Perspective

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Reconceptualising Stroke Research to Inform the Question of Anaesthetic Neurotoxicity

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Introduction

Since the first public demonstration of ether anaesthesia in 1846, there has been concern about anaesthetic-induced neurotoxicity. Shortly after observing this demonstration, Henry Jacob Bigelow, a Professor of Surgery at Massachusetts General Hospital, began characterizing the post-etherized state of these particular patients. 'The character of the lethargic state, which follows this inhalation, is peculiar', he initially remarked. He later provided the following vivid description of a patient: narcotism was complete during more than twenty minutes, the insensibility approached to coma'. More than a century later, Bedford suggested in 1955 that minor dementias and even catastrophic mental impairment sometimes occur in the aftermath of general anaesthesia. He went on to recommend, operations on elderly people should be confined to unequivocally necessary cases [1]. In 1961, Eckenhoff and colleagues characterized the phenomenon of 'post-anaesthetic excitement', which occurred with disproportionate frequency in paediatric patients. Today, the question of whether anaesthetic agents at clinically relevant concentrations are neurotoxic represents a major clinical and scientific controversy in the field.

Description

In recent years, endovascular stroke therapy has received considerable attention after multiple trials demonstrating positive outcomes. The pathological target of this intervention involves large-vessel occlusion with a severely ischaemic core and susceptible penumbra region, which includes brain cells with tenuous viability. Cells in this penumbra region receive some collateral perfusion, but signs of cellular and metabolic stress are present, and infarction ensues without timely restoration of blood flow [2]. Furthermore, the extent of the stroke and long-term neurological outcomes might be related to the anaesthetic technique. Retrospective data from multiple studies show worse stroke outcomes in patients who received general anaesthesia compared with conscious sedation. These results could certainly have been interpreted to suggest that the practice of administering general anaesthesia for stroke interventions was clinically inappropriate. Before a change in practice, however, important potential confounders in these retrospective studies needed to be addressed [3].

The Sedation vs Intubation for Endovascular Stroke Treatment trial prospectively tested conscious sedation vs general anaesthesia in the setting of acute ischaemic stroke in the anterior circulation. The 150-patient trial had a single-center design with a dedicated stroke-intervention team that helped minimize institutional and provider variability [4].

Anaesthetic neurotoxicity study model, dosing information is an important element to consider. Indeed, neurotoxicity risk may follow a dose-dependent pattern, whereby increased exposure portends higher risk.8 However; a post hoc analysis from the Intraoperative Hypothermia for Aneurysm Surgery Trial suggests that additional anaesthetic delivery, implemented for achieving burst suppression during cerebral-aneurysm surgery in patients with subarachnoid haemorrhage, had no clinically detectable

effect on neurological outcome. Nonetheless, anaesthetic variation during endovascular stroke rescue may impact outcomes, and intraoperative burst suppression might be an independent risk factor for postoperative delirium [5]. Final results from the GOLIATH trial may allow for additional evaluation of neurological injury and outcomes in relation to anaesthetic dosing.

These studies were conducted in order to answer a clinical question: is general anaesthesia and its attendant consequences safe for patients undergoing procedures related to the cerebrovascular system. However, we would argue that these clinical studies focused on stroke actually have broader implications related to the question of anaesthetic neurotoxicity for non-cerebrovascular interventions, especially in older surgical patients. Findings from trials studying the effects of general anaesthesia on stroke pathophysiology can serve as a novel scientific model for studying anaesthetic neurotoxicity in humans [6]. Stroke represents a known situation in which the brain is especially vulnerable to injury. We suggest that the recent randomized controlled data gathered for the primary purpose of understanding the best clinical care for stroke patients can be reinterpreted to assess whether general anaesthesia is injurious to vulnerable neurons in humans.

This strategy is motivated by two primary observations: first, there is a known neurological insult with a neuronal population (i.e. the penumbra) that is susceptible to injury, and secondly, there is equipoise about general anaesthesia and conscious sedation. Neurological effects specific to anaesthetics can be studied in a relatively isolated manner, as there is no major surgical intervention or surgery-associated stress response in stroke-intervention patients, and baseline patient characteristics, comorbidities, and stroke characteristics are well balanced. Ultimately, by leveraging this stroke-research framework as a scientific model [7], the field can advance the understanding of clinically relevant anaesthetic neurotoxicity in the older brain. As recently described during the British Journal of Anaesthesia seminar on anaesthetic neurotoxicity and neuroplasticity, the clinical trial design for addressing neurotoxicity depends on the specific questions to be answered, and results from these stroke trials could address purported toxicity in the older, vulnerable brain. Targeted neurological outcomes that reflect proposed models of neurotoxicity could be investigated accordingly.

First, measuring the final stroke characteristics in both groups could address the question of anaesthetic-induced neuroapoptosis and cellular metabolic stress. If general anaesthetics indeed initiate a cellular cascade of events that leads to neural cell damage and death, then patients undergoing stroke rescue in the setting of general-anaesthetic administration could accordingly have a larger infarct volume and a possibly higher risk of short-term stroke recurrence than patients undergoing conscious sedation. Vulnerable penumbral neurons in these patients may be particularly prone to such cellular events. None of the trials discussed earlier SIESTA, An Stroke, or GOLIATH demonstrated larger infarct volumes in stroke patients receiving general anaesthesia. In fact, the final infarct volume was significantly larger in the conscious-sedation group in the GOLIATH trial. Furthermore, patients randomized to general anaesthesia in the An Stroke trial had similar stroke recurrence rates compared with those who underwent sedation.20 Thus, these trials do not present evidence of larger stroke volume or increased recurrence risk in stroke patients undergoing general anaesthesia [8]. Secondly, assessing for precipitation of dementia and performing longitudinal, post-stroke cognitive-function testing could address related models of neurotoxicity. For example, general anaesthetics have been shown to propagate amyloid-β and tau-protein pathophysiology in laboratory studies, which are the pathophysiological hallmarks of Alzheimer's disease. Measuring cognitive trajectory and new-onset dementia in groups receiving general anaesthesia compared with conscious sedation could indicate whether such a pathophysiological burden exists. Additionally, covert stroke drives cognitive decline in the non-surgical setting,33, 34 and comparing cognitive function between groups may also be indicative of new silent infarction not initially detected. Lastly, toxic overdose is an additional mechanism by which neural injury is proposed to occur.8 By correlating anaesthetic exposure with targeted measures, such as infarct volume,

deficit scales, and disability burden, we could begin to evaluate the question of anaesthetic exposure and post-exposure neurological function. Although such efforts will not unambiguously settle whether these doses and studies are too small to detect signs of clinical neurotoxicity [9], they serve as a foundation for better addressing the issue in the older brain, and could reveal whether large, clinically significant effects become readily apparent during a period of known neural vulnerability. Additional prospective efforts are ongoing, and multidisciplinary collaboration may be key to answering these questions.

Finally, neuroprotective properties could be studied as well. As noted, the SIESTA trial and the GOLIATH trial showed improved mRS scores and reduced final infarct volume, respectively, in patients receiving general anaesthesia. This aligns with laboratory-model findings, in which isoflurane administration after stroke has been associated with reduced infarct size and improved neurological scores after 8 weeks. These proposed benefits may be as a result of optimized cerebral metabolism and blood flow during ischaemic injury, although the clinical efficacy of this protective mechanism remains in question. Nonetheless, volatile anaesthetics reduce cerebral metabolism whilst increasing cerebral blood flow, and volatile agents have been associated with favourable outcomes after endovascular stroke rescue [10]. Certain volatile agents (e.g. sevoflurane) have also been associated with mild cognitive-impairment progression. Thus, specific anaesthetic agents used in these trials should be included for analysis as well as for establishing associations with neurotoxicity or neuroprotection.

Conclusion

Recent randomized controlled trials trying to answer specific questions about safe clinical care for stroke patients undergoing general anaesthesia can be reinterpreted as a scientific model for anaesthetic neurotoxicity in humans that has implications well beyond the clinical condition of stroke or related interventions. Indeed, the findings from recent randomized clinical trials do not support the results from lower-quality observational studies of anaesthetic neurotoxicity, but they are consistent with randomized studies showing similar cognitive outcomes after cardiac surgery under general anaesthesia vs percutaneous coronary intervention with conscious sedation. This highlights the potential danger of relying on low-quality evidence to inform scientific and public opinion. Low-quality evidence, including the seminal study by Bedford, has formed the basis of the now entrenched hypothesis that surgery and general anaesthesia carry a long-term cognitive cost. Importantly, available data from randomized endovascular stroke trials do not present evidence of neurological injury in older patients receiving general anaesthesia with either propofol or sevoflurane. This is compelling, given the vulnerability of penumbral neurons to pathophysiological insults. By investigating the final stroke characteristics, cognitive trajectory, and neurological outcomes related to cumulative anaesthetic exposure, we could gain important information as to whether general-anaesthetic agents are neurotoxic, neuroprotective, or innocuous in a specific and real-world brain vulnerability model that has scientific implications well beyond patients with cerebrovascular disease.

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