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Corticosteroids for acute ischaemic stroke (Review)

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[Intervention Review]

Corticosteroids for acute ischaemic stroke

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ABSTRACT

Background

The majority of strokes are due to cerebral infarction. Ischaemic cerebral tissue tends to develop cytotoxic oedema which, if the blood-brain barrier is disrupted, may be followed by vasogenic oedema. Large infarcts can develop life-threatening massive oedema. Early treatment with corticosteroids could theoretically help reduce both cytotoxic and vasogenic oedema and so improve the clinical outcome after a stroke.

Objectives

To assess the effect of corticosteroids in acute presumed ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched: 17 February 2011).

Selection criteria

Published randomised trials comparing corticosteroids with placebo or a control group in people with acute (presumed or definite) ischaemic stroke. Trials were included if treatment began within 48 hours of stroke onset and if clinical outcomes were assessed.

Data collection and analysis

Two review authors independently applied the inclusion criteria, assessed trial quality and extracted the data.

Main results

Eight trials involving 466 people were included. Details of trial quality that may relate to bias were not available for most trials. No difference was shown in the odds of death within one year (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.57 to 1.34). Treatment did not appear to improve functional outcome in survivors. Seven trials reported neurological impairment but pooling the data was impossible because no common scale or time interval was used. The results were inconsistent between individual trials. The only adverse effects reported were small numbers of gastrointestinal bleeds, infections and deterioration of hyperglycaemia across both groups. The results are unchanged since the previous update.

Authors' conclusions

There is not enough evidence to evaluate corticosteroid treatment for people with acute presumed ischaemic stroke. The conclusions are unchanged since the previous update.

PLAIN LANGUAGE SUMMARY

Corticosteroids for acute ischaemic stroke

There is no evidence of benefit from corticosteroids for acute ischaemic stroke. Stroke from blockage of an artery to a part of the brain causes swelling of that part of the brain. The swelling produces pressure effects, may cause additional brain cells to die, or delays the recovery of damaged but recoverable brain cells. Reduction of this swelling may relieve pressure on adjacent parts of the brain, reduce the number of brain cells that are killed and allow better recovery of damaged brain cells. Corticosteroids have been used to reduce this brain swelling in order to help limit damage and speed recovery. However, from the small and inadequate amount of evidence available from eight trials involving 466 participants, this review found no benefit of corticosteroids on reducing the number of deaths or improving functional outcome in survivors.

BACKGROUND

Cerebral oedema can cause clinical deterioration and death after ischaemic stroke by producing direct pressure and vascular occlusive effects, as well as indirect effects through vasospasm and necrosis (Battistini 1981; Gomes 2005). Massive cerebral oedema following a large hemispheric infarction can lead to transtentorial herniation and death, but in appropriately selected younger patients decompressive hemicraniectomy can be life-saving (Staykov 2011). Oedema complicating ischaemic stroke therefore remains of considerable potential relevance to acute stroke care. Cerebral oedema may be classified into cytotoxic and vasogenic types where cytotoxic oedema is related to cell membrane dysfunction while vasogenic oedema is related to the breakdown of the function of the blood-brain barrier. Vasogenic cerebral oedema associated with intracranial tumours often responds well to corticosteroids (Shapiro 1975; Gomes 2005), and though most of the oedema associated with large cerebral infarcts is vasogenic, some of the brain swelling in cerebral infarcts is due to cytotoxic oedema. It is not clear if corticosteroids reduce cytotoxic oedema (Battistini 1981). Although studies of their use in acute stroke have been disappointing, some physicians continue to treat stroke with corticosteroids. For example, some 20% of patients with acute ischaemic stroke in the USA in the 1980s, who were involved in the Stroke Data Bank study, were treated with corticosteroids (Faulkes 1988). In a survey in China, 19% of physicians reported that they used corticosteroids routinely and 61% said that they used them at times for certain patients (Chen 1997). However, there are potentially serious side-effects from the use of corticosteroids.

OBJECTIVES

To determine whether the administration of intravenous corticosteroids in patients with acute presumed ischaemic stroke is a safe and effective treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All attempts were made to identify all unconfounded, definitely or possibly truly randomised trials in which treatment with corticosteroid therapy was compared with control in patients following an acute (presumed) ischaemic stroke. We excluded trials in which allocation to a treatment or control group was not definitely truly random or in which treatment allocation was not concealed since prior knowledge of treatment allocation may have led to biased treatment allocation (Schulz 1995).

Types of participants

We included patients with acute (presumed or definite) ischaemic stroke where attempts were made to exclude intracerebral haemorrhage. Definite ischaemic stroke implies patients in whom a computerised tomography (CT) scan was performed before randomisation. Presumed ischaemic stroke means patients who did not have a CT scan and, therefore, where haemorrhage could not be reliably excluded.

Types of interventions

Corticosteroid (intravenous, intra-muscular or oral) versus control.

Types of outcome measures

The main outcomes of interest were:

1. the number of patients who died from any cause during the scheduled follow-up period;
2. functional outcome among survivors;
3. adverse effects of treatment, where documented.

Wherever possible, we analysed results on an intention-to-treat basis.

Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module.

We identified trials in the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor on 17 February 2011.

For the original review, the review authors contacted numerous researchers in an effort to identify unpublished and ongoing studies, and also asked investigators of published trials to provide additional information on cause of death. We have not repeated this exercise for this update.

One new trial meeting the inclusion criteria has been identified for this update.

Data collection and analysis

For the original review, two review authors (NQ, SL - see [Acknowledgements](#)) independently selected the trials for inclusion.

For this update, we independently agreed that one additional study was eligible for inclusion. We re-assessed the methodological quality of each study for this update. We did not use a scoring system to assess quality but noted the following details: randomisation method, blinding, whether intention-to-treat (ITT) analyses were documented and possible from the published data, and the number of patients lost to follow-up. We independently extracted and cross-checked the data, and discussed discrepancies. We sought data on the number of patients with each outcome measure (where available) by allocated treatment group. To allow an ITT analysis, we sought the data irrespective of compliance, and whether or not the patient was subsequently deemed ineligible or otherwise excluded from treatment or follow-up. We also sought data on whether or not CT scanning was performed prior to randomisation.

For the original review, if any of the above data were not available in the publications, the review authors requested further information through correspondence with the trialists. Where no further information was obtained, the results from the 'on-treatment' analysis were used, based on the data extractable from the publication. Due to the age of many of the studies, data regarding disability were difficult to obtain. Where data were not available about the type of stroke and cause of death, these were sought by the original review authors from the trialists. For this update, we did not seek to contact any of the trialists.

For the original review both proportional and absolute risk reductions were calculated for each outcome. A test for

heterogeneity of treatment effect between the trials was made using a standard χ^2 statistic. The typical treatment effect across trials, the 'typical odds ratio (OR)' (that is the odds of an unfavourable outcome amongst treatment-allocated patients to the corresponding odds amongst controls), was calculated using the Peto OR method.

RESULTS

Description of studies

See [Characteristics of included studies](#). We identified 24 trials from the search of the Cochrane Stroke Group Trials Register of which eight fulfilled the entry criteria. We did not identify any ongoing trials. All included trials used dexamethasone except two, which used betamethasone. Four trials compared dexamethasone with an unspecified placebo, two trials compared dexamethasone with placebo water, one trial compared betamethasone with vitamin C and one trial compared betamethasone with an unspecified placebo.

The mean age of the patients in the trials, where it was quoted, ranged from 66 years to 75 years. Approximately half the patients were male. Only one trial ([Norris 1986](#)) used CT scanning to exclude haemorrhage. The severity of stroke as judged by overall case fatality ranged from 7% to 79%, though this assessment is confounded with duration of follow-up. Only three trials had follow-up beyond one month: three months for [McQueen 1978](#), and 12 months for [Mulley 1978](#) and [Ogun 2001](#). The timing of treatment from onset of stroke was within 24 hours for four trials, 48 hours for three trials and not specified for one trial ([McQueen 1978](#)). Only two trials used a measure of functional disability ([Mulley 1978](#); [Ogun 2001](#)), the remainder used neurological impairment scales.

Risk of bias in included studies

Eight trials met our inclusion criteria and have been included in the analysis and are summarised in the [Characteristics of included studies](#) table. The reasons for excluding the 15 trials from the analysis are summarised in the [Characteristics of excluded studies](#) table. Information about trial quality that may relate to bias was not available from many trials for:

1. reporting of randomisation and concealment;
2. whether concealment was adequate;
3. whether blinding was adequate;
4. assessment of the success of blinding;
5. any important imbalances in the treatment groups;
6. number of patients excluded from the analysis.

Adverse events were reported in a systematic fashion in only one trial, so the adverse event data have not been pooled but merely described.

Effects of interventions

The total number of individuals included in the eight trials was 466. There was no evidence of statistical heterogeneity. The eight trials showed a non-significant decrease in the odds of death (within one year) of 0.87 (95% CI 0.57 to 1.34). Only one small trial reported a marginal statistically significant hazard in the odds of death and all other trials were statistically non-significant. There was no evidence that the effect on deaths within one month (OR 0.97; 95%

CI 0.63 to 1.47) was substantially different from the effect on deaths within one year. The results of the trials that used betamethasone did not substantially differ from those using dexamethasone.

We could not do analysis by cause of death since we did not receive appropriate data from the trial investigators.

Six trials reported neurological impairment scales but pooling these data was impossible because no common scale nor time interval was used. Four trials reported no difference in neurological impairment, one reported a statistically significant benefit ([Patten 1972](#)) and one reported a statistically significant worsening ([Norris 1976](#)). The only trials to report functional disability found a non-significant difference at 12 months. Mulley et al found full independence in 10 survivors in the dexamethasone group and eight in the placebo group; for severe disability the figures were four in the dexamethasone group and three in the placebo group ([Mulley 1978](#)). Ogun et al found of the three survivors in the dexamethasone group two were ambulant and one was chair bound, whilst in the placebo group the two survivors were bed bound and chair bound ([Ogun 2001](#)).

Only one of the eight trials reported non-fatal adverse effects in a systematic manner ([Norris 1986](#)); there were generally few adverse events and these were limited to gastrointestinal bleeding, infection and hyperglycaemia. Diabetes or its worsening was reported to be more frequent in the treatment group in three trials (12 versus 0). Infection was more frequent in the treatment group in two trials (4 versus 0) but less frequent in one trial (0 versus 4). Gastrointestinal bleeding was reported as being more frequent in the treatment group in three trials (7 versus 4) but less frequent in one trial (0 versus 3). [Norris 1986](#) reported withdrawals from adverse events as follows (treatment versus control): gastrointestinal bleeding (3 versus 2), infection (0 versus 4), worsening hyperglycaemia (4 versus 0).

DISCUSSION

The results of this review do not support the hypothesis that intravenous or intramuscular corticosteroids reduce all-cause case fatality following stroke. However, the small number of patients and events in the trials mean that there is great imprecision and that this treatment could increase the odds of death by as much as 34%, or reduce it by as much as 43% (95% CI). Few patients had the diagnosis of ischaemic stroke confirmed by a CT scan, and it is conceivable that the results were influenced by the inclusion of haemorrhagic strokes. It is possible that the relative treatment effects of corticosteroids may vary between patients with differing levels of absolute risk. Although the evidence is limited, the present review would be compatible with the notion that corticosteroids are beneficial in high-risk patients with large infarcts and much vasogenic oedema ([Mulley 1978](#)), and either ineffective or harmful among low-risk patients with smaller infarcts and less vasogenic oedema. Two trials with higher case-fatality rates in the control groups ([Mulley 1978](#); [Norris 1986](#)) both reported trends (statistically non-significant) in favour of treatment. However, one other trial with a higher case-fatality rate did not favour treatment ([Ogun 2001](#)). There was no significant heterogeneity of results from the different trials, nor was there any evidence to suggest bias from selective reporting of trials based on the results. The point estimates of the ORs for the different trials were evenly spread around the pooled point estimate.

In general, neither neurological nor functional outcome was any better in those patients who survived. Treating severe disability and death as one endpoint (from the one trial that measured functional outcome) made no difference to the conclusion.

Adverse effects of treatment were few (approximately 10%). They were generally more frequent in the treatment group, for infection, worsening hyperglycaemia and gastrointestinal bleeding, as would be expected from the mode of action of corticosteroids. Given the unsystematic manner of reporting adverse events in these trials, there may have been under-reporting as trials of dexamethasone using similar doses in cerebral haemorrhage report much higher adverse event rates in the treatment group ([Poungvarin 1987](#)). Evidence from a much larger-scale trial of high-dose corticosteroids in traumatic brain injury highlights the potential hazards. The MRC CRASH study, a randomised controlled trial of high-dose corticosteroids in over 10,000 patients with acute traumatic brain injury, showed that allocation to corticosteroids was associated with a significant excess of deaths from all causes, and was not associated with any significant reduction in disability in survivors ([CRASH 2005](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Trials of corticosteroids do not provide evidence of a beneficial effect on death following acute (presumed) ischaemic stroke. Nor

do the data on neurological impairment or functional outcome suggest any benefit in survivors. There is, therefore, no evidence to support the routine use of corticosteroids in the management of acute ischaemic stroke.

Implications for research

Given the adverse effects of corticosteroids, the benefits on both case fatality and functional outcome would need to be substantial for this treatment to be recommended. We do not feel that the present data hold enough promise of clinically worthwhile benefits to advocate a large-scale trial.

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Ongoing trials

We are not aware of any ongoing trials of corticosteroids but would be grateful for any information about any other relevant trials not included in this review.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Bauer 1973

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: 5 (including 1 lost to follow-up, none included in analysis) Number lost to follow-up: 1
Participants	USA 54 in total (after exclusions): 30 female, 24 male Mean age: 66 years Time from onset of stroke to enrolment: within 48 hours Method of diagnosis: clinical, lumbar puncture 100% 28 dexamethasone 26 placebo
Interventions	Dexamethasone versus placebo Intervention: dexamethasone 12 mg i.v. stat, 4 mg i.m. 6 hourly for 3 days, 4 mg i.m. 8 hourly for 3 days, 4 mg i.m. 12 hourly for 2 days, 4 mg i.m. 24 hourly for 2 days: total dose: 120 mg dexamethasone Placebo: unspecified

Corticosteroids for acute ischaemic stroke (Review)

Bauer 1973 (Continued)

All patients: prophylactic ulcer diet and antacid (30 cc Maalox) 4 times a day where oral intake possible

Duration: 10 days

Outcomes	Death at 14 days Neurological impairment in the level of consciousness, the motor system and of mentation at 14 days
Notes	Exclusions: more than 300 red blood cells per cc in the cerebrospinal fluid; history of gastro-intestinal bleeding or symptomatic duodenal ulcer Follow-up: 14 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated, but assumed computer-generated by Merck, Sharp & Dohme
Allocation concealment (selection bias)	Unclear risk	"randomisation was performed on a consecutive admission basis". Blind until last patient assessed
Blinding (performance bias and detection bias) All outcomes	Low risk	"coded vials which contained either Decadron [dexamethasone] or a similarly appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients withdrawn (3 placebo, 2 dexamethasone). These were not included in analyses
Selective reporting (reporting bias)	Low risk	

Gupta 1978

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: not stated Number of losses to follow-up: not stated
Participants	India 30 patients (sex breakdown and age not stated) Time from onset of stroke to enrolment: less than 24 hours Method of diagnosis: clinical, lumbar puncture to exclude haemorrhage (100%) 13 Betamethasone 17 Placebo
Interventions	Betamethasone versus placebo Intervention: betamethasone 10 mg stat, 10 mg/day in divided doses for 2 days, 8 mg/day in divided doses for 3 days, 6 mg/day in divided doses for 3 days, 4 mg/day for 3 days, 2 mg/day for 10 days: total dose: 94 mg betamethasone Placebo: unspecified Duration: 21 days

Corticosteroids for acute ischaemic stroke (Review)

Gupta 1978 (Continued)

Outcomes	Death at 21 days Neurological status (self-made method) at 1, 2 and 3 days, and at 1, 2 and 3 weeks Cerebrospinal fluid pressures Adverse events not reported
Notes	Exclusions: not stated Follow-up: 21 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"ampoules of the drug and placebo were similar in appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors do not indicate if there were any patients excluded or lost to follow-up prior to analysis

McQueen 1978

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: not stated Number of losses to follow-up: not stated
Participants	New Zealand 48 in total (sex breakdown and age not stated) Time from onset of stroke to enrolment: not stated Method of diagnosis: clinical diagnosis of cerebral thrombosis, lumbar puncture ?% 24 betamethasone 24 placebo
Interventions	Betamethasone versus placebo Interventions: betamethasone 12 mg i.m. stat, 4 mg i.m. 8 hourly for 1 day, 4 mg i.m. 8 hourly for 9 days, 4 mg i.m. 2 hourly for 2 days, 2 mg i.m. 2 hourly for 2 days: total dose: 345 mg betamethasone Placebo: vitamin C Duration: 14 days
Outcomes	Death at 12 weeks Causes of death Neurological scores (not available) at 14th to 15th day and week 12
Notes	Exclusions: subarachnoid haemorrhage; severe diabetes; pre-existing steroid treatment; known peptic ulceration

Corticosteroids for acute ischaemic stroke (Review)

McQueen 1978 (Continued)

Follow-up: 12 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated, but probably prepared by outsider to study
Allocation concealment (selection bias)	Unclear risk	"each centre received packages of betamethasone or identical placebo in randomised order within blocks of six. As patients were entered into the trial they were given the medication designated by the next number in the treatment block"
Blinding (performance bias and detection bias) All outcomes	Low risk	"packages of betamethasone or identical placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors do not indicate if there were any patients excluded or lost to follow-up prior to analysis

Mulley 1978

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: 16 (not included in analysis, 5 due to alternative diagnoses (subarachnoid haemorrhage, cerebral tumour, demyelinating disease and ethanol overdose), 5 due to history revealing previous stroke or onset over 48 hours previously, 1 due to developing tuberculosis, and 1 at the request of the admitting physician, treatment allocations not stated) Number lost to follow-up: 4 (2 dexamethasone, 2 placebo, not included in analysis)
Participants	UK 134 in total (118 included in final analysis) Mean age: 70 years (no breakdown by sex) Time from onset of stroke to enrolment: within 48 hours Method of diagnosis: clinical, lumbar puncture ?% 61 dexamethasone 57 placebo
Interventions	Dexamethasone versus placebo Interventions: dexamethasone 4.2 mg i.m. 6 hourly for 10 days, 4.2 mg i.m. 8 hourly for 1 day, 4.2 mg i.m. 12 hourly for 2 days, 4.2 mg i.m. once for 1 day: total dose: 201.6 mg dexamethasone Placebo: water Duration: 14 days
Outcomes	Death at day 10 and at 3 and 12 months Functional disability (Adams method) at 12 months Adverse effects of treatment Quality of life Duration of hospital stay
Notes	Exclusions: previous stroke; considered to have intracranial tumour, injury or subarachnoid haemorrhage; diabetes mellitus; peptic ulcer; already receiving steroids.

Corticosteroids for acute ischaemic stroke (Review)

Mulley 1978 (Continued)

Follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	"each of the four wards contained a series of sealed envelopes containing randomised treatment instructions ... After entering into the trial the next envelope was opened"
Blinding (performance bias and detection bias) All outcomes	Low risk	"treatment ampoules identified only by a code number", "the treatment code was available to [one of the trial organisers], who did not participate in assessment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients excluded after randomisation and not included in analysis. 4 patients lost to follow-up (2 placebo, 2 treatment) not included in analysis

Norris 1976

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: not stated Number of losses to follow-up: 1 (lost after assessment on day 22, included in analysis)
Participants	Canada 53 in total (including 1 lost to follow-up): 24 female, 29 male Mean age: 70 years Time from onset of stroke to enrolment: within 24 hours Method of diagnosis: clinical, lumbar puncture 100%, brain scan 100%, angiography ?% 26 dexamethasone 27 placebo
Interventions	Dexamethasone versus placebo. Intervention: dexamethasone 8 mg stat bolus, 4 mg 6 hourly gradually decreased over 12 days: total dose: 140 mg dexamethasone Placebo: unspecified Duration: 12 days
Outcomes	Death at day 29 Cause of death at day 29 Neurological status (self-made scale) at days 1, 8, 15, 22 and 29 Adverse effects of treatment
Notes	Exclusions: recent peptic ulcer; concurrent infection, psychiatric disturbances Follow-up: 29 days

Risk of bias

Norris 1976 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Correspondence with author suggests random number tables
Allocation concealment (selection bias)	Unclear risk	"patients ... were randomly allocated on admission to a placebo or steroid group in a double-blind manner"
Blinding (performance bias and detection bias) All outcomes	Low risk	"each patient received either dexamethasone or matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient lost to follow-up but included in analysis, not stated if any patients were excluded after randomisation: "53 patients completed the study"

Norris 1986

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: 13 (6 placebo and 7 dexamethasone due to presumed side effects: diabetes (4 steroid, 0 placebo), infection (0 steroid, 4 placebo), gastrointestinal bleed (3 steroid, 2 placebo)) Number of losses to follow-up: not stated
Participants	Canada 113 in total: 61 female, 52 male Mean age: 75 years Time from onset of stroke to enrolment: within 48 hours Method of diagnosis: CT used in (not stated but implied) 100% ? 54 dexamethasone 59 placebo
Interventions	Dexamethasone versus placebo Intervention: dexamethasone 24 mg p.o./i.v. 6 hourly with progressive reduction of dose until day 12: total dose: 480 mg dexamethasone Placebo: unspecified Duration: 12 days
Outcomes	Death at day 21 Cause of death at day 21 Neurological impairment (Toronto stroke method) at days 6, 12, 21 Adverse effects of treatment
Notes	Exclusions: cerebral haemorrhage by CT, mild stroke, massive previous stroke, terminal stroke, dementia, diabetes mellitus, concurrent sepsis, gastrointestinal haemorrhage, or cardiac embolic source Follow-up: 21 days

Risk of bias

Bias	Authors' judgement	Support for judgement
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Norris 1986 (Continued)

Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Unclear risk	"consecutive patients admitted to the stroke unit were entered into the study", "patients were assigned to receive either dexamethasone or placebo according to random number"
Blinding (performance bias and detection bias) All outcomes	Low risk	"material was supplied in identical-appearing vials bearing the patients number in the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 patients excluded after randomisation and not included in analysis. ? patients lost to follow-up (likely 0)

Ogun 2001

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: 0 Number of losses to follow-up: 0
Participants	Nigeria 13 in total (cannot determine age and sex breakdown) Time from onset of stroke to enrolment: within 24 hours Method of diagnosis: clinical, using Siriraj stroke score to distinguish haemorrhagic from ischaemic stroke 5 dexamethasone 8 placebo
Interventions	Dexamethasone versus placebo Interventions: dexamethasone 100 mg stat, 16 mg 6 hourly for 2 days: total dose: 228 mg dexamethasone Placebo: water Duration: 2 days
Outcomes	Death at 1 and 6 months Adverse effects of treatment
Notes	Exclusions: presentation after 24 hours; primary subarachnoid haemorrhage; symptoms suggestive of head injury, subdural, tumour; brainstem stroke; diabetes mellitus; peptic ulcer; sepsis; previous stroke in same hemisphere; impairment of consciousness Follow-up: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"by simple ballot"

Ogun 2001 (Continued)

Allocation concealment (selection bias)	Unclear risk	"patients were sequentially paired and randomised", "the code was broken after the first 20 patients ... by [one author] who was not involved in assessment of patients"
Blinding (performance bias and detection bias) All outcomes	Low risk	"ampoules were prepared by MCA Chemical, Italy and contained either dexamethasone or distilled water ... these were indistinguishable and kept in identically numbered boxes; one box for each patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors do not state if there were any patients excluded subsequent to randomisation. None were lost to follow-up

Patten 1972

Methods	Double-blind, placebo controlled Randomised Number of patients excluded after randomisation: 7 (3 placebo due to alternative diagnosis (subdural haematoma), alternative cause of death (ruptured abdominal aortic aneurysm) and 1 due to concomitant administration of dextran 40; 3 dexamethasone due to exacerbation of diabetes and stopping of steroid, alternative diagnosis (subarachnoid haemorrhage) and 1 due to concomitant administration of anticoagulant therapy; 1 (? allocation) who had not received any treatment due to nursing error) Number of losses to follow-up: not stated
Participants	USA 31 in total: 15 female, 16 male Mean age: 69 years Time from onset of stroke to enrolment: within 24 hours Method of diagnosis: clinical, lumbar puncture ?%, isotope brain scan ?%, angiography ?% 17 dexamethasone 20 placebo
Interventions	Dexamethasone versus placebo Intervention: dexamethasone 10 mg i.v. stat, 4 mg i.m. 6 hourly for 10 days, dose gradually decreased to 0 over 7 days: total dose: unknown Control: placebo All patients: oral antacid Duration: 17 days
Outcomes	Death at day 17 Motor function (self-made scoring) at days 3, 6, 10 and 17 Mental function (self-made scoring) at days 3, 6, 10 and 17 Adverse effects of treatment
Notes	Exclusions: subarachnoid haemorrhage Follow-up: 17 days

Risk of bias

Bias	Authors' judgement	Support for judgement
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Patten 1972 (Continued)

Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Low risk	randomisation not broken until end of trial
Blinding (performance bias and detection bias) All outcomes	Low risk	"the material was supplied in identical appearing vials bearing the patients number in the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow-up not stated. The authors provide outcome data on those randomised and subsequently excluded, so that an ITT analysis can be performed
Selective reporting (reporting bias)	Unclear risk	Patient excluded from the analysis due to alternative mechanism of death despite meeting inclusion criteria and receiving treatment

CT: computerised tomography
i.m.: intramuscular
ITT: intention-to-treat
i.v.: intravenous
p.o.: per os (by mouth)
stat: immediately

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Albizzati 1979	Glycerol treatment compared with dexamethasone and not placebo
Barolin 1976	Not randomised - alternate allocation
Dyken 1956	Alternate allocation
Freeman 1978	No data on deaths in each treatment group given. Contained haemorrhagic stroke. Dexamethasone plus mannitol versus placebo
Gahlot 1982	Glycerol compared with dexamethasone and not placebo
Gilsanz 1975	Glycerol treatment compared with dexamethasone and not with placebo
Hasan 1989	Subarachnoid haemorrhage only
Hetzel 1957	No information on randomisation procedure or blinding
Kaste 1976	Dexamethasone plus dextran versus placebo
Kumar 1989	Uneven allocation between treatment (25 participants) and control (15 participants) and confounded by the administration of antacids to the treatment group only
Paal 1981	Dexamethasone plus dextran plus aspirin versus placebo
Poungvarin 1987	Haemorrhagic stroke only
Rompel 1980	No data available

Corticosteroids for acute ischaemic stroke (Review)

Study	Reason for exclusion
Rubinstein 1965	Not randomised - unequal allocation between treatment (21 participants) and placebo (6 participants)
Russek 1955	Open, uncontrolled study
Santambrogio 1978	No data provided on number of deaths
Tellez 1973	Haemorrhagic stroke only
Wright 1974	No randomised allocation

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All deaths	8	466	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.57, 1.34]
2 Deaths within one month	8	466	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.63, 1.47]

Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 All deaths.

Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 Deaths within one month.

FEEDBACK

Comment

Summary

Is it possible to compare outcomes between included and certain excluded trials where the latter were excluded on the grounds that they were confounded?

Reply

Since non-randomised studies may be biased towards a positive treatment effect (Schulz 1995), it would introduce a systematic bias into the analysis by comparing outcomes between included studies and those excluded trials which were confounded. Larger scale randomised evidence is required if it is still considered appropriate to further test these drugs.

Contributors

Walid Matat

WHAT'S NEW

Date	Event	Description
9 March 2011	New citation required but conclusions have not changed	New review team.
9 March 2011	New search has been performed	We have updated the search and have included one new study (13 patients), bringing the total number of included trials to eight, involving 466 participants. We have revised the text. The overall conclusions are unchanged.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1997

Date	Event	Description
5 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Peter Sandercock: article selection, data abstraction, analysis construction, co-writer of the review.

Tim Soane: article selection, data abstraction, analysis construction, co-writer of the review.

DECLARATIONS OF INTEREST

None known

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Internal sources

- University of Oxford, UK.

External sources

- NHS Anglia and Oxford Region Research and Development Programme, England, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Brain Edema [*drug therapy] [etiology]; Brain Ischemia [complications] [drug therapy]; Glucocorticoids [*therapeutic use]; Randomized Controlled Trials as Topic; Steroids; Stroke [complications] [*drug therapy]

MeSH check words

Humans