Controversy: The Essence of Medical Debate

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Experience is fallacious and judgment difficult.
Sir William Osler, 1904

Why does controversy exist? We have always known that it is human nature to enjoy the cut and thrust of debate. Subjective opinion is the essence of personality and is often based on singular experiences, which may have a disproportionate impact on clinical judgment. In the time of Osler,1 the opinions of senior physicians, based on experience, were regarded as the gold standard on which clinical management was based. When we trained as neurologists, this system was still very much in place. Even with the dramatic change in practice with the introduction of evidence-based medicine,2 controversies exist, because the evidence may not be well disseminated or may be of dubious quality. Furthermore, experts may disagree on the generalizability of the accumulated evidence or the relevance to an individual clinical problem.

So far in our Controversies Section, we have tried to address issues that are common to practicing physicians. By doing this we feel that most readers of Stroke are more likely to be personally engaged. Issues of this magnitude tend to ignite passions; this adds color to the text and has been a feature of the controversies covered to date.

A very large number of trials in acute stroke have generated a substantial evidence base in relation to thrombolysis, antiplatelet agents, neuroprotection, and the role of imaging in selection of patients for therapy. No issue has caused greater controversy than the view that intravenous tPA should be a standard form of therapy for acute stroke. Not only our selection of patients for therapy, but also those of other journals, such as Stroke,3 feature of the controversies covered to date.

As time window and identification of neuroimaging parameters, such as diffusion/perfusion MRI, that might predict treatment responders,5 perhaps because of its deeply rooted historical origins, dating from the time when no other therapies were available.

Neuroprotection was heralded as the perfect acute stroke treatment because of its presumed low risk, ease of administration, knowledge about the neurotoxic cascade, and highly encouraging results from animal models of stroke. Disappointment followed disappointment, as what appeared early to be a simple translational research issue has become one of the great clinical research conundrums. Trial design was the controversy we addressed. Certainly early design faults such as time window, small sample sizes, and choice of outcome measures were an issue. We expressed concern at the unseemly haste of pharmaceutical companies to rush to phase III trials with inadequate data from animal models or better-designed phase II trials. A stepwise approach seems more logical with larger animal models and surrogate outcome studies in humans, using imaging parameters to optimize translation of infarct limitation in the laboratory to attenuation of infarct growth in stroke patients.

Secondary prevention is now an important part of stroke management. Within 20 years, the use of antiplatelet agents, carotid endarterectomy, warfarin for atrial fibrillation, and, more recently, blood pressure lowering with perindopril and indapamide have been sequentially introduced. Although
aspirin has been the gold standard in antiplatelet therapy, it has been seriously challenged by the latecomers clopidogrel and combined therapy with aspirin and dipyridamole. One would think that the decisions concerning initial therapy with an antiplatelet agent would be simple. However, the issue is clouded by cost and the disparity between positive trial results yet modest biological effects in terms of absolute risk reduction. Hence, it seems reasonable that the workhorse, aspirin, should maintain its premier place as the agent of choice as first-line therapy after TIA or stroke until these issues can be resolved. We suspect that combination therapies will become first-line treatments after the current generation of comparative clinical trials that are now underway. We must bear in mind that at only an \( \sim 20\% \) relative risk reduction in composite vascular endpoints with antiplatelet therapy, there is still a long way to go.

Neurologists are becoming accustomed to enthusiastic talks given by cardiologists on the apparent safety and efficacy of angioplasty/stenting for symptomatic and asymptomatic carotid stenosis, despite the lack of randomized trial evidence to date. There is a regression toward the mean in that cardiologists are becoming interventionalists, as are vascular surgeons and now some neurologists. As neurologists, we would maintain that this is an opportunity not to be lost given our acquiescence to our radiological colleagues in the 1960s, contrasting with the experience in cardiology. A new breed of interventional “strokologists” is required to advance both the practical and research aspects of acute stroke management. Angioplasty/stenting is a logical procedure, which is continuing to evolve with the development of distal protection devices. Nonetheless, only carotid endarterectomy has been proven to date (level 1 evidence) as an intervention for high-grade carotid stenosis. Therefore, regardless of which interventional group actually does the procedure, we strongly advocate that all cases of symptomatic and asymptomatic extracranial stenosis are randomized within a controlled trial setting, so that level 1 evidence about management strategies can be generated. This will avoid our untenable position in the 1970s and 1980s with carotid endarterectomy, where a then-unproven form of therapy was commonly and often inappropriately used.

These are some of the controversies we have touched on during the last year, but this merely scrapes the surface of the barrel of clinical uncertainty. In future editions of this journal, we have commissioned expert colleagues to address such contentious issues as the benefits of evacuation of intracerebral hemorrhage, the management of asymptomatic intracerebral aneurysms, whether MR or PET provides the best measure of the ischemic penumbra, the efficacy of surgical decompression for large middle cerebral infarcts, and whether ACE inhibition or blood pressure lowering is the key to the secondary prevention against stroke.

To return to our original theme, controversy will continue to be the grist of everyday clinical discussions as long as there are advances in medicine, particularly at the current exponential rate. Despite the arrival of the somewhat more measured era of evidence-based medicine and clinical guidelines, controversy should continue to excite us all. Watch this space!

**References**


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