Supplementary magnesium in traumatic brain injury: where do we go from here?

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A key aspect of providing good quality care to patients who have sustained moderate to severe traumatic brain injury (TBI) is taking on the heavy burden of electrolyte homeostasis for which their neuroaxis is temporarily unable to manage. Typically, the first focus of the neurosurgeon and neurointensivist is close regulation of sodium and potassium delivery and excretion due to the immediate and overwhelming influence of the neuroendocrine axis on these,[1 2] together with the natural compartmental fluid shift that will accompany such changes and their effects on TBI outcome.[3 4] However, much less clearly defined and understood is the influence of actively manipulating magnesium homeostasis in such cases. Current practice tends towards the avoidance of significant depletion; however, magnesium has a number of well-recognised interactions with major neurotransmitters such as glutamate, and through them has been identified as modulating the neuroinflammatory response through multiple in vivo models.[5–7] From these observations, a considerable body of preclinical and pilot clinical evidence as to the positive effects of supplementary magnesium within the context of major neurological trauma has been assembled.[8 9] Despite this promising data, unfavourable outcomes reported by key clinical studies[10] suggest the translational relationship between experimental observations and clinical application is complex and not fully understood. Therefore, as yet the routine therapeutic use of magnesium supplementation is not within the current mainstream of TBI treatment.[11 12]

In response to the lack of clarity on this issue, Lyons *et al*[13] present a summary of the current evidence regarding the use of supplemental magnesium within this context. Within the field of TBI research, there is a strong sense of feeling that magnesium represents a likely potential target for disease modifying therapy despite (as yet) the absence of a formal reference to support this. Lyons *et al* astutely point out that the fact that within this field many practitioners consider the case closed for supplemental magnesium (sulfate) due to a large (greater than 400 patient) randomised placebo controlled trial undertaken by Temkin *et al*,[10] in which no benefit or indeed a slight adverse effect was observed in patients selected for treatment. This trial very much represents the fulcrum of judgement regarding this topic. However, the strength of evidence in preclinical models is very difficult to ignore and therefore stimulates an appetite to explore the potential oversights within what is considered the definitive literature. It is worth mentioning that a similar index of suspicion exists as to the utility of magnesium in the treatment of aneurysmal subarachnoid haemorrhage. In this situation also, a robust body of preclinical evidence has yet to translate into a measurable clinical benefit.[14]

A number of factors must be considered when attempting to offer an explanation to this lack of translatability. First, the dose relationship between potential beneficial effect, no effect and harm is likely to be complex and nuanced due to the significant influence the administration of magnesium has on multiple body systems (especially cardiovascular). Therefore, until a better understanding of the in vivo distribution and effects of specific dose regimes of magnesium are known (potentially through a mechanistic cerebral microdialysis study), any trial designed will potentially not hit the theoretical dose 'sweet spot' that may be required. TBI as a disease is very heterogeneous (although certain mechanisms of tissue injury will be common to most patterns of injury e.g cytoskeletal disruption, and loss of electrolytic membrane integrity), and therefore any future investigations into the potential role for supplemental magnesium may require more specific target stratification. Focal and semifocal injury patters such as those manifested by local contusion, or direct tissue disruption due to mechanical impingement, may have significantly different responses and requirements (with regard to electrolyte physiology) than a broadly diffuse and global insult such as those in large external hemispherical mass effect or diffuse axonal injury. Such careful injury phenotype selection may provide a clear answer to where any beneficial role for magnesium may lie and in whom.

Such patient selection and stratification may not necessarily be via radiological/anatomical methods; biomarkers specifically characterising the immediate immune response to traumatic insult[15] (particularly considering the inferred relevance of neuroinflammation to magnesium) may play a significant role in such experimental design. A key aspect (some may say a requirement) of in vivo (animal) TBI modelling is the homogeneity of the neuroaxial insult delivery.[16] Each animal receives a carefully orchestrated impact, modelling with a range of insult mechanisms may elude to which 'type' of injury response better to which therapy. It should be mentioned here however that there are a number of different models of both focal and diffuse moderate/severe TBI in vivo, but investigations using them usually do so in isolation. This type of injury modelling may be considered as not entirely representative of the extremely variable/mixed system pattern of energy absorption seen in clinical TBI practice. It is therefore possible that these characteristics of preclinical modelling, together with inadequate patient selection stratification and injury phenotype identification may be contributing to the lack of beneficial effect seen in translational studies into the use of magnesium (and numerous other disease modifying agents for use in TBI).

The review by Lyons *et al* within this issue represents a positive first step in revisiting this (potentially) suboptimally investigated topic. A better understanding of the current evidence, and an appreciation of the limitations of the studies, which represent it, is critical in order to proceed with better-designed investigations. TBI represents the most complex pattern of injury, in the most complex organ in the body[17] (would this author had been so fortunate as to coin that phrase), and such needs the most intricate and comprehensive investigations to make meaningful progress.

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