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Papers

Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials

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Abstract

Objective: To quantify the effectiveness and safety of corticosteroids in the treatment of acute traumatic brain injury.
Design: Systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury. Summary odds ratios were estimated as an inverse variance weighted average of the odds ratios for each study.
Setting: Randomised trials available by March 1996.
Subjects: The included trials with outcome data comprised 2073 randomised participants.
Results: The effect of corticosteroids on the risk of death was reported in 13 included trials. The pooled odds ratio for the 13 trials was 0.91 (95% confidence interval 0.74 to 1.12). Pooled absolute risk reduction was 1.8% (-2.5% to 5.7%). For the 10 trials that reported death or disability the pooled odds ratio was 0.90 (0.72 to 1.11). For infections of any type the pooled odds ratio was 0.92 (0.69 to 1.23) and for the seven trials reporting gastrointestinal bleeding it was 1.05 (0.44 to 2.52). With only those trials with the best quality of concealment of allocation, the pooled odds ratio estimates for death and death or disability became closer to unity.
Conclusions: This systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury shows that there remains considerable uncertainty over their effects. Neither moderate benefits nor moderate harmful effects can be excluded. The widely practicable nature of the drugs and the importance of the health problem suggest that large simple trials are feasible and worth while to establish whether there are any benefits from use of corticosteroids in this setting.

Top
Abstract
Introduction
Methods
Results
Discussion
References

Key messages

- Traumatic brain injury is an important global cause of death and disability
- Corticosteroids are a widely practicable intervention
- This systematic review shows continued uncertainty over the effects of steroids
- The estimate of absolute risk reduction for death is 1.8% (95% confidence interval -2.5 to 5.7)
- Further large scale randomised controlled trials are needed

Introduction

Traumatic brain injury is a leading cause of premature death and disability. Motor vehicle accidents account for most fatal head injuries.[1] Although road death rates are falling in most industrialised countries, in the rapidly motorising Asian countries they are rising and will almost certainly continue to do so. Road death rates per head in China are already similar to those in the United States, even though there are only five vehicles per 1000 population in China compared with 770 vehicles per 1000 population in the United States.[2] Overall, about 75% of the estimated 850 000 deaths due to road accidents each year occur in the developing world.[3]

Top
Abstract
Introduction
Methods
Results
Discussion
References

In the United States the incidence of disability related to brain injury is estimated to be 33 new cases per 100 000 people per year.[4] As this often occurs in young people and is long term, disability related to traumatic brain injury is a major cause of ill health worldwide. In 1961 Galicich and French reported rapid and significant improvement in response to corticosteroids in 28 of 34 people with cerebral oedema either due to brain tumours or postoperatively.[5] This led to their use in other intracranial problems characterised by raised intracranial pressure and in severe head injury.[6] Eighty per cent of patients with fatal head injuries show evidence of increased intracranial pressure at necropsy.[7]

For a problem as common as brain injury, even a moderate reduction in mortality or disability from an intervention as widely practicable as corticosteroids would be important. There have been several randomised controlled trials of corticosteroids in head injury with apparently conflicting findings. Continuing uncertainty about the effects of corticosteroids for this indication is reflected in substantial variation in their use. A recent study in the United Kingdom found that corticosteroids were used in just under half of the intensive care units surveyed.[8] We reviewed the randomised trials that have examined the effects of corticosteroids in acute traumatic brain injury on subsequent death and disability.

Methods

Inclusion criteria
We included studies in the review if they met the following criteria. Firstly, study participants had to have a clinically diagnosed acute traumatic brain injury of any severity. Secondly, the experimental intervention was corticosteroids (those steroids with predominantly glucocorticoid effects–namely, prednisolone, betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and triamcinolone) administered in any dose by any route for any duration started within seven days of the injury. Thirdly, study participants were randomly assigned to treatment or control groups. Studies that used quasi-random methods of allocation, such as alternation, were excluded.

Top
Abstract
Introduction
Methods
Results
Discussion
References

Identification of relevant trials
We searched Medline for 1966 to December 1995 using a combination of the March 1996 update of the optimally sensitive search strategy for trials

from the Cochrane Collaboration (earlier version published as referenced[9]) with the MeSH headings "head injuries," "intracranial pressure," "brain edema," and "brain-concussion" including all subheadings. The resulting citations were examined on screen to identify possibly relevant trials and those thus identified were retrieved in full and compared with the inclusion criteria. A search of Embase, years 1974-1996 (performed in March 1996) was done by using a similar approach to that for Medline.

We searched the Cochrane Library in August 1996 using each of the text terms "head," "brain," "dexamet*," and "steroids."[10] We asked the Ottawa Stroke Trials Registry and the United Kingdom based Intensive Care National Audit and Research Centre to search their databases, which contain the results of hand searching many neurological, neurosurgical, intensive care, and emergency medicine journals. Several other journals were also hand searched for this review. All the journals from these sources are listed in an appendix, which is available on the internet atwww.bmj.com .

The reference lists of all trials found were searched for additional trials. We attempted to contact all the trialists identified, asking them to identify any further published or unpublished trials. No language restrictions were used.

Data extraction and study appraisal

We each extracted the following information independently from each trial: strategy for concealment of allocation, number of randomised patients, duration of follow up, and number lost to follow up. The major outcome data sought were numbers of deaths and numbers of people disabled at the end of the study period. All but one study (see Faupel et al[18]) used the Glasgow outcome scale[11] to assess neurological outcome; the categories for persistent vegetative state, severe disability, and moderate disability were combined into "disability" for this review. This enabled inclusion of the one trial that did not use the Glasgow outcome scale but used a similar ordinal categorisation of function. Where there was more than one steroid group in a trial (for example, low dose and high dose) those groups were combined. We also extracted data on side effects or complications when they were reported by using the authors' definitions of these.

As there is evidence that the quality of concealment of allocation particularly affects the results of studies, each of us scored this quality on the scale used by Schulz et al as shown below, assigning 1 to poorest quality and 3 to best quality[12]: 1=trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth); 2=trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and, 3=trials deemed to have taken adequate measures to conceal allocation (for instance, central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

When the method used to conceal allocation was not clearly reported the author was contacted, if possible, for clarification. We then compared the scores allocated and resolved differences by discussion.

Statistical methods

Summary odds ratios were calculated in RevMan 3.0 software[13] with the Mantel-Haenszel method. We tested for heterogeneity using a χ^2 test.

Results

Top
Abstract
Introduction
Methods
Results
Discussion
References

The combined search strategies identified 18 reports of trials that satisfied the inclusion criteria.[14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31] Two were reports of the same trial[28 29]: this trial was excluded after contact with the first author showed that concealment of allocation had been inadequate. Contact with one trialist showed that allocation had been concealed by using a third party to prepare and supply the drug and placebo preparations.[26] The trial by Hernesniemi and Troupp was published as an abstract with no results, but the first author, when contacted, was able to provide full outcome data for the 169 randomised participants.[20] Contact with Pitts revealed a further unpublished randomised trial of 279 participants,[21] and the author was also able to provide complete outcome data for death and disability. The trial with 100 participants by Tahara et al was reported as an abstract in 1972 with no usable outcome data.[17] The authors were contacted but were unable to locate the trial data. Similarly, the abstract published by Hoyt et al of a trial on 16 patients provided insufficient detail of outcomes.[15] We were unable to contact the author.

A total of 2073 participants were randomised in 14 included trials. Table 1) describes the participants, intervention, period of follow up, numbers of participants, and quality of concealment of allocation for each trial assessed. The rate of exclusions or losses to follow up was highest in the trial by Cooper because the trial was reported before all patients had been evaluated.[19] Table 2) shows the numbers of deaths, numbers disabled, and complication rates for the trials.

Table 1 Summary of participants, interventions, follow up period, size of trial, and quality of concealment of allocation

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Table 2 Summary of outcome data. In some trials, denominators vary between outcomes: this is assumed to be effects of time on loss to follow up

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Summary odds ratios

Figures 1 and 2 present summary odds ratio charts for the two main outcomes for all trials in chronological order. For death the odds ratio was 0.91 (95% confidence interval 0.74 to 1.12), and when the categories of death and disability were summed for analysis it was 0.90 (0.72 to 1.11). The summary odds ratio was 0.92 (0.69 to 1.23) for infections and 1.05 (0.44 to 2.52) for gastrointestinal bleeds.

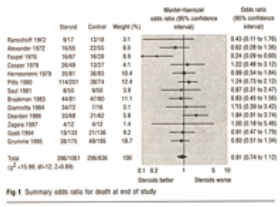

Fig 1 Summary odds ratio for death at end of study

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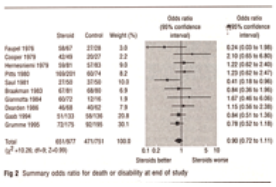

Fig 2 Summary odds ratio for death or disability at end of study

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Subgroup analysis–For the two main outcomes–death and death or disability–we performed a subgroup analysis by analysing the trials with only the highest quality of concealment of allocation. This was not done for the other two outcomes because of the small numbers of events involved. For death, the summary odds ratio was 1.04 (0.83 to 1.30) and for death and disability 0.97 (0.77 to 1.23).

Discussion

Top
Abstract
Introduction
Methods
Results
Discussion
References

This systematic review summarises the evidence from randomised controlled trials of corticosteroids in acute traumatic brain injury.

Methodological issues
The inclusion of an Embase search identified one study not found on Medline.[17] Contact with trialists enabled us to include data from two large unpublished studies[20 21] but not from others.[15 17 21]

Numbers of events were small for infections and gastrointestinal bleeds, resulting in wide confidence intervals around the estimate of effect.

None of the tests for heterogeneity yielded significant results. When death was the outcome, however, the upper limit of the 95% confidence interval in the trial by Faupel et al[18] did not overlap with the lower limit in the trial by Dearden et al.[26] In Faupel's trial the outcome was assessed "at discharge," yet overall 19% of the participants were classified as "unconscious stabilised." The apparently short follow up period may account for the incongruous result.

Other sources of variation may include severity and pathology of the head injury, variations in corticosteroid regimens (for example, drug, dose, route), and temporal trends in the use of other interventions. The use of corticosteroids in spinal cord injury suggests that the timing of administration is important,[32] so this is another possible source of variation.

When we excluded trials with less than the highest quality of concealment of allocation the differences between experimental and control groups was reduced for both death and death or disability. This is consistent with the evidence that inadequate concealment of allocation results in overestimates of the effect of treatment,[12] but it could also be due to random variation. There were several trials in which the true quality of concealment was not known, which makes interpretation difficult.

Implications
Despite 25 years of randomised controlled trials of the use of corticosteroids in patients with head injury, their effects are still not clear. In this review the risk of death in those given corticosteroids was 1.8% less than in the control groups (95% confidence interval 5.7% less to 2.5% more) when we used the trials' average control death rate of 35.4% as the background rate.

The recent guidelines from the Brain Trauma Foundation on the management of severe head injury include a standard (a recommendation made with a "high degree of clinical certainty") that "the use of glucocorticoids is not recommended."[33] These guidelines reviewed six of the randomised trials used in this systematic review and did not attempt a quantitive overview of them. Even with 14 trials, as in this systematic review, considerable uncertainty remains over the effects of corticosteroids.

Can this uncertainty be resolved? To do so would require large randomised trials. For example, a trial with 90% power to detect a 2.6% reduction in risk of death from 35.4% (the total control mortality in this review) to 32.8% at the 0.01 level of significance would require about 20 000 participants.[34] Such large trials to detect effects of this size can be justified when the health problem is important and the treatment widely practicable.[35] Corticosteroids for acute traumatic head injury meet these criteria. Without such a trial clinicians and patients and their families are being forced to make important decisions on the basis of inadequate evidence.

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References

Top
Abstract
Introduction
Methods
Results
Discussion
References

1. Jennett B. Epidemiology of head injury. *J Neurol Neurosurg Psychiatry* 1996;60:362-9. [Medline]
2. Roberts I. Letter from Chengdu: China takes to the roads. *BMJ* 1995;310:1311-3. [Free Full Text]
3. Murray CJL, Lopez AD, eds. *Global comparative assessments in the health sector*. Geneva: World Health Organisation, 1994.
4. Kraus JF. Epidemiology of head injury. In: Cooper PR, ed. *Head injury*. 3rd ed. Baltimore: Williams and Wilkins, 1993:1-25.
5. Galicich JH, French LA. Use of dexamethasone in the treatment of cerebral edema resulting from brain tumours and brain surgery. *American Practitioner* 1961;12:169-74.
6. Pickard JD, Czosayka M. Management of raised intracranial pressure. *J Neurol Neurosurg Psychiatry* 1993;56:845-58.
7. Miller JD, Jones PA, Dearden NM, Tocher JL. Progress in the management of head injury. *Br J Surg* 1992;79:60-4.
8. Jeevaratnam DR, Menon DK. Survey of intensive care of severely head injured patients in the United Kingdom. *BMJ* 1996;312:944-7. [Abstract/Free Full Text]
9. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;309:1286-91.
10. Cochrane Collaboration. *Cochrane Library (database on disk and CD-ROM). Issue 2.* Oxford: Update Software, 1996.
11. Jennett B, Bond M. Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975;i:480-4.
12. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
13. Update Software. *RevMan. Version 3.0 for Windows*. Oxford: Update Software, 1996.
14. Alexander E. Medical management of closed head injuries. *Clin Neurosurg* 1972;19:210-50.

15. Hoyt HJ, Goldstein FP, Reigel DH, Holst R. Clinical evaluation of highly water-soluble steroids in the treatment of cerebral edema of traumatic origin (a double blind study). *Pharmacol Ther* 1972;13:141.
16. Ransohoff J. The effects of steroids on brain edema in man. In: Reulen HJ, Schurmann K, eds. *Steroids and brain edema*. New York: Springer-Verlag, 1972: 211-3.
17. Tahara I, Fujii C, Tanaka N, Ogawa M, Katsurada K. Effects of steroid therapy on acute head injury. *Neurol Med Chir (Tokyo)* 1972;12:111-2.
18. Faupel G, Renlen H J, Muller D, Schurmann K. Double-blind study on the effects of steroids on severe closed head injury. In: Pappius MM, Feindel W, eds. *Dynamics of brain edema*. Berlin: Springer-Verlag, 1976:337-43.
19. Cooper PR, Moody S, Clark WK, Kirkpatrick J, Maravilla K, Gould AL, et al. Dexamethasone and severe head injury. *J Neurosurg* 1979;51:307-16.
20. Hernesniemi J, Troupp H. A clinical retrospective and a double blind study of betamethasone in severe closed brain injuries. *Acta Neurochir* 1979;suppl 28:499.
21. Pitts LH, Kaktis JV. Effect of megadose steroids on ICP in traumatic coma. In: Shulman K, Marmarou A, Miller JD, et al, eds. *Intracranial pressure IV*. Berlin: Springer-Verlag, 1980:638-42.
22. Saul TG, Ducker TB, Salcman M, Carro E. Steroids in severe head injury. *J Neurosurg* 1981;54:596-600.
23. Braakman R, Schouten HJA, Blaauw-van Dishoeck M, Minderhoud JM. Megadose steroids in severe head injury. *J Neurosurg* 1983;58:326-30.
24. Giannotta SL, Weiss MH, Apuzzo MLJ, Martin E. High dose glucocorticoids in the management of severe head injury. *Neurosurgery* 1984;15:497-501. [Medline]
25. Braun SR, Levin AB, Clark KL. Role of corticosteroids in the development of pneumonia in mechanically ventilated head-trauma victims. *Critical Care Medicine* 1986;14:198-201.
26. Dearden NM, Gibson JS, McDowall DG, Gibson RM, Cameron MM. Effect of high dose dexamethasone on outcome from severe head injury. *J Neurosurg* 1986;64:81-8. [Medline]
27. Zagara G, Scaravilli P, Carmen Belluci M, Seveso M. Effect of dexamethasone on nitrogen metabolism in brain-injured patients. *J Neurosurg* 1987;31:207-12.
28. Kloti J, Fanconi S, Zachmann M, Zaugg H. Dexamethasone therapy and cortisol excretion in severe paediatric head injury. *Childs Nerv Syst* 1987;3:103-5. [Medline]
29. Fanconi S, Kloti J, Meuli M, Zaugg H, Zachmann M. Dexamethasone therapy and endogenous cortisol production in severe pediatric head injury. *Intensive Care Med* 1988;14:163-6. [Medline]
30. Gaab MR, Trost HA, Alcantara A, Karimi-Nejad A, Moskopp D, Schultheiss R, et al. "Ultrahigh" dexamethasone in acute brain injury. *Zentralbl Neurochir* 1994;55:135-43.
31. Grumme T, Baethmann A, Kolodziejczyk D, Krimmer J, Fischer M, von Eisenhart Rothe B, et al. Treatment of patients with severe head injury by triamcinolone: a prospective, controlled multicenter trial of 396 cases. *Exp Med* 1995;195:217-29.
32. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS. A randomised controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. *N Engl Med J* 1990;322:1405-11.
33. Task Force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care. *Guidelines for the management of severe head injury*. Brain Trauma Foundation, 1995.
34. Centers for Disease Control and Prevention. *Epi Info 6. Version 6.03*. Geneva: World Health Organisation, 1996.
35. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomised trials? *Stat Med* 1984;3:409-20.

(Accepted 10 April 1997)

This article has been cited by other articles:

- Moppett, I. K. (2007). Traumatic brain injury: assessment, resuscitation and early management. *Br J Anaesth* 99: 18-31 [Abstract] [Full text]
- Mishra, L., Rajkumar, N, Hancock, S. (2006). Current controversies in neuroanaesthesia, head injury management and neuro critical care. *Contin Educ Anaesth Crit Care Pain* 6: 79-82 [Full text]
- Thompson, H. J, Bakshi, A. (2005). Methylprednisolone was associated with an increase in death after head injury. *Evid. Based Nurs.* 8: 51-51 [Full text]
- Guha, A (2004). Management of traumatic brain injury: some current evidence and applications. *Postgrad. Med. J.* 80: 650-653 [Abstract] [Full text]
- Smith, M. (2003). Diffuse axonal injury in adults. *Trauma* 5: 227-234 [Abstract]
- Lecky, F E (2002). Trauma care in England and Wales: Is this as good as it gets?. *Emerg. Med. J.* 19: 488-489 [Full text]
- (2002). The MRC CRASH Trial: study design, baseline data, and outcome in 1000 randomised patients in the pilot phase. *Emerg. Med. J.* 19: 510-514 [Abstract] [Full text]
- Roberts, I. (2002). CRASH. *J. R. Soc. Med.* 95: 162-162 [Full text]
- Lockey, D. J, Manara, A. R (2001). The role of steroids following major trauma. *Trauma* 3: 53-61 [Abstract]
- Yates, D., Roberts, I. (2000). Corticosteroids in head injury. *BMJ* 321: 128-129 [Full text]
- Alderson, P., Roberts, I. (1999). Design of CRASH trial. *BMJ* 319: 1068a-1068 [Full text]
- Gregson, B, Todd, N V, Crawford, D, Gerber, C J, Fulton, B, Tacconi, L, Crawford, P J, Sengupta, R P (1999). CRASH trial is based on problematic meta-analysis. *BMJ* 319: 578-578 [Full text]
- Roberts, I., Schierhout, G., Alderson, P. (1998). Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 65: 729-733 [Abstract] [Full text]
- Newell, D. W, Temkin, N. R, Bullock, R., Choi, S., Alderson, P., Roberts, I. (1998). Corticosteroids in acute traumatic brain injury. *BMJ* 316: 396-396 [Full text]

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