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Roberts I.
Aminosteroids for acute traumatic brain injury.
Cochrane Database of Systematic Reviews 1999, Issue 3. Art. No.: CD001527.
DOI: 10.1002/14651858.CD001527.

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[Intervention Review]

Aminosteroids for acute traumatic brain injury

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Editorial group: Cochrane Injuries Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 6, 2010.

Citation: Roberts I. Aminosteroids for acute traumatic brain injury. *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001527. DOI: 10.1002/14651858.CD001527.

ABSTRACT

Background

Traumatic brain injury is a leading cause of premature death and disability. Post-traumatic membrane lipid peroxidation has been proposed as one mechanism leading to secondary brain damage following head injury. Aminosteroids have been shown to inhibit lipid peroxidation in laboratory animals and have the potential to improve outcome following head injury.

Objectives

To quantify the effectiveness and safety of aminosteroids in the treatment of acute traumatic brain injury.

Search methods

We searched the Cochrane Injuries Group specialised register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the National Research Register, Web of Science, web-based trials databases and conducted a general internet search. We contacted experts in the field and the company that manufactures tirilazad. The searches were last updated in March 2006.

Selection criteria

We sought to identify all randomised controlled trials of aminosteroids versus placebo in the treatment of acute traumatic brain injury. Studies using a quasi-random form of allocation, such as alternation, were excluded from the review.

Data collection and analysis

One author examined the electronic search results for reports of possibly relevant trials for retrieval in full. Two authors (IR and PA) applied the selection criteria independently to the trial report, with no disagreement.

Main results

Two randomised controlled trials have examined the effect of the aminosteroid tirilazad mesylate on death and disability following head injury. To date, only the results of one of these trials are available for analysis. The risk of death in patients treated with tirilazad was almost identical to those given placebo RR = 1.05 (95% confidence interval 0.86 to 1.29). The risk of death and severe disability in patients treated with tirilazad was again almost identical to those given placebo RR = 1.07 (95% confidence interval 0.93 to 1.23).

Authors' conclusions

There is no evidence to support the routine use of aminosteroids in the management of traumatic head injury. On the basis of the existing evidence from randomised trials of aminosteroids in head injury, it is not possible to refute the possibility of moderate but potentially clinically important benefits or harms. A further randomised controlled trial of tirilazad mesylate with 1156 participants has been completed, the results of which should become available in the near future.

PLAIN LANGUAGE SUMMARY

Use of aminosteroids to treat traumatic brain injury

Traumatic brain injury is a leading cause of death and disability. After the initial blow to the head, additional brain damage can occur through a reduction of oxygen to the brain tissues (cerebral hypoxia). Chemicals called aminosteroids have been shown to help stop cell membrane damage and cell death in animals.

The review author searched the medical literature to find out if aminosteroids help people with traumatic brain injury when given within seven days of the injury. The author looked for randomised controlled trials in which one group of patients received a treatment (aminosteroids) while a similar group received non-active treatment (placebo) in addition to standard care. To reduce possible bias, each patient is randomly assigned to a group. The author found two such studies, which used the aminosteroid tirilazad mesylate, but the results of one of the studies were not available at the time of review. The completed study involved 1131 patients. The results of this study showed no benefit from the aminosteroid. The aminosteroid group did not have more side effects than the placebo group but aminosteroids are fairly new drugs that may have unknown less common side effects.

More research is needed on the use of aminosteroids to treat traumatic brain injury but currently there is no evidence to recommend their use.

BACKGROUND

Traumatic brain injury is a leading cause of premature death and disability. Road crashes account for the majority of fatal head injuries (Jennet 1996). Insights from pathophysiological studies have shown that acute traumatic head injury marks only the beginning of a continuing encephalopathic process. Secondary brain damage from on-going pathophysiological mechanisms and cerebral hypoxia is believed to be an important cause of avoidable death and long term disability. The modern management of head injury is primarily aimed at preventing secondary brain damage, which in turn requires an understanding of the pathophysiological processes involved in its development (Gentleman 1990). Demopoulos 1982 have proposed that the molecular basis for post-traumatic neuronal degeneration is oxygen free radical induced lipid peroxidation. Lipid peroxidation once initiated is considered to be a self-propagating process that leads to cell membrane damage and cell death. Tirilazad mesylate is a 21-aminosteroid that has been shown to inhibit lipid peroxidation in experimental animals (Hall 1988). There is considerable debate in the basic science community about whether or not the agent crosses the blood brain barrier: if it does not then any experimental protection would be because of lipid peroxidation in the vascular space, rather than cell membranes within the brain. Tirilazad has been evaluated in a number of randomised controlled trials. To assess the safety and effectiveness of aminosteroids in patients with head injury we conducted a systematic review of randomised controlled trials.

OBJECTIVES

To quantify the effectiveness and safety of aminosteroids in the treatment of acute traumatic brain injury.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of aminosteroids versus placebo (or no aminosteroid) for the treatment of acute traumatic brain injury.

Types of participants

People of all ages with clinically diagnosed acute traumatic brain injury secondary to head injury treated with aminosteroids within seven days of the injury. All severities of head injury were eligible. Trials in people with non-traumatic subarachnoid haemorrhage were excluded.

Types of interventions

Any regimen of any aminosteroid versus placebo, if started within seven days of head injury.

Types of outcome measures

- All-cause fatality.
- Any valid and reliable measure of neurological functioning.
- Quality of life measures.
- Side effects.
- Economic outcomes were considered relevant if available.

Search methods for identification of studies

There was no language restriction applied to the search.

An updated search was conducted in March 2006.

Electronic searches

We searched:

- the Cochrane Injuries Group's specialised register,
- the Cochrane Central Register of Controlled Trials,
- MEDLINE,
- EMBASE,
- the National Research Register.

Search strategies for each database are given in Appendix 1.

Searching other resources

We searched relevant websites, and reference lists of all potentially eligible studies were examined for other relevant articles.

We also contacted an expert in the field and the company that manufactures tirilazad.

Data collection and analysis

Selection of studies

One author examined the electronic search results for reports of possibly relevant trials for retrieval in full and applied the selection criteria to the trial report.

Data extraction and management

Information on the following was extracted: method of allocation concealment, number of randomised patients, type of participants and the interventions. The outcome data sought were as listed in the selection criteria. The reviewer was not blinded to the authors or journal when doing this, as evidence for the value of this is far from conclusive (Berlin 1997).

Where there was insufficient information in the published report, the authors were contacted for clarification.

Disability was assessed using the Glasgow Outcome Scale, with a favourable outcome defined as good recovery (e.g. return to work) or moderate disability.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), the author scored this quality on the scale used by Schulz 1995 as shown below, assigning C to poorest quality and A to best quality:

- C=trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth)
- B=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
- A=trials deemed to have taken adequate measures to conceal allocation (that is, 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)

Where the method used to conceal allocation was not clearly reported, the reviewer planned to contact the author, but this was not necessary.

Information on blinding and the degree of loss to follow up, was also collected but a score was not assigned to this.

Data synthesis

The author planned to calculate summary statistics for the trial using intention to treat.

The author planned to examine trials for statistical evidence of heterogeneity using a chi squared test. If there was no obvious heterogeneity on visual inspection or statistical testing, pooled relative risks and 95% confidence intervals would be calculated using a fixed effects model. For continuous data, we would examine the mean and standard deviation to look for evidence of skewness as described by Altman (Altman 1996) and, if not present, calculate pooled weighted mean differences.

The effect of excluding trials judged to have inadequate (scoring C) allocation concealment was planned as a sensitivity analysis.

The author also intended to prepare funnel plots if there were sufficient trials to look for evidence of publication bias (Egger 1997).

RESULTS

Description of studies

Marshall 1998: The trial randomised 1131 patients to receive tirilazad mesylate or placebo. Eleven patients were excluded from the analysis because they did not complete their assigned protocol. Efforts to obtain these data from the study authors have so far been unsuccessful. A further 55 participants were lost before the six month follow up (38 in the tirilazad group and 28 in the placebo group). Data on side effects were collected from 1016 participants. Despite the use of random allocation, there were substantial pre-treatment imbalances in hypotension and hypoxia.

Bleck (ongoing): A second randomised controlled trial of tirilazad mesylate in the treatment of head injury in 1156 patients has been conducted but the results are not yet available for inclusion in this review.

Bleck 1995 (unpublished): Randomised double-blind vehicle controlled study of tirilazad mesylate at three escalating dosage tiers (0.6, 2.0, 6.0 mg/kg/day) in a total of 181 adults patients with Glasgow Coma Scores of 4 to 12 within four hours of closed head injury. Data were collected on mortality, GOS, and side effects. The study author was contacted to obtain the unpublished data and has agreed to discuss provision of the data with Pharmacia and Upjohn, as the material is covered by a confidentiality agreement. However, data on mortality were presented at conference and are in the public domain. These data have therefore been included.

Mathew 1993 (unpublished): Thirty moderately head-injured patients shown by CT scan to have a focal intracranial lesion allocated to treatment with tirilazad or placebo in a randomised, double-blind protocol. Treatment commenced within 24 hours of injury and continued for four days. MR imaging with Gadolinium was performed at five days and the presence and extent of enhancement in the region of the lesion was measured. Also late MRI scans (six months) are being performed to detect if the ultimate resolution of a lesion is influenced by the therapy. The code was broken in the spring of 1993. The authors have been contacted for the unpublished data but, as yet, no data are available for inclusion.

Risk of bias in included studies

Marshall 1998: Allocation concealment was by the use of matching placebo. There were 66 participants excluded from the final analysis (about 6% of those randomised) - eleven due to protocol violation and 55 others lost to follow up. All personnel involved in the study were blinded to whether the patient received drug or placebo.

Effects of interventions

Two randomised controlled trials have examined the effect of the aminosteroid tirilazad mesylate on death and disability following head injury. To date, only the results of one of these trials are available for analysis. The risk of death in patients treated with tirilazad was almost identical to those given placebo RR=1.05 (95% confidence interval 0.86 to 1.29). The risk of death and disability in patients treated with tirilazad was again almost identical to those given placebo RR = 1.07 (95% confidence interval 0.93 to 1.23).

Because aminosteroids are new drugs, there was little information that could be used to predict the side effect profile. As a result, the side effects reported in this review were those reported in the trial itself. The criterion for reporting side effects in the trial was events that occurred in more than 2% of cases. There was no clear evidence of increased side effects in the aminosteroid treated group. However, the precision of the point estimates for many of the side effects was low and it is not possible to refute the possibility of clinically important adverse effects.

DISCUSSION

There is no evidence that aminosteroids reduce the risk of death or disability following head injury. However, on the basis of the existing evidence it is not possible to refute the possibility of moderate but potentially clinically important benefits or harms.

The published trial (Marshall 1998) pointed out that there were imbalances in some prognostic factors between treatment and control groups (pretreatment hypotension and hypoxia). It is not possible to tell what effect this confounding had on the overall result but it would be unlikely to make a major difference to the point estimate.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the routine use of aminosteroids in the management of traumatic head injury.

Implications for research

On the basis of the existing evidence from randomised trials of aminosteroids in head injury it is not possible to refute the possibility of moderate but potentially clinically important benefits or harms. A further randomised controlled trial of tirilazad mesylate

with 1156 participants has been completed, the results of which should become available in the near future.

ACKNOWLEDGEMENTS

Thanks to Reinhard Wentz, Fiona Renton and Karen Blackhall for their help with searching.

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References to studies included in this review

Bleck 1995 *{published data only (unpublished sought but not used)}*

Bleck TP, Germanson TP, Jane JA and the participants in the Tirilazad Head Trauma Trial, phase II. Tirilazad mesylate is safe in patients with moderate or severe head injury. *Neurology* 1995;**45**(suppl 4):A345.

Marshall 1998 *{published data only}*

Marshall LF, Maas AIR, Bowers Marshall S, Bricolo A, Fearnside M, Iannotti F, et al. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *Journal of Neurosurgery* 1998;**89**:519-25.

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References to ongoing studies

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Bleck T. Tirilazad mesylate in the treatment of head injury.

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Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analyses detected by a simple graphical test. *BMJ* 1997;**315**:629-34.

Gentleman 1990

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Hall ED, Yonkers PA, McCall JM, et al. Effects of the 21 aminosteroid U-74006F on experimental head injury in mice. *Journal of Neurosurgery* 1988;**68**:456-61.

Jennet 1996

Jennett B. Epidemiology of head injury. *Journal of Neurology, Neurosurgery, and Psychiatry* 1996;**60**(4):362-9.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bleck 1995

Methods	Randomised double-blind controlled study.
Participants	Adult patients with GCS 4-12 within 4 hours after closed head injury.
Interventions	Tirilazad mesylate at three escalating dosage tiers (0.6, 2.0, 6.0 mg/kg/day).
Outcomes	Death at the end of the study period. Unpublished data on non-fatal outcome is being sought.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Marshall 1998

Methods	Randomised double-blind placebo controlled trial. Randomisation stratified by severity of head injury as assessed on the Glasgow Coma Scale (4-8 severe, 9-12 moderate). About 1% of participants excluded due to protocol violations and about a further 5% were lost to follow up before the 6-month evaluation.
Participants	1131 randomised patients with moderate and severe head injury. Patients were eligible for inclusion in the trial if the following criteria were met: Glasgow Coma Score 4-12, age between 15 and 65 years, abnormalities could be observed on computerised tomography scanning, treatment could be initiated within four hours from the time of injury. Exclusion criteria: pregnancy, other investigational drugs taken within 30 days, any disease expected to make outcome meaurement difficult.
Interventions	1) Tirilazad mesylate 10 mg/kg by i.v. infusion every 6 hours for 5 days. (n=562, excluding protocol violators) 2) Placebo. (n=558, excluding protocol violators)
Outcomes	Death. Favourable outcome (good recovery and moderate disability) at six months as determined by the Glasgow Outcome Scale.
Notes	Other treatment by 'standardised protocols'. Patients not allowed to be given calcium antagonists or megadose steroids.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of ongoing studies *[ordered by study ID]*

Bleck

Trial name or title	North American phase III trial of tirilazad mesylate
Methods	
Participants	Patients with moderate and severe head injury
Interventions	Tirilazad mesylate
Outcomes	Death and disability
Starting date	Recruitment now complete (1156 randomised participants)
Contact information	Thomas Bleck Professor of Neurological Surgery and Internal Medicine The University of Virginia USA
Notes	

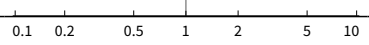
DATA AND ANALYSES

Comparison 1. Any aminosteroid at any dose versus no aminosteroid or placebo.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	1240	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.28]
2 Death or disability (GOS)	1	1065	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.93, 1.23]
3 Sepsis	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.35]
4 Cardiac arrest	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.06]
5 hypotension	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.54, 2.06]
6 multiple organ failure	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.84, 4.16]
7 brain edema	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.46]
8 intraparenchymal haemorrhage	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.58, 1.70]
9 epidural haematoma	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.48, 2.43]
10 cerebral infarction	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.60, 2.41]
11 brain herniation	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.49, 1.10]
12 intracranial hypertension	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.21]
13 pneumonia	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.58]
14 ARDS	1	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.67, 3.53]

Analysis 1.1. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 1 Death.

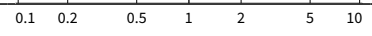
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleck 1995	24/114	12/61		10.46%	1.07[0.58,1.99]
Marshall 1998	140/528	135/537		89.54%	1.05[0.86,1.29]
Total (95% CI)	**642**	**598**		**100%**	**1.06[0.87,1.28]**
Total events: 164 (Treatment), 147 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					



Favours aminosteroid — Favours control

Analysis 1.2. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 2 Death or disability (GOS).

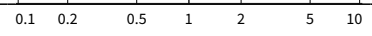
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Marshall 1998	232/528	220/537		100%	1.07[0.93,1.23]
Total (95% CI)	**528**	**537**		**100%**	**1.07[0.93,1.23]**
Total events: 232 (Treatment), 220 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					



Favours aminosteroid — Favours control

Analysis 1.3. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 3 Sepsis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Marshall 1998	18/561	24/555		100%	0.74[0.41,1.35]
Total (95% CI)	**561**	**555**		**100%**	**0.74[0.41,1.35]**
Total events: 18 (Treatment), 24 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					



Favours aminosteroid — Favours control

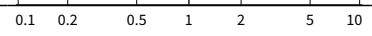
Analysis 1.4. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 4 Cardiac arrest.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Marshall 1998	20/561	18/555		100%	1.1[0.59,2.06]
Total (95% CI)	**561**	**555**		**100%**	**1.1[0.59,2.06]**
Total events: 20 (Treatment), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.77)					

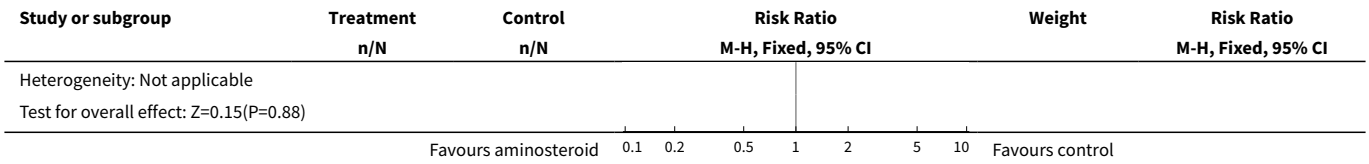
Favours aminosteroid — Favours control

Analysis 1.5. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 5 hypotension.

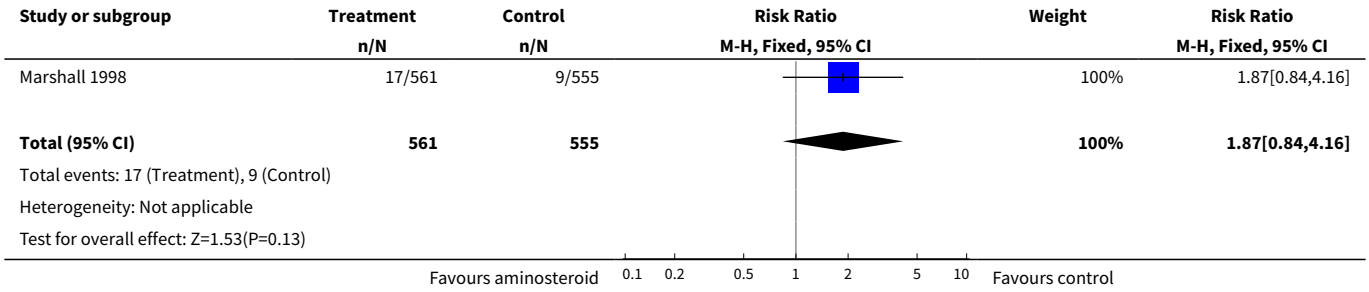
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Marshall 1998	17/561	16/555		100%	1.05[0.54,2.06]
Total (95% CI)	**561**	**555**		**100%**	**1.05[0.54,2.06]**
Total events: 17 (Treatment), 16 (Control)					



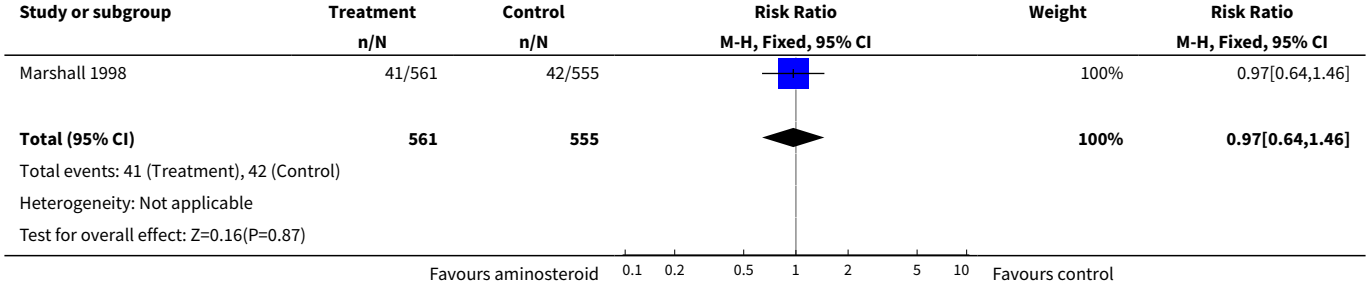
Favours aminosteroid — Favours control



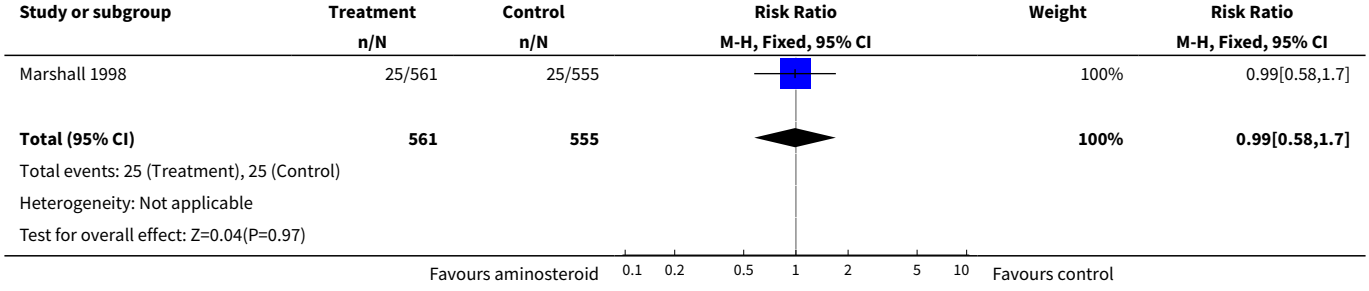
Analysis 1.6. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 6 multiple organ failure.



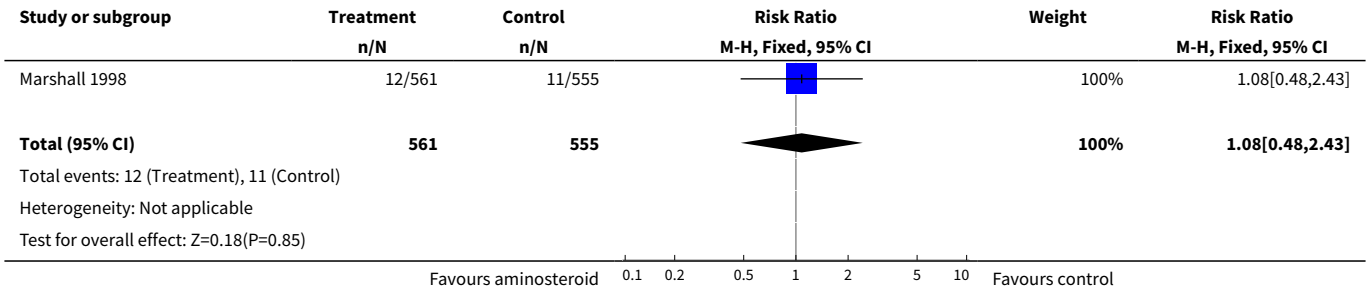
Analysis 1.7. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 7 brain edema.



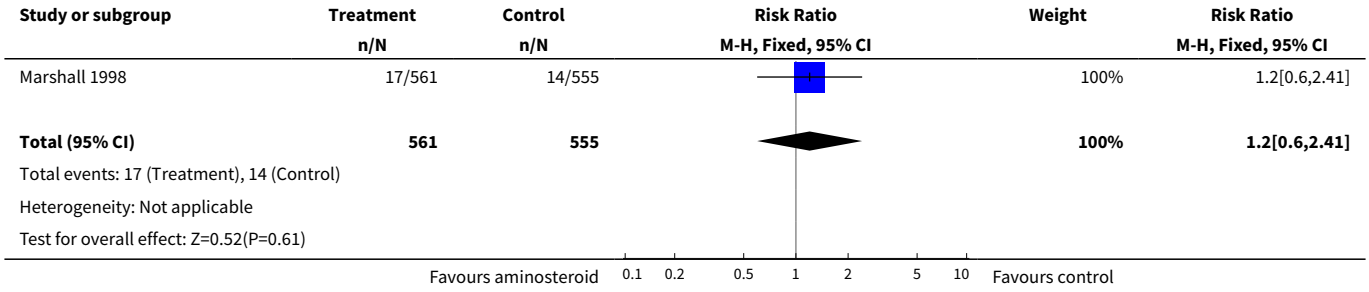
Analysis 1.8. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 8 intraparenchymal haemorrhage.



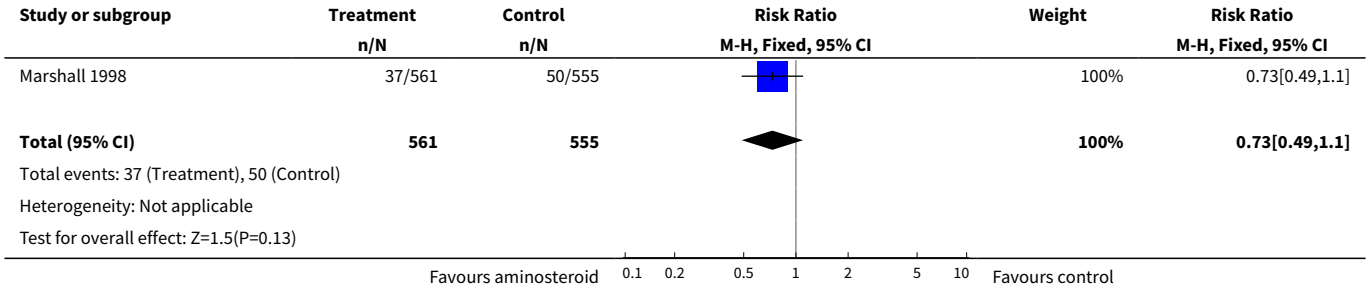
Analysis 1.9. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 9 epidural haematoma.



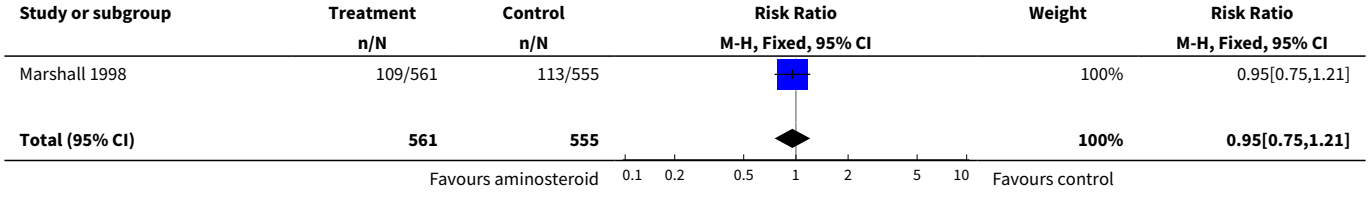
Analysis 1.10. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 10 cerebral infarction.

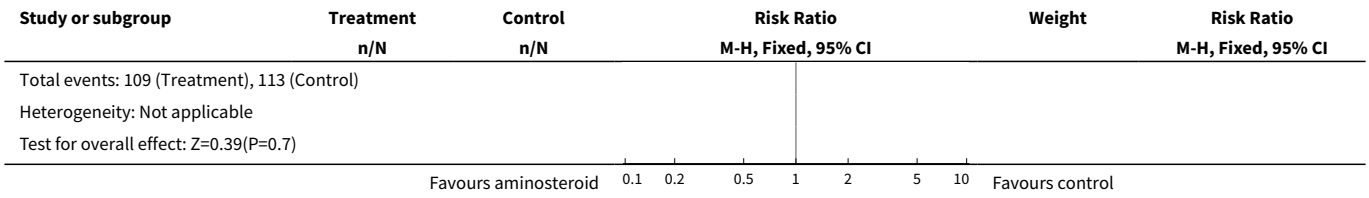


Analysis 1.11. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 11 brain herniation.

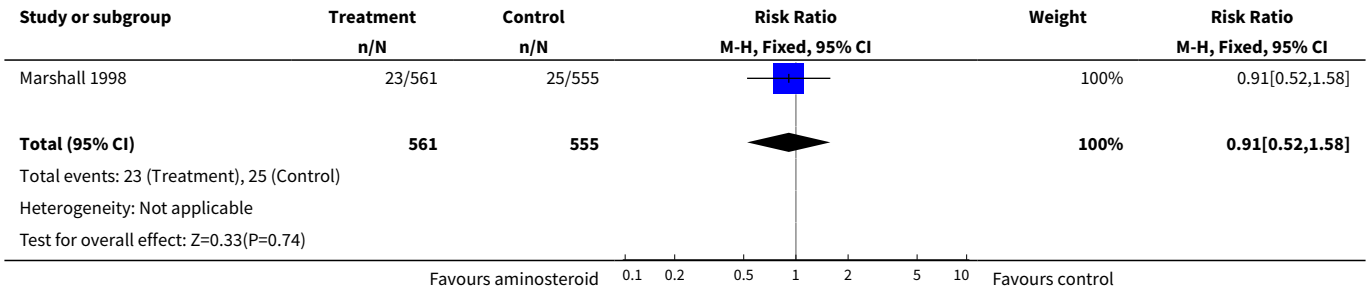


Analysis 1.12. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 12 intracranial hypertension.

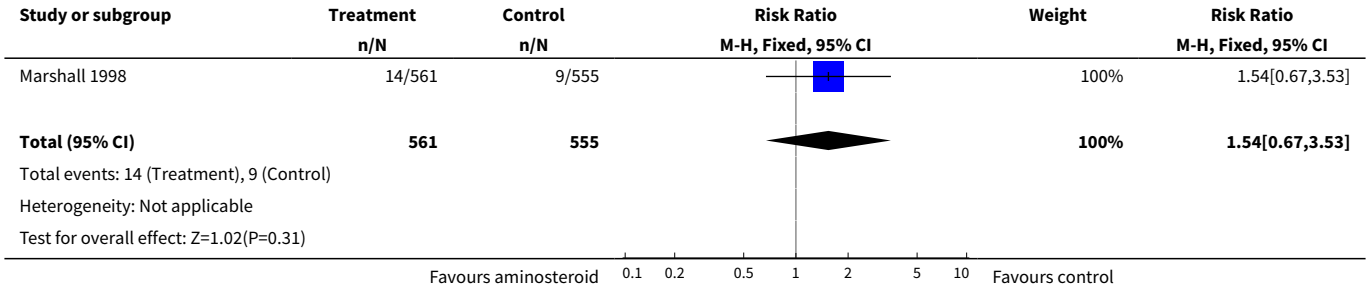




Analysis 1.13. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 13 pneumonia.



Analysis 1.14. Comparison 1 Any aminosteroid at any dose versus no aminosteroid or placebo., Outcome 14 ARDS.



APPENDICES

Appendix 1. Search strategy

CENTRAL, MEDLINE, National Research Register
#1 TIRILAZAD in MeSH
#2 PREGNATRIENES in MeSH
#3 AMINOSTEROIDS in MeSH
#4 lazaroid* OR antioxidan* OR aminosteroid*
#5 #1 OR #2 OR #3 OR #4
#6 CRANIOCEREBRAL TRAUMA in MeSH
#7 (head OR brain) AND (injur* OR trauma*)
#8 #6 OR #7
#9 #8 AND #5
#10 RCT filter (Clarke 2001)

EMBASE

#1 TIRILAZAD/
#2 PREGNATRIENES/
#3 AMINOSTEROIDS/
#4 lazaroid$ OR antioxidan$ OR aminosteroid$
#5 #1 OR #2 OR #3 OR #4
#6 HEAD INJURY/
#7 (head OR brain) AND (injur$ OR trauma$)
#8 #6 OR #7
#9 #8 AND #5

WHAT'S NEW

Date	Event	Description
6 May 2010	Review declared as stable	Aminosteroids are no longer produced.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 4, 2000

Date	Event	Description
17 July 2008	Amended	Converted to new review format.
1 March 2006	New search has been performed	An updated search for new trials was done in March 2006. No new trials for inclusion have been identified.

CONTRIBUTIONS OF AUTHORS

IR examined the search results and selected relevant trials, extracted data, contacted trialists and wrote the review. PA selected relevant trials, extracted data and helped to write the review.

DECLARATIONS OF INTEREST

Ian Roberts is a principal investigator in the MRC CRASH trial, a large simple randomised controlled trial of 48 hours of methylprednisolone in adults with head injury. Pharmacia Corporation are donating drug and placebo for the MRC CRASH trial but the design, management and finance of the study are entirely independent of them. Pharmacia Corporation also manufacture tirilazad.

SOURCES OF SUPPORT

Internal sources

- Institute of Child Health, University of London, UK.

External sources

- NHS Research and Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Brain Injuries [*drug therapy]; Drug Evaluation; Neuroprotective Agents [*therapeutic use]; Pregnatrienes [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans