Practice Uncertainties Page

How effective are some common treatments for traumatic brain injury?

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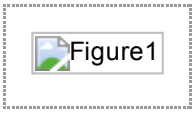
Surveys show that mannitol, hyperventilation, cerebrospinal fluid drainage, and barbiturates are commonly used in the United Kingdom, Europe, and the United States to treat traumatic brain injury.[1] [2] [3] Yet the effects of such treatments are uncertain.

Traumatic brain injury is a major cause of death and disability worldwide. Every year at least 10 million people sustain a traumatic brain injury serious enough to result in death or admission to hospital.[4] Bearing in mind that almost half of all patients with traumatic brain injury experience long term disability[5] [6] and that most injury occurs in young adults, the medical, social, and financial burden is clear.

What is the evidence of the uncertainty?

The Cochrane Injuries Group maintains a specialised register of randomised controlled trials of interventions for traumatic brain injury and has searched extensively for trials evaluating the effects of mannitol, hyperventilation, cerebrospinal fluid drainage, and barbiturates. The group has also prepared, and regularly updates, systematic reviews to assess the effects of barbiturates,[7] hyperventilation,[8] and mannitol.[9]

In 1998 the Cochrane Injuries Group highlighted the absence of reliable evidence for the effectiveness of these four treatments[10] when searches identified only three small trials of barbiturates,[11] [12] [13] none of cerebrospinal fluid drainage, one small trial of hyperventilation,[14] and one small trial of the use of mannitol.[15] Our latest searches, to January 2008, indicate that there remains a lack of adequately powered randomised controlled trials of these interventions, with no additional trials found. The uncertainty is evident in the meta-analyses presented in the figure⇓. The relative risks of death for barbiturates, hyperventilation, and mannitol are compatible with both moderate decreases and moderate increases in the risk of death, and no estimate is available for cerebrospinal fluid drainage owing to the absence of any clinical trial data. The existing trials are far too small to detect clinically plausible treatment effects.



Summary of relative risks for death at the end of studies on mannitol, hyperventilation, and barbiturates. No estimate is available for cerebrospinal fluid drainage as no clinical trials were found

Evidence of improved clinical outcomes with high dose mannitol compared with low dose mannitol[16] [17] [18] provided indirect evidence that mannitol administration may be useful, but an investigation by the Cochrane Injuries Group could not confirm the validity of the trials in question,[19] which have now been withdrawn from the Cochrane Review.

The previous uncertainty surrounding the use of corticosteroids in traumatic brain injury, however, was resolved by the large scale (10 008 randomised patients) CRASH-1 trial in 2004 (www.crash.lshtm.ac.uk).[20] The current evidence shows that administration of corticosteroids after brain injury does more harm than good.

Is ongoing research likely to provide relevant evidence?

To the best of our knowledge no clinical trials are currently being conducted aimed at resolving these uncertainties. Searches by the Cochrane Injuries Group covering all dates to January 2008 have not identified any further unpublished or ongoing trials that would contribute relevant evidence about the effectiveness of barbiturates, cerebrospinal fluid drainage, hyperventilation, and mannitol in the treatment of traumatic brain injury.

What should we do in the light of the uncertainty?

It is essential that clinicians and the public—as users and potential healthcare users—are fully informed of the uncertainties surrounding the efficacy of these commonly used treatments. Until these uncertainties are resolved, clinicians should continue to make treatment decisions based on their judgment and experience according to the best available evidence. However, influencing the research agenda in order to tackle these uncertainties is the key challenge.

Trauma is one of the most neglected areas of research.[21] [22] The reasons for this are unclear, although the following may be contributing factors. Firstly, traumatic brain injury is an acute, unexpected condition with a high case-fatality rate. These patients, at the time of their need for treatment, are not in the position to consider the uncertainties of treatments and lobby for further trials.

Secondly, conducting clinical trials in the emergency setting is challenging, with a major obstacle being the failure to appreciate that unconscious patients in emergency situations are an exception to the general requirement for informed consent for medical research.[20]

Thirdly, although trauma is a leading cause of death and disability worldwide, it is largely a problem for low and middle income countries, where 90% of the deaths occur.[23] Most research infrastructure and funding, however, are found in high income countries, where although trauma is an important cause of premature mortality, it is not a leading cause, and thus may not be a research priority. Pharmaceutical companies also show less interest in examining uncertainties surrounding commonly used licensed treatments, such as those featured here, preferring to invest in research into new patentable treatments —for obvious commercial reasons.

Need for a different approach

Ten years after the Cochrane Injuries Group highlighted the uncertain effectiveness of these four treatments,[10] there has been little progress. A different approach is needed. Lessons could be learned from research strategies for other neglected conditions, such as a neglected tropical disease initiative recently launched with support from governmental and non-governmental organisations.[24] Global partnerships, including such organisations as the new Carso Health Institute (which has recognised the huge health burden from injuries in Latin America and made injury research a priority), may raise the profile and generate the necessary financial resources to tackle these and other important uncertainties in trauma research.

Notes

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Footnotes

- This is a series of occasional articles that highlights areas of practice where management lacks convincing supporting evidence. The series advisers are David Tovey, editorial director, BMJ Knowledge, and Charles Young, editor of BMJ Clinical Evidence, and editor in chief, BMJ Point of Care.
- Contributors: IR conceived the idea for the article. KB ran the database searches and screened the records with PP and KK. KK performed data entry and analysis. KK, PP, and IR drafted and edited the manuscript. The final version was approved by all authors. KK and PP are guarantors.
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