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[Intervention Review]

Corticosteroids for acute traumatic brain injury

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ABSTRACT

Background

Traumatic brain injury is a leading cause of death and disability. Corticosteroids have been widely used in treating people with traumatic brain injury.

Objectives

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

Search methods

We searched: CENTRAL (The Cochrane Library 2007, Issue 4), MEDLINE (Ovid SP), PubMed [www.ncbi.nlm.nih.gov/sites/entrez/], EMBASE (Ovid SP) and PsycINFO (Ovid SP). The searches were last updated in January 2008.

Selection criteria

All randomised controlled trials of corticosteroid use in acute traumatic brain injury with adequate or unclear allocation concealment.

Data collection and analysis

Both authors independently scored quality of allocation concealment. Study authors were contacted for additional information. One author independently extracted data on numbers of participants randomised, numbers lost to follow up, length of follow up, case fatality rates, disablement, infections and gastrointestinal bleeds and this was checked by the other author.

Main results

We identified 20 trials with 12,303 randomised participants. The effect of corticosteroids on the risk of death was reported in 17 included trials. Due to significant heterogeneity we did not calculate a pooled estimate of the risk of death. The largest trial, with about 80% of all randomised participants, found a significant increase in the risk ratio of death with steroids 1.15 (95% CI 1.07 to 1.24) and a relative risk of death or severe disability of 1.05 (95% CI 0.99 to 1.10). For infections the pooled risk ratio from five trials was 1.03 (95% CI 0.99 to 1.07) and for the ten trials reporting gastrointestinal bleeding 1.23 (95% CI 0.91 to 1.67).

Authors' conclusions

In the absence of a meta-analysis, we feel most weight should be placed on the result of the largest trial. The increase in mortality with steroids in this trial suggest that steroids should no longer be routinely used in people with traumatic head injury.

PLAIN LANGUAGE SUMMARY

Corticosteroids to treat brain injury

Traumatic brain injury is a leading cause of death and disability. After the injury the brain may swell, causing a potentially fatal condition called raised intracranial pressure (ICP). Corticosteroid drugs have been widely used, for many years, to treat patients with brain injury because they are thought to reduce intracranial pressure. Some examples of corticosteroids are dexamethasone and methylprednisolone.

The review authors searched the medical literature to determine how effective and safe corticosteroids are for treating brain injury. They focused their search on randomised controlled trials in which one group of people received a medical treatment (corticosteroids) and was compared with a similar group who received a different treatment or no treatment other than standard care. The review authors found 20 of these studies with 12,303 participants. When the review was first done the results of the research were inconclusive. A new large study with about 80% of the total participants was completed by the time of the 2006 update of this review. This study, called CRASH, showed a significant increase in number of deaths in patients given steroids compared with patients who received no treatment. The significant increase in deaths with steroids suggests that steroids should no longer be routinely used in people with traumatic head injury.

BACKGROUND

Traumatic brain injury is a leading cause of premature death and disability. Road crashes account for the majority of fatal head injuries (Jennett 1996). 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, in spite of the fact that there are only five vehicles per 1,000 population in China, compared with 770 vehicles per 1,000 population in the US (Roberts 1995). Overall, about 75% of the estimated 850,000 road crash deaths each year occur in the developing world (Murray 1994).

In the US, the incidence of brain injury related disability is estimated to be 33 new cases/100,000 people per year (Kraus 1993). Since this often occurs in young people and is long term, traumatic brain injury related disability 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 post-operative (Galicich 1961). This led to their use in other intracranial problems characterized by raised intracranial pressure, including their use in severe head injury (Pickard 1993). Eighty percent of patients with fatal head injuries show evidence of increased intracranial pressure at necropsy (Miller 1992).

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 a number of 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 UK study found that corticosteroids were used in just under half of the intensive care units surveyed (Jeevaratnam 1996).

OBJECTIVES

- To quantify the effectiveness of corticosteroids in reducing mortality and morbidity in people with acute traumatic brain injury.
- To quantify the incidence of side effects of the use of corticosteroids.
- To quantify the economic effects of corticosteroid use in this situation.

METHODS

Criteria for considering studies for this review

Types of studies

We sought to identify all randomised controlled trials of a corticosteroid drug versus any control in the treatment of acute traumatic brain injury. Studies using a quasi random form of allocation were excluded from the review.

Types of participants

People of all ages with clinically diagnosed acute traumatic brain injury secondary to head injury who were treated with steroids or control within seven days of the injury. All severities of head injury were included.

Types of interventions

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. Trials with these interventions were included irrespective of other treatments used.

Types of outcome measures

All causes of case fatality, any valid and reliable measure of neurological functioning, any other valid and reliable quality of life measures and economic outcomes were considered relevant if available. We sought numbers of infections (however defined) and significant gastrointestinal bleeds (however defined).

Search methods for identification of studies

The searches were not restricted by date, language or publication status.

Electronic searches

We searched the following databases:

- CENTRAL (The Cochrane Library 2007, Issue 4);
- MEDLINE (Ovid SP) 1950 to Nov (week 2) 2007;
- PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 7 Jan 2008: added to PubMed in the last 60 days);
- EMBASE (Ovid SP) 1980 to (week 1) Jan 2008;
- PsycINFO (Ovid SP) 1806 to April 2007.

The search strategies used for previous versions of this review can be found in Appendix 1. The strategies used for this update can be found in Appendix 2.

Searching other resources

We also searched specialised databases, handsearched journals and contacted trialists.

Data collection and analysis

We each extracted the following information independently from each trial: strategy for allocation concealment, 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, using the Glasgow Outcome Scale (Jennett 1975) to assess the neurological outcome; the categories for persistent vegetative state and moderate disability were combined into 'disability' for this review. This enabled inclusion of the one trial which did not use the Glasgow Outcome Scale but a similar ordinal categorisation of function. We also extracted data on side effects or complications where these were reported, using the authors' definitions of these complications.

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Higgins 2008), each of us scored this quality on the scale used by Higgins (Higgins 2008) as

shown below, assigning 'No' to poorest quality and 'Yes' to best quality:

- No = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth);
- Unclear = 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;
- Yes = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomizations; 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).

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

We calculated relative risks and 95% confidence intervals for mortality for each trial on an intention to treat basis. Heterogeneity between trials was tested using a chi-squared test, where P less than or equal to 0.05 was taken to indicate significant heterogeneity. As long as statistical heterogeneity did not exist, for dichotomous data, we calculated summary relative risks and 95% confidence intervals using a fixed-effect model.

2004 update

For the October 2004 update of the review, the Cochrane Injuries Group staff searched the Group's register for more trials but found none. In October 2004, the initial results of the CRASH trial, previously listed as an ongoing study, were published. Since Ian Roberts was a principal investigator on this trial, Phil Alderson extracted data and updated the review, with Ian Roberts checking for correctness.

The inclusion of the CRASH trial introduced significant heterogeneity, and the original review's methods section did not clearly specify how heterogeneity would be investigated. It was therefore decided that the only investigation of heterogeneity would be to undertake a sensitivity analysis, removing those trials with less than adequate allocation concealment. If that failed to remove heterogeneity, the trials would not be pooled in the review, and reasons for heterogeneity suggested but not examined formally.

2006 update

Searches were repeated by the Cochrane Injuries Group in November 2005. The final results of CRASH are now available and have been included. No other new data were identified by the searches. Phil Alderson added the new data and updated the text of the review. As the results of CRASH dominate the other trial results for death or severe disability, the results were not pooled.

2009 update

The search was updated by the Cochrane Injuries Group in January 2008. No new trials were found; the results and conclusions remain the same.

RESULTS

Description of studies

The combined search strategies identified 19 trials which satisfied the inclusion criteria. The earliest was from 1972 and the most recent from 1995. There were two reports of the same trial (see Fanconi 1988). Two were previously unpublished studies for which outcome data were obtained (Hernesniemi 1979; Pitts 1980). For one other unpublished study (Tahara 1972) the authors were unable to provide outcome data, and in one other we have been unable to trace the author (Hoyt 1972). The 2004 update added one more trial (CRASH 2005), which is the largest of all the trials in the review.

A total of 11,792 participants are included in outcome of death.

Risk of bias in included studies

Methodological quality was variable – *see* table 'Characteristics of included studies' for details.

Effects of interventions

The effect of corticosteroids on the risk of death was reported in 17 included trials. There was significant heterogeneity for this outcome when using a fixed-effect risk ratio model (Chi^2 26.46, P = 0.03, I^2 43%). Excluding the trials with less than adequate allocation concealment failed to remove the heterogeneity, and so the trials were not pooled. The largest single trial (CRASH 2005) reported a risk ratio for death of 1.18 (95% CI 1.09 to 1.27), indicating a significant increase in death with steroids.

The CRASH trial reported a relative risk of 1.05 (95%CI 0.99 to 1.10) for death or severe disability. There was no significant heterogeneity between the results from the 10 trials reporting this outcome, but it was decided not to pool the results as the data from CRASH dominate the other results.

Five trials reported infections, and the pooled relative risk was 1.03 (95% CI 0.99 to 1.07) making a decrease in infectious complications unlikely with steroids. For the ten trials reporting gastrointestinal bleeding the pooled relative risk was 1.23 (95% CI 0.91 to 1.67) which neither confirms nor excludes an important increase or decrease in this complication. For both these outcomes, data on about 2% of the CRASH trial participants were missing, and these patients have been excluded from the analysis. Sensitivity analysis was not undertaken due to the low proportion and because it had not been prespecified.

No study included economic data.

DISCUSSION

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 (Tahara 1972). Contact with trialists enabled us to include data from two large unpublished studies (Hernesniemi 1979; Pitts 1980), but not from others (Hoyt 1972; Tahara 1972).

The addition of the CRASH 2005 trial's early results introduced significant heterogeneity. A sensitivity analysis based on the quality of allocation concealment failed to remove this. The most obvious reason for the presence of heterogeneity is the contrasting results of the Faupel 1976 and CRASH 2005 trials. It is difficult to come up with a convincing reason post hoc for excluding either of these trials from a meta-analysis. We noted in a previous version of this review that in the Faupel trial "...the outcome was assessed at discharge", yet overall 19% of the participants were classified as "unconscious stabilized". The apparently short follow up period may account for the incongruous result. Other sources of variation between trials may include severity and pathology of the head injury, variations in corticosteroid regimens (e.g. drug, dose, route) and temporal trends in the use of other interventions. The CRASH trial was stopped early because of the apparent harmful effect of steroids, and stopping trials because of extreme results may select extreme results by chance. Trials of the use of corticosteroids in spinal cord injury suggest that the timing of administration is important (Bracken 1990), but the CRASH trial followed the protocol from spinal cord trials closely, so this is unlikely to explain the excess mortality in the CRASH trial. However, as none of these hypotheses was listed in the original review methods, we think it is safer not to pool the trial results.

There is no clear evidence of a difference in the occurrence of infectious complications and the risk of gastrointestinal bleeding with steroids, making these an unlikely explanation of the increased mortality in the CRASH trial.

In the absence of a meta-analysis, interpretation of the whole body of evidence has to be qualitative. The high methodological quality and large size of the CRASH trial suggest that its result should be the main basis of a summary. This is reinforced by its finding of a significant increase in mortality, which should not be ignored despite the more optimistic results in some other trials.

AUTHORS' CONCLUSIONS

Implications for practice

The results of the large CRASH trial suggest that steroids should not be used in head injury, as they appear to increase mortality. Despite the heterogeneity, we feel that the results of this trial are the most relevant to current practice and should be the basis for clinical decisions, rather than any of the earlier trials or their meta-analysis.

Implications for research

The mechanism of harm is unclear and there will need to be a reassessment of the understanding of the pathophysiology of traumatic brain injury. There seems no reason to start other trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alexander 1972

Methods	Paper states that patients were randomized, half of them receiving dexamethasone.
Participants	Those admitted to hospital with acute non missile head injuries who responded to painful stimuli by withdrawal or rigidity but who would not respond to voice command.
Interventions	1. Dexamethasone 10mg IV; then 4mg IM every 6 hours for 10 days. 2. No steroid, no mention of placebo.
Outcomes	Death (time of assessment not stated). Complications.
Notes	States all patients uniformly supervised. Author contacted, no further details of trial available.

Risk of bias

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

Braakman 1983

Methods	Randomized into two groups using identical vials in identical boxes prepared by a Pharmacy Department. Code not broken until all patients were evaluated for outcome.
Participants	Patients of any age with severe non missile related head injury who were in a coma on admission to hospital. Coma was defined as no eye opening, no spoken response to painful stimuli and not obeying commands. Exclusions were those already brain dead (apnoea, flaccidity, dilated pupils not reacting to light, absence of reflex eye movements) or expected to become so within 1 hour, those who regained consciousness during initial examination, those who had already been given steroids and those with diabetes mellitus or a history of peptic ulcer.
Interventions	1. Dexamethasone phosphate: initial dose 100mg IV (less than 6 hours from injury), days 1 to 4 100mg/day IV, days 5 to 7 16mg/day IV or IM, day 8 12mg IV/IM, day 9 8mg IV/IM, day 10 4mg IV/IM. 2. Placebo.
Outcomes	Glasgow Coma Scale at 6 months after injury. Complication rate.
Notes	Other care was determined by the result of a CT scan: those with a mass lesion had immediate operation, those without had monitored control of intracranial pressure using controlled ventilation and/or osmotic diuretic. Cerebrospinal fluid was drained in some patients. Barbiturates were not used.

Risk of bias

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

Braun 1986

Methods	Patients randomly assigned in emergency room to one of four groups.

Braun 1986 *(Continued)*

Participants	Those head trauma victims admitted from the emergency room to the adult neurosurgical intensive care unit.
Interventions	1. Dexamethasone 6mg/kg IV in the emergency room; then 6mg/kg IV 6 hourly for 1 day, then 1mg/kg IV 6 hourly for 4 days followed by a tapering dose. 2. Dexamethasone 6mg/kg IV in the emergency room; then 0.1mg/kg IV 6 hourly for 5 days followed by a tapering dose. 3. Dexamethasone 6mg/kg IV in the emergency room: single dose only. 4. No steroids, no mention of placebo.
Outcomes	Incidence of pneumonia defined as a new alveolar or alveolar-interstitial infiltrate identified by a radiologist and one of the authors and two of: 1. Fever greater than 100F. 2. White cell count greater than 15,000/ml. 3. Increased sputum with a predominant organism on either Gram stain or culture of sputum.
Notes	Otherwise treated with a standardised protocol including ICP monitoring, initial hyperventilation, hyperosmotic agents. Thiopentone in some.

Risk of bias

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

Chacon 1987

Methods	Patients randomized 'by lottery method' to two groups. Blinding not clear.
Participants	Children admitted to hospital with severe head trauma, a Glasgow Coma Score of 7 or less and evidence of cerebral oedema on computerised tomography.
Interventions	1. Dexamethasone - dose not stated. 2. No dexamethasone.
Outcomes	Mortality at discharge.
Notes	Other interventions - fluid restriction guided by central venous pressure and urine output, hyperventilation to PCO2 of 25 to 30 torr, head up position of 35 to 40 degrees.

Risk of bias

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

Cooper 1979

Methods	Random allocation using identical coded vials prepared and supplied by a drug company, who retained the code until the 6 month outcome assessment had been made.

Cooper 1979 *(Continued)*

Participants	All patients with head injury admitted with a Grady Coma Grade of 3, 4 or 5. Glasgow Coma Scale also measured and in all except two patients GCS was 8 or less. Patients were excluded due to inability to obtain informed consent, previous administration of steroids or arrival at hospital more than 6 hours after the injury.
Interventions	1. High dose dexamethasone phosphate: 60mg initial dose, 24mg every 6 hours thereafter for 6 days. 2. Low dose dexamethasone phosphate: 10mg initial dose, 4 mg every 6 hours thereafter for 6 days. 3. Placebo (water, sodium bisulphite, methylparaben, propylparaben). All doses were contained in the same volume of fluid. Medication decreased gradually from day 7 and all were finished by day 11. Children aged 16 or younger given weight related doses.
Outcomes	GOS at 6 months after injury.
Notes	CT scan used or diagnosis in most patients followed by operation for mass lesions. Other co-interventions not specifically described.

Risk of bias

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

CRASH 2005

Methods	Stratified random allocation via central randomisation service or identical coded treatment packs.
Participants	Adults (16 or older) less than 8 hours after head trauma with GCS of 14 or less on admission to hospital.
Interventions	1. High dose methylprednisolone for 48 hours. 2g over 1 hour, then 0.4g per hour for 48 hours. 2. Identical placebo.
Outcomes	Mortality and GOS at 6 months. Complications (admission to intensive care, gastrointestinal bleeding, infections, neurosurgical operation).
Notes	

Risk of bias

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

Dearden 1986

Methods	Randomly allocated to receive treatment or placebo.
Participants	All ages, patients with severe head injury (no definition given). Exclusions were due to incorrect administration of steroid or placebo during the trial and those receiving steroids before admission.

Dearden 1986 *(Continued)*

Interventions	1. Dexamethasone: initial dose 50mg IV (0.75mg/kg for children), days 1, 2, 3 100mg/day IV, day 4 50mg/day IV, day 5 25mg/day IV. 2. Placebo.
Outcomes	Glasgow Outcome Scale at 6 months after injury. Duration of artificial ventilation.
Notes	Other interventions guided by CT and ICP monitoring. Controlled hypocapeic ventilation and osmotic diuretics used to control ICP.

Risk of bias

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

Faupel 1976

Methods	Randomly allocated using identical, coded vials containing the same volumes of clear solution.
Participants	All adult patients with severe (not defined) closed head injury. Exclusions were due to being a child (age cut off not given), impression fractures, missile injuries, imminent brain death and open head injuries. After randomization, 3 patients considered to be brain dead on angiography, one given steroids outside the trial and one who died of other injuries were excluded.
Interventions	1. Dexamethasone: initial dose 100mg IV, then 100mg IM after 6 hours, then 4mg IM every 6 hours for 8 days, then tapered off by daily reduction of 4mg. 2. Dexamethasone: initial dose 12mg IV, then 4mg IM every 6 hours for 8 days, then tapered off by daily reduction of 4mg. 3. Placebo.
Outcomes	Disability status scale at discharge from hospital. Frequency of complications.
Notes	Mass lesions removed following angiography. Other interventions not specified.

Risk of bias

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

Gaab 1994

Methods	Patients were randomized in blocks of 6. Stated to be double blind design.
Participants	Age 15 to 55 with moderate central nervous system injury (two or more of disturbed consciousness, eye opening to stimulation, no adequate verbal response, disorientation in time and place) or severe central nervous system injury (comatose on injury and/or on admission to hospital, no eye opening to painful stimuli). Patients also were required to have obvious neurological symptoms (e.g. hemiparesis or hemiplegia) or CT evidence of lesions requiring surgical intervention or hypodense area(s) in the brain.

Gaab 1994 *(Continued)*

	Reasons for exclusion were: time to treatment was more than 3 hours, they had already had steroids, penetrating head injury, primary bulbar symptoms present, prognosis considered hopeless, known malignancy, peptic ulcer, tuberculosis, Cushing's syndrome, non traumatic neurological or psychiatric disease, spinal injury, suspected coagulation defects.
Interventions	1. Dexamethasone: initial dose 200mg IV, then 300mg over next 3 hours, then 200mg 3 hours later, then 200mg 6 hourly for 8 doses. 2. Placebo.
Outcomes	Modified GOS at 10 to 14 months (good recovery classified as fit for work or for rehabilitation, extra category indicating degree of care required for disabled). GCS on day 5. Interval to regaining consciousness.
Notes	Co-interventions are not specified, but the study states that other care was not controlled.

Risk of bias

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

Giannotta 1984

Methods	Randomly allocated to treatment or placebo using identical, coded vials. Code not broken until all outcomes had been collected.
Participants	Patients with blunt head trauma and a GCS of 8 or less 6 hours after the injury. Exclusions were due to history of peptic ulcer, an undiagnosed or untreated medical condition or who had been taking steroids during the two weeks before injury, penetrating brain injuries, other injuries expected to cause rapid death, and pregnancy.
Interventions	1. Methylprednisolone 30mg/kg IV every 6 hours for 2 doses, then 250mg IV every 6 hours for 8 doses, then tapering off over the next 8 days. 2. Methylprednisolone 1.5mg/kg IV every 6 hours for 2 doses, then 25mg IV every 6 hours for 8 doses, then tapering off over 8 days. 3. Placebo. NB Patients randomized in 2:2:1 ratio for these groups.
Outcomes	Glasgow Outcome Scale at 6 months.
Notes	CT guided management. Controlled ventilation, cerebrospinal fluid drainage, osmotic diuretics and barbiturates were used to control ICP.

Risk of bias

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

Grumme 1995

Methods	Random allocation to treatment or control using identical vials.
Participants	Patients of all ages admitted with head injury. Excluded groups were those with contraindication to steroids (not specified), impaired level of consciousness not due to trauma and absence of relevant brain damage (not specified).
Interventions	1. Triamcinolone acetonide: 200mg IV, then 40mg 8 hourly for 4 days, then 20mg 8 hourly for 4 days. 2. Placebo.
Outcomes	GOS at discharge from hospital and at approximately 1 year from the injury.
Notes	CT was used to guide treatment. Osmotic diuretics, controlled ventilation and cerebrospinal fluid drainage were used to control ICP.

Risk of bias

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

Hernesniemi 1979

Methods	Random allocation using sealed opaque envelopes. Double blind.
Participants	Age 15 or above with severe closed brain injury. Five exclusions; three not head injury, one 14 years old, one imminent death.
Interventions	1. Betamethasone 100mg IV on admission, then 80mg/day IV for 7 days, then tapering off over further 7 days. 2. Placebo.
Outcomes	Glasgow Outcome Scale at 6 or 12 months. Complications.
Notes	

Risk of bias

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

Hoyt 1972

Methods	Assigned "sequentially in random order".
Participants	Patients with cranial trauma.
Interventions	1. Dexamethasone, dose not stated. 2. Triamcinolone, dose not stated. 3. Placebo.

Hoyt 1972 *(Continued)*

Outcomes	Proportion demonstrating a "marked improvement".
Notes	Unable to contact author for further details.

Risk of bias

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

Pitts 1980

Methods	"Prospectively randomized" into three groups.
Participants	Head injured adults admitted to hospital who were comatose on admission or who lapsed into coma for six hours or more.
Interventions	1. Dexamethasone: initially 24mg IV per day, for a maximum of 7 days, tapering of for the last 5. 2. Dexamethasone: initially 16mg IV daily, for a maximum of 7 days, tapering off for the last 5. 3. Placebo.
Outcomes	Glasgow Outcome Scale at 6 months. Gastrointestinal bleeding. Infections (signs of pneumonia, wound infection, urinary infection, blood culture, CSF culture).
Notes	

Risk of bias

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

Ransohoff 1972

Methods	Stated to be "random steroid studies" and a double blind study of steroids against placebo.
Participants	Critically ill acute closed head injury patients without evidence of angiographic shift or significant clots, but with documented increase in intracranial pressure. Age not stated.
Interventions	1. Methylprednisolone 125mg IV every 6 hours for 4 days, starting within 24 hours of admission. 2. Placebo.
Outcomes	Death. Complications (no data presented).
Notes	Also received fluid restriction.

Risk of bias

Bias	Authors' judgement	Support for judgement

Ransohoff 1972 *(Continued)*

Allocation concealment?	Unclear risk	Unclear

Saul 1981

Methods	States that 100 patients were "randomized into two groups of 50". One group received steroid, there was no placebo.
Participants	Patients admitted with craniocerebral trauma within 6 hours of injury. No other body systems injured, Glasgow Coma Scale 7 or less on admission. Average age 31 years.
Interventions	1. 250mg methylprednisolone IV initially, then 125mg every 6 hours. 2. Some in steroid group received dexamethasone in equivalent dose. 3. No steroid, no placebo.
Outcomes	Glasgow Outcome Scale at 6 months.
Notes	Also received mechanical hyperventilation and surgery if indicated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Unclear

Stubbs 1989

Methods	"Randomized and double-blind" study. Allocation concealment not described. Separate randomization for patients over and under 40 years old.
Participants	Patients were more than 6 years old with closed head trauma within the previous 48 hours and a GCS of 9 to 12. The first dose had to be administered within 6 hours of the GCS measurement. Exclusions were pregnancy, hypersensitivity to steroids and presence of infectious disease.
Interventions	1. High dose MPSS: 30mg/kg IV twice in 6h, then 250mg IV every 6h until 48 h after the first dose. Then a tapering schedule: days 3 to 5 25mg IV/IM 6 hrly, day 6 10mg IV/IM 6 hrly, day 7 5mg IV/IM 6 hrly days 8 and 9 10mg IV/IM daily. 2. Low dose MPSS: 1mg/kg IV twice in 6h followed by 25mg IV every 6h until day 6. Then the tapering schedule above. 3. Placebo
Outcomes	Glasgow Outcome Scale, Glasgow Coma Scale, Karnofsky Rating Scale at discharge, 3 and 6 months. Complications listed.
Notes	Glasgow Outcome Scale reported as mean score. Attempting to locate authors for further information.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Unclear

Tahara 1972

Methods	Random allocation to one of three groups.
Participants	Seriously head injured.
Interventions	1. Prednisolone 2,680mg over 2 weeks. 2. Prednisolone 160mg on first day, tapering over two weeks, total dose 1,000mg. 3. No steroid.
Outcomes	None reported.
Notes	Trial of 100 participants; author contacted but unable to provide details.

Risk of bias

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

Zagara 1987

Methods	Randomization by table into steroid or no therapy groups.
Participants	Average age 29. Severe isolated head trauma with average GCS of 5.7 (sd 1.2) in one group and 5.8 (sd 1.2) in the other.
Interventions	1. Dexamethasone 0.36mg/kg/day IV for 9 days. 2. No steroid, no placebo mentioned.
Outcomes	Glasgow Outcome Scale at 3 months. Nitrogen balance.
Notes	Also received mechanical hyperventilation, surgery if required, mannitol infusion and benzodiazepine sedation.

Risk of bias

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

Zarate 1995

Methods	"Randomly allocated", no further details given. 60 patients, 30 in each group.
Participants	Children admitted with head injury with a Glasgow Coma Scale of 9 to 15.
Interventions	1. Corticosteroids - no details given. 2. Symptomatic treatment.
Outcomes	Mortality at discharge.

Zarate 1995 *(Continued)*

Notes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Unclear

CT: computerised tomography
GCS: Glasgow Coma Scale
CSF: Cerebrospinal Fluid
GOS: Glasgow Outcome Scale
ICP: intracranial pressure
IM: Intramuscular
IV: Intravenous
MPSS: methylprednisolone sodium succinate

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

Study	Reason for exclusion
Cheng 1991	Randomised trial of high versus low dose steroids. No group with no steroids.
Fanconi 1988	Judged to have inadequate allocation concealment after contact with authors.
Gobiet 1976	Study was retrospective.
James 1979	Allocation consisted of the first four patients being given no or low dose steroids and the next five given high dose steroids. There was therefore no concurrent control group and no concealment of allocation.
Robertson 1985	Patients were alternately allocated.

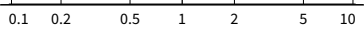
DATA AND ANALYSES

Comparison 1. Any steroid administered in any dose against no steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at end of follow up period	17		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Death or severe disability at the end of the study period	10		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Infections of any type	5	10798	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.99, 1.07]
4 Major or significant gastrointestinal bleed	10	11302	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.91, 1.67]

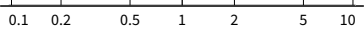
Analysis 1.1. Comparison 1 Any steroid administered in any dose against no steroid, Outcome 1 Death at end of follow up period.

Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Alexander 1972	16/55	22/55		0.73[0.43,1.23]
Braakman 1983	44/81	47/80		0.92[0.7,1.21]
Chacon 1987	1/5	0/5		3[0.15,59.89]
Cooper 1979	26/49	13/27		1.1[0.69,1.77]
CRASH 2005	1248/4854	1075/4819		1.15[1.07,1.24]
Dearden 1986	33/68	21/62		1.43[0.94,2.19]
Faupel 1976	16/67	16/28		0.42[0.24,0.71]
Gaab 1994	19/133	21/136		0.93[0.52,1.64]
Giannotta 1984	34/72	7/16		1.08[0.59,1.98]
Grumme 1995	38/175	49/195		0.86[0.6,1.25]
Hernesniemi 1979	35/81	36/83		1[0.7,1.41]
Pitts 1980	114/201	38/74		1.1[0.86,1.42]
Ransohoff 1972	9/17	13/18		0.73[0.43,1.25]
Saul 1981	8/50	9/50		0.89[0.37,2.12]
Stubbs 1989	13/98	5/54		1.43[0.54,3.8]
Zagara 1987	4/12	4/12		1[0.32,3.1]
Zarate 1995	0/30	0/30		Not estimable



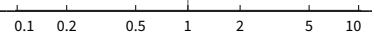
Analysis 1.2. Comparison 1 Any steroid administered in any dose against no steroid, Outcome 2 Death or severe disability at the end of the study period.

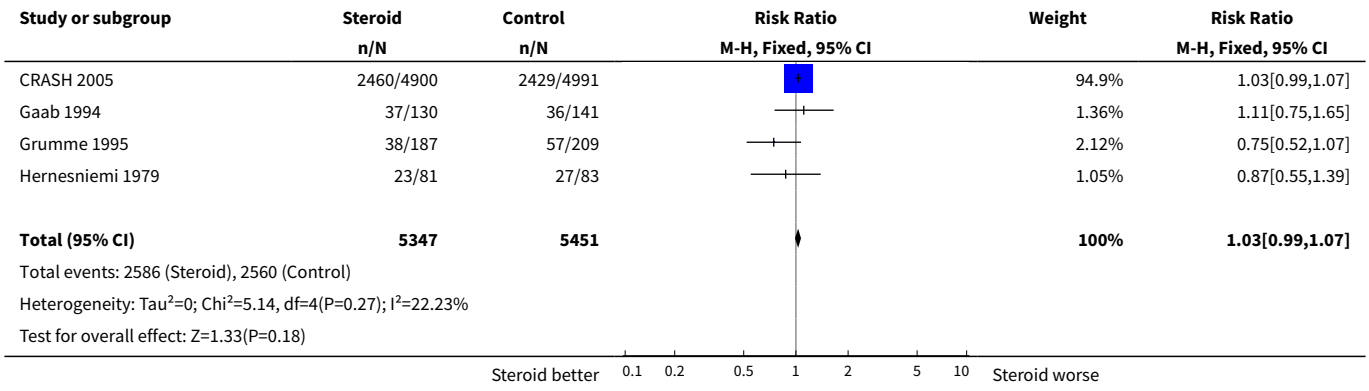
Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Braakman 1983	57/81	54/80		1.04[0.85,1.28]
Cooper 1979	31/49	17/27		1[0.7,1.44]
CRASH 2005	1828/4800	1728/4754		1.05[0.99,1.1]
Dearden 1986	38/68	27/62		1.28[0.9,1.83]
Faupel 1976	41/67	19/28		0.9[0.66,1.24]
Gaab 1994	39/133	43/136		0.93[0.65,1.33]
Giannotta 1984	56/72	11/16		1.13[0.8,1.61]
Grumme 1995	57/175	72/195		0.88[0.67,1.17]
Hernesniemi 1979	46/81	48/83		0.98[0.75,1.28]
Pitts 1980	140/201	49/74		1.05[0.87,1.27]



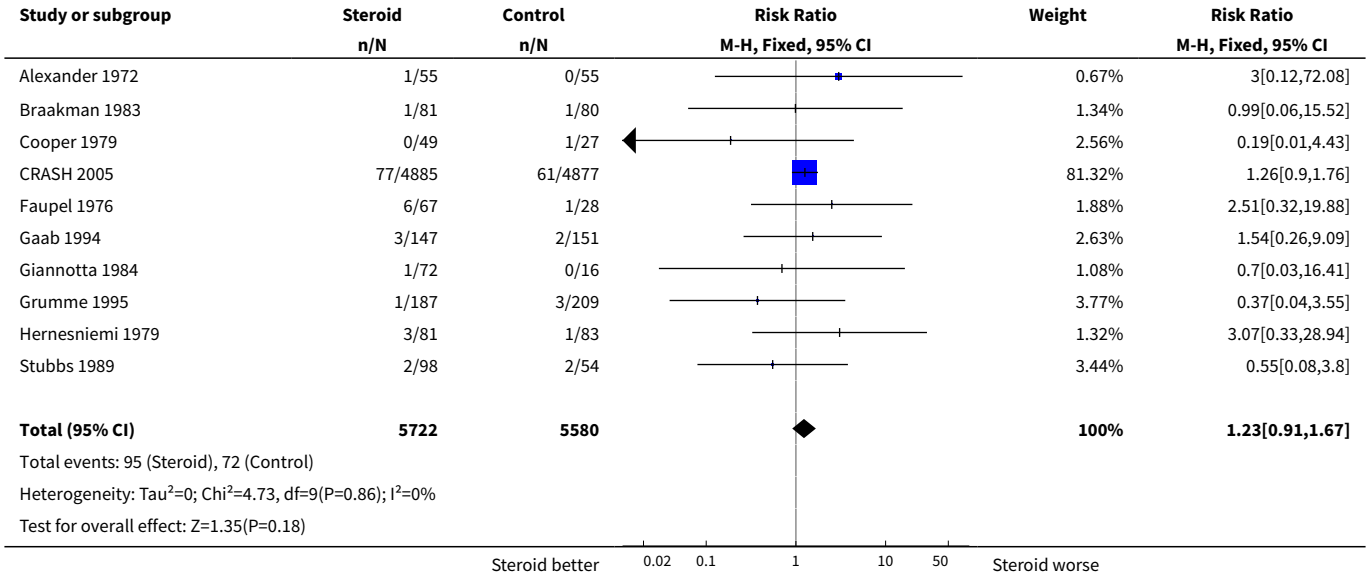
Analysis 1.3. Comparison 1 Any steroid administered in any dose against no steroid, Outcome 3 Infections of any type.

Study or subgroup	Steroid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1979	28/49	11/27		0.56%	1.4[0.84,2.35]





Analysis 1.4. Comparison 1 Any steroid administered in any dose against no steroid, Outcome 4 Major or significant gastrointestinal bleed.



APPENDICES

Appendix 1. Previous search strategies

CENTRAL SEARCH STRATEGY (The Cochrane Library 2005, Issue 4)
#1 (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) in ab or ti
#2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*) in ab or ti
#3 (#1 and #2)
#4 BRAIN INJURIES
#5 DIFFUSE AXONAL INJURY
#6 CRANIOCEREBRAL TRAUMA
#7 #3 or #4 or #5 or #6
#8 (steroid* or glucocorticoid* or prednisolone* or betamethasone* or cortisone* or dexamethasone* or hydrocortisone* or methylprednisolone* or prednisone* or triamcinolone* or corticosteroid*) in ab or ti
#9 GLUCOCORTICOIDS

#10 ADRENAL CORTEX HORMONES
#11 (#8 or #9 or #10)
#12 (#7 and #11)

MEDLINE SEARCH STRATEGY (1966 to November 2005)
1. explode "Craniocerebral-Trauma" / all SUBHEADINGS in MIME,MJME
2. (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) near (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)
3. 1 or 2
4. explode "Adrenal-Cortex-Hormones" / all SUBHEADINGS in MIME,MJME
5. explode "Glucocorticoids-" / all SUBHEADINGS in MIME,MJME
6. steroid* or glucocorticoid* or prednisolone* or betamethasone* or cortisone* or dexamethasone* or hydrocortisone* or methylprednisolone* or prednisone* or triamcinolone* or corticosteroid*
7. 4 or 5 or 6
8. 3 and 7
9. 8 and (Cochrane highly sensitive RCT strategy)

EMBASE SEARCH STRATEGY (1980 to November 2005, week 46)
1. exp Head Injury/
2. ((head or crani$ or capitis or brain$ or forebrain$ or skull$ or hemisphere$ or intracran$ or orbit$) adj3 (injur$ or trauma$ or lesion$ or damag$ or wound$ or destruction$ or oedema$ or edema$ or fracture$ or contusion$ or commotion$ or pressur$)).mp.[title,abstract]
3. 1 or 2
4. exp CORTICOSTEROID THERAPY/
5. (steroid$ or glucocorticoid$ or prednisolone$ or betamethasone$ or cortisone$ or dexamethasone$ or hydrocortisone$ or methylprednisolone$ or prednisone$ or triamcinolone$ or corticosteroid$).mp. [title, abstract]
6. Glucocorticoid/dt [Drug Therapy]
7. 4 or 5 or 6
8. 3 and 7

Appendix 2. Search strategy: 2008 update

CENTRAL (The Cochrane Library 2007, Issue 4)
#1MeSH descriptor Craniocerebral Trauma explode all trees
#2MeSH descriptor Cerebrovascular Trauma explode all trees
#3MeSH descriptor Brain Edema explode all trees
#4(brain or cerebral or intracranial) near3 (oedema or edema or swell*)
#5MeSH descriptor Glasgow Coma Scale explode all trees
#6MeSH descriptor Glasgow Outcome Scale explode all trees
#7MeSH descriptor Unconsciousness explode all trees
#8glasgow near3 (coma or outcome) near3 (score or scale)
#9(Unconscious* or coma* or concuss* or 'persistent vegetative state') near 3 (injur* or trauma* or damag* or wound* or fracture*)
#10"Rancho Los Amigos Scale"
#11(head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)
#12Diffuse near3 axonal near3 injur*
#13(head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
#14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)

PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 7 Jan 2008 (added to PubMed in the last 60 days)
#1Craniocerebral Trauma [mh] OR Brain Edema [mh] OR Glasgow Coma Scale [mh] OR Glasgow Outcome Scale [mh] OR Unconsciousness [mh] OR Cerebrovascular Trauma [mh] OR ((head OR cranial OR cerebral OR brain* OR intra-cranial OR inter-cranial) AND (haematoma* OR hematoma* OR haemorrhag* OR hemorrhage* OR bleed* OR pressure)) OR (Glasgow AND scale) OR ("diffuse axonal injury" OR "diffuse axonal injuries") OR ("persistent vegetative state") OR ((unconscious* OR coma* OR concuss*) AND (injury* OR injuries OR trauma OR damage OR damaged OR wound* OR fracture* OR contusion* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR pressure))
#2(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))
#3Search #1 AND #2 Limits: published in the last 60 days

MEDLINE (Ovid SP) 1950 to Nov (week 2) 2007
1.exp Craniocerebral Trauma/

2.exp Brain Edema/
3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Unconsciousness/
6.exp Cerebrovascular Trauma/
7.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma $ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
8.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ti,ab.
9.(Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
10."rancho los amigos scale".ti,ab.
11.("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
12.((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
13.((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab.
14.or/1-13
15. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
16.clinical trial.pt.
17.randomized controlled trial.pt.
18.17 or 18 or 19
19.exp models, animal/
20.exp Animals/
21.exp Animal Experimentation/
22.exp Disease Models, Animal/
23.exp Animals, Laboratory/
24.or/21-25
25.Humans/
26.20 not 25
27.18 not 26
28.14 and 27
29.2007$.ed.
30.28 and 29

EMBASE (Ovid SP) 1980 to (week 1) Jan 2008
1.exp Brain Injury/
2.exp Brain Edema/
3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Rancho Los Amigos Scale/
6.exp Unconsciousness/
7.((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
8.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma $ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
9.(Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab.
12.Diffuse axonal injur$.ab,ti.
13.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ab,ti.
14.or/1-13
15.exp animal model/
16.Animal Experiment/
17.exp ANIMAL/
18.exp Experimental Animal/
19.1 or 2 or 3 or 4
20.Human/
21.5 not 6
22.(randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
23.exp clinical trial/
24.8 or 9
25.10 not 7

26.14 and 25
27.2007$.em.
28.26 and 27

PsycINFO (Ovid SP) 1806 to April 2007
1.explode "Head-Injuries" in MJ,MN
2.explode "Brain-Damage" in MJ,MN
3.explode "Traumatic-Brain-Injury" in MJ,MN
4.explode "Brain-Concussion" in MJ,MN
5.explode "Coma-" in MJ,MN
6.Unconscious* or coma* or concuss* or "persistent vegetative state"
7.(head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near (injur* or trauma* or damag* or wound* or fracture* or contusion*)
8.(head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
9.#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

WHAT'S NEW

Date	Event	Description
7 January 2008	New search has been performed	New studies sought but none found.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 3, 1997

Date	Event	Description
7 July 2008	Amended	Converted to new review format.
14 February 2006	New search has been performed	The finalised data for CRASH 2005 have been incorporated.
1 November 2005	New search has been performed	New studies sought but none found.

CONTRIBUTIONS OF AUTHORS

Both authors selected studies for inclusion, extracted data and wrote the text. Both authors contacted trialists for further information.

DECLARATIONS OF INTEREST

Ian Roberts collaborated on the design and conduct of the CRASH trial of corticosteroids in head injury, funded by the UK Medical Research Council.

Philip Alderson has no known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Institute of Child Health, University of London, UK.
- London School of Hygiene and Tropical Medicine, UK.
- NHS R&D Programme, UK.

External sources

- NHS R&D Programme, Mother and Child Health, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans