

Supplementary magnesium in traumatic brain injury

Davies, David

DOI:

[10.1136/jramc-2018-000985](https://doi.org/10.1136/jramc-2018-000985)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Davies, D 2018, 'Supplementary magnesium in traumatic brain injury: where do we go from here?', *Journal of the Royal Army Medical Corps*. <https://doi.org/10.1136/jramc-2018-000985>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 16/08/2018

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

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

David James Davies

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 studies¹⁰ 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 insult¹⁵ (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 body¹⁷ (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.

Collaborators Antonio Belli, Kamal Yakoub, Valentina DiPietro.

Contributors I am the sole author and compiler of this editorial document.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.



OPEN ACCESS

Correspondence to Mr David James Davies, Trauma Neurosurgery, University Hospitals Birmingham, Birmingham B15 2TH, UK; d.j.davies.1@bham.ac.uk

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Davies DJ. *J R Army Med Corps* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jramc-2018-000985

Accepted 15 May 2018

J R Army Med Corps 2018;0:1–2.
doi:10.1136/jramc-2018-000985

REFERENCES

- 1 Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008;7:728–41.
- 2 Van Beek JG, Mushkudiani NA, Steyerberg EW, et al. Prognostic value of admission laboratory parameters in traumatic brain injury: results from the IMPACT study. *J Neurotrauma* 2007;24:315–28.
- 3 Donkin JJ, Vink R. Mechanisms of cerebral edema in traumatic brain injury: therapeutic developments. *Curr Opin Neurol* 2010;23:293–9.
- 4 Earle SA, Proctor KG, Patel MB, et al. Ubiquitin reduces fluid shifts after traumatic brain injury. *Surgery* 2005;138:431–8.
- 5 Burd I, Breen K, Friedman A, et al. Magnesium sulfate reduces inflammation-associated brain injury in fetal mice. *Am J Obstet Gynecol* 2010;202:e1–292.e9.
- 6 Muir KW. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. *Curr Opin Pharmacol* 2006;6:53–60.
- 7 Dorsett CR, McGuire JL, DePasquale EA, et al. Glutamate neurotransmission in rodent models of traumatic brain injury. *J Neurotrauma* 2017;34:263–72.
- 8 Vink R, O'Connor CA, Nimmo AJ, et al. Magnesium attenuates persistent functional deficits following diffuse traumatic brain injury in rats. *Neurosci Lett* 2003;336:41–4.
- 9 Bareyre FM, Saatman KE, Raghupathi R, et al. Postinjury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. *J Neurotrauma* 2000;17:1029–39.
- 10 Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. *Lancet Neurol* 2007;6:29–38.
- 11 Marehbani J, Muehlschlegel S, Edlow BL, et al. Medical management of the severe traumatic brain injury patient. *Neurocrit Care* 2017;27:430–46.
- 12 Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017;80:6–15.
- 13 Lyons MWH, Blackshaw WJ. Does magnesium sulfate have a role in the management of severe traumatic brain injury in civilian and military populations? A systematic review and meta-analysis. *J R Army Med Corps* 2018. doi: 10.1136/jramc-2018-000916. [Epub ahead of print].
- 14 Dorhout Mees SM, Algra A, Wong GK, et al. Early magnesium treatment after aneurysmal subarachnoid hemorrhage: individual patient data meta-analysis. *Stroke* 2015;46:3190–3.
- 15 Hazeldine J, Naumann DN, Toman E, et al. Prehospital immune responses and development of multiple organ dysfunction syndrome following traumatic injury: A prospective cohort study. *PLoS Med* 2017;14:e1002338.
- 16 Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nat Rev Neurosci* 2013;14:128–42.
- 17 Wheble JL, Menon DK. TBI-the most complex disease in the most complex organ: the CENTER-TBI trial-a commentary. *J R Army Med Corps* 2016;162:87–9.