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MEDICINE

Alfred ICU Journal Club Review of "Bhullar et al, 2014: antiseizure prophylaxis after Traumatic Brain Injury"

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THE QUESTION

In adults with severe blunt traumatic brain injury (TBI), compared to no seizure prophylaxis, does phenytoin change the rate of seizures at 7 days?

In addition, as a secondary question, does phenytoin affect hospital length of stay (LOS) and functional outcome (as measured by the Glasgow Outcome Scale (GOS) and the Modified Rankin Scale (MRS))?

STUDY DESIGN

TYPE OF STUDY

Retrospective review at a level 1 trauma centre in the USA utilising data from the American College of Surgeons National Trauma Registry between Jan 2008-Jan 2010

POPULATION

n = 93 adults (out of 766 with a positive CT brain scan) with severe blunt TBI who stayed in hospital for more than 7 days

Severe TBI defined as GCS 3-8 with a positive CT brain scan (subarachnoid, subdural, or extradural haemorrhage or diffuse axonal injury)

Inclusion criteria

Age >18
GCS 3-8 on admission
Hospital stay at least 7 days

Exclusion criteria

Age <18
GCS 9-15 on admission (n=450, 59%)
Seizure in field or en route before possible antiseizure prophylaxis could be given (n=3, 0.4%)
Death within 72 hours (n=76, 10%)
Use of levetiracetam (n=144, 19%)

INTERVENTIONS/ COMPARISONS

Intervention: phenytoin as seizure prophylaxis, n=50 (53.8% of study cohort)

Intravenous loading dose 20mg/kg (max 2g) and maintenance 5mg/kg/day Q8H
Oral phenytoin when appropriate
Maintained for 7 days

Comparison: no seizure prophylaxis, n=43 (46.2% of study cohort)

OUTCOMES

Primary outcome

There was no significant difference in seizure rate at 7 days between phenytoin and no prophylaxis (4% vs 2% p=0.5)

Secondary outcomes

Statistically significant differences in mean values for:

Hospital length of stay (36d vs 25d, p= 0.03)
Glasgow outcome score (GOS) score (2.9 vs 3.4, p=0.01)
Modified Rankin Score (MRS) (3.1 vs 2.3, p= 0.02)

COMMENTARY AND CRITICISMS

Criticisms

This study appeared to be an attempt to increase compliance with the BTF guidelines, which advise the use of phenytoin for 7 days after traumatic brain injury in high risk cases.

1. However, by excluding patients with GCS >8, the article does not actually assess BTF guidelines, which suggest consideration of post-TBI seizure prophylaxis if GCS<10.

2. The significance of early seizures is uncertain. There is a theoretical risk of secondary brain injury, but early (<7 day) seizures have not been shown to lead to long-term epilepsy or worse outcomes (1).

The study is likely confounded by bias from numerous sources, and lacks internal validity as a result

1. Data abstraction is not detailed and there is considerable scope for observer/ misclassification bias (e.g. How many abstractors were there? Was a standardised abstraction form used? Was there inter-observer variability between abstractors? How was the accuracy of the abstracted information checked?)

2. The study is limited by a small sample size.

3. The study did not report any baseline differences between intervention and comparison groups. However, the initial Glasgow Coma scale (GCS) was not included in the analysis of baseline clinical characteristics for each group. This may be an important confounder, as although GCS 7 and GCS 3 are both classified as 'severe traumatic brain injury' the latter predicts a much worse long-term prognosis.

4. It is unclear how seizures were diagnosed – this appears to based on what was written in the notes. Seizures may be difficult to diagnoses, especially subtle or non-convulsive seizures. This may contribute to measurement bias.

5. This study suffers from allocation bias. Although the individual interventions for the two groups were not statistically significant, it is clear that when bundled together the patients receiving phenytoin were more likely to have received surgical interventions – which may predispose those patients to seizures, and may make them more likely to receive phenytoin. Also, the decision to use phenytoin was at the neurosurgeon's discretion.

6. The study compares categorical ordinal variables (GOS and MRS) as if they were continuous, which made it difficult to gauge clinical significance.

7. Some centres / neurosurgeons prefer to use leviteracetam in preference to phenytoin. A small randomised controlled trial has previously found worse cognitive outcomes with phenytoin when compared with leviteracetam for seizure prophylaxis (2).

8. The relevance of specific anti-epileptic drugs in addition to the high dose sedatives commonly used in the early phase of modern severe TBI intensive care management is questionable.

FINAL WORDS

The findings of this study cannot be interpreted reliably as the study lacks internal validity.

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