limited to the voluntary notification of catastrophes, endovascular clinicians cannot rely solely on the industry or regulatory agencies to advance their field and improve the outcome of their patients. The recent approval of intracranial stents and new coils with surface modifications without any clinical trial demonstrating their safety is eloquent. In this context, approval by regulatory agencies does not mean that the clinical use of the new device is indicated, judicious, or even ethical.

Some pilot studies are meant to give best possible results at minimal costs and may not reveal limitations that become apparent when the technique applies to a large group of unselected patients (8). Of course, the clinical introduction of a device has to start somewhere. A potential solution is to integrate the pilot study into a well-designed clinical trial, with stepwise continuation into the more scientific phase of the trial once unexpected complications have been excluded with the first cohort of patients.

New coils are now beyond the stage of a pilot study. Despite the increased costs of these new devices and the pressure from the industry to offer these alternatives to our patients, there is no scientific proof that they perform any better than conventional platinum coils in clinical practice. Worse, their use could be associated with early rebleeding when lesions are treated after rupture. Immediate thromboembolic risks may also be increased. Thus, new embolic agents should first demonstrate, within the controlled environment of scientific trials of a sufficient scale, safety characteristics that are equivalent to standard platinum coils, before considering a widespread application. For example, if the current endovascular procedure involves 10% of thromboembolic risks, a randomized trial comparing at least 176 patients in each group is necessary to exclude with statistical credibility that complications have not been doubled with the use of the new coils.

A valid trial is a randomized, prospective, controlled trial comparing the new-generation coils to standard platinum coils. Blinding, if at all possible, is preferable to minimize bias, at least for follow-up angiographic studies that should cover a period of 18 months. The study would enroll approximately 500 patients equally divided between the two groups, to demonstrate a decrease in the recurrence rate, the primary outcome measure, from 20% to 10%. A study of such a scale is clearly feasible when one considers that some new coils have been used in more than 1800 patients worldwide and yet there is still no clear indication of their safety nor efficacy (10).

Scientific rigor requires independence and objectivity and safeguarding such principles is difficult when sponsors are virtually in complete control (8). The direct implication of neurointerventionists in the design and management of pertinent clinical trials, as well as funding from peer-reviewed public agencies, are vital for the development of our field. Although this approach is sometimes extraordinarily difficult, it has led to most significant advances in the past, such as the ISAT trial, a turning point in the history of endovascular treatment of intracranial aneurysms (1).

There are major intrinsic difficulties to the realization of a multicentric randomized trial, one of which is costs. Depending on design, the costs of a 500-patient trial may reach \$3–\$20 million, if devices and follow-up studies are included. Such expenses are a significant burden on the industry, and many publicly funded programs will not contribute to device testing trials; however, new devices are currently promoted through complex and costly marketing efforts that include sponsored conferences, proctoring programs, company-based postmarketing registries and the detailed data are frequently not available for analysis. As a group, we should resist the repetitive introduction of fashionable devices that "need" to be purchased, despite unproven safety and efficacy, in an effort to keep ever-increasing inventories updated, in an aimless escalation of costs. On the other hand, stringent premarket requirements may strangle technological developments. Clinicians could contribute by forming networks of centers with centralized, standardized data collection, to propose a well-organized milieu for the realization of trials. Federations should offer guidelines for valid clinical trials, as well as promote the scientific assessment of new devices. Money is a major incentive for the stimulation of scientific progress. Many difficulties mentioned here confront physicians and industry in general (8). The alliance between academia and industry carries inevitable tensions, but it can be fruitful (8). It is our duty to ensure that the message we send to the industry is that their devices will become commercially successful once their safety and efficacy have been demonstrated in scientifically valid trials.

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