Is cerebral microdialysis a clinical tool?

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Cerebral microdialysis has been utilised in a wide range of contexts for more than 20 years [5]. Nevertheless, despite this longstanding experience and a wealth of literature, it has not taken off as a routine clinical tool in many units. Bossers et al. provide a systematic review of the literature on cerebral microdialysis, specifically in the context of intraoperative monitoring. Their thoughtful and thorough review highlights the poor methodological quality of all current studies in this field when assessed against the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria [6]. This lack of studies that meet the conventional criteria used in evidence-based medicine grading systems reflects the pragmatic difficulties in utilising microdialysis. While proponents of the technique will point to anecdotal evidence for early identification of deranged physiology allowing early institution of treatment, this has been difficult to demonstrate on a population basis in systematic studies.

Microdialysis is unique in its ability to dynamically sample the brain extracellular space and provide a direct tissue metric of metabolism [2]. The commonest mediators that are assayed are lactate, pyruvate, glucose, glutamate and glycerol. These small molecules are freely permeable from within the cytosol into the extracellular space where they can cross into the microdialysis catheter. Samples are collected intermittently and assayed at the bedside. The lactate/pyruvate ratio is a surrogate for the cellular redox state. Glucose is a direct measure of substrate delivery to the brain tissue, and glycerol is a marker of cell membrane breakdown. As well as its use in intraoperative monitoring, cerebral microdialysis is also commonly used in the intensive care setting, usually with hourly sampling, as part of multimodality

monitoring of intubated and ventilated neurosurgical patients: typically in subarachnoid haemorrhage or traumatic brain injury [4]. Relationships between brain chemistry and clinical outcome have been established [3]. The key difference between intraoperative and intensive care use of microdialysis is the time course over which derangements in physiology need to be identified. Surgical manipulations may result in abrupt changes (e.g. over minutes) in tissue physiology as compared with brain swelling following TBI or vasospasm in SAH. Intraoperative monitoring therefore requires modification of the microdialysis methodology with a higher pump flow rate to allow more frequent sampling, as well as rapid or online assay techniques.

Microdialysis is a focal monitoring technique, sampling the immediate vicinity of the catheter tip. This can limit the generalizability of sampling data to the brain as a whole. Consensus guidelines suggest targeting of the ‘at risk’ brain such as peri-contusional brain following TBI or the vascular territory of the parent aneurysm in aneurysmal SAH [1]. The practicalities of targeting microdialysis catheters via burr holes or intracranial access devices can be difficult. We have utilised neuronavigation techniques to assist in this circumstance, although this is not routine. In this respect, intraoperative monitoring can allow more reliable targeting of catheter insertion as craniotomy provides additional anatomical landmarks and surgical access to improve accuracy. The reliability and sensitivity of microdialysis data can only be assessed in relation to the location of the catheter tip in relation to the putative pathology. This creates difficulties in providing a robust protocol for catheter insertion and data interpretation in systematic studies.

As with any intermittent monitoring modality, the most reliable conclusions are drawn from trends in the data, particularly in relation to other monitoring or clinical parameters. If microdialysis-derived data change abruptly, there is a concern that this could represent an aberrant or erroneous result. In

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practice, in the absence of concordant changes in other monitoring modalities, it is only when there are two consecutive abnormalities in microdialysis parameters that there is sufficient confidence to alter the clinical management of the patient. This provides a temporal limitation to the use of microdialysis as an ‘early-warning’ technique that provides additional sensitivity over and above other monitoring.

With the proliferation of monitoring techniques in neuroscience, there is a risk of progressive diminution in the benefits of each additional monitor that is employed. For example, if a patient has normal blood pressure (arterial line monitoring), normal arterial oxygenation (blood gas), normal intracranial pressure (ICP monitoring), normal brain oxygenation (brain tissue oxygen), no seizures (continuous EEG monitoring) and so on, the additional diagnostic benefit of microdialysis monitoring (or any other novel technique) is progressively narrowed. Additionally, as intensive care, anaesthetic and neurosurgical advances are instituted, there become fewer and fewer instances in which there are marked derangements of neural physiology that provide the ‘opportunity’ for microdialysis to provide a metric of abnormality.

All of the points above relate to the reliable identification of metabolic abnormalities using microdialysis. The other aspect of the clinical utility of microdialysis is the clinical interventions that are available should an abnormality be identified. In the intraoperative setting, surgical manipulations that lead to changes in microdialysis parameters such as temporary clipping or brain retraction may be readily reversed. In the context of intensive care monitoring, the situation is more complex. An increase in L/P ratio, for example, may reflect a number of underlying derangements, for example, an increase in the diffusion barrier, a reduction in oxygen delivery or an underlying abnormality in the ability of mitochondria to utilise oxygen (‘mitochondrial dysfunction’). There are therefore many potential therapeutic avenues available, such as hyperosmolar agents, reduction of intracranial pressure by other means, hypertension to supplement cerebral perfusion pressure or hyperoxia. In our experience, there is a wide variation in the responsiveness of individual patients to these various interventions and there is not a reproducible response in every patient. This is likely to reflect the complexities of the underlying pathology as well as patient-specific factors.

Taken together, these limitations make it difficult to ‘protocolise’ the use of microdialysis. Any abnormalities in microdialysis parameters must be interpreted in the context of the patient’s pathology, the location of the microdialysis catheter and data from other monitoring techniques. Furthermore, potential therapeutic options must be considered on an individual basis by clinicians familiar with the intricacies of microdialysis. We commonly employ trials of therapeutic manoeuvres in an attempt to correct microdialysis derangements on a case-by-case basis. This individualisation of

therapy does not sit easily with an evidence-based approach to medicine. Even if we were providing some benefit to individual patients, it would be very difficult to show this benefit in a heterogeneous group of patients with heterogeneous pathologies and a heterogeneous menu of interventions. Our view is that this is a reflection of our own lack of understanding of the underlying metabolic derangements in neurosurgical pathology, and it is only by careful observation and further interventional studies that we will be able to elevate clinical microdialysis to the heady heights of level 1 evidence. Nevertheless, we still believe that in patients on neuro-intensive care we can provide additional benefit by using microdialysis to individualise therapy.

The QUADAS criteria are designed to gauge the ‘accuracy’ of diagnostic tests; however this might not be a fair barometer against which to compare a monitoring technique such as microdialysis. In the case of all monitoring techniques, they do not provide any benefit to the patient unless the data generated can be appropriately interpreted, integrated into clinical decision making and appropriate therapies instituted. As Bossers et al. point out, there is a wide variation in what constitutes a ‘reference standard’ in microdialysis studies that makes it difficult to make a systematic assessment of the utility of the technique. We hope to convene an updated consensus meeting on the use of microdialysis in neurosurgical pathology in order to further clarify these issues and provide a consistent approach that will inform future study design and clinical practice.

Conflicts of interest None.

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