Corticosteroids for treating dengue shock syndrome (Review)

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[Intervention Review]

Corticosteroids for treating dengue shock syndrome

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ABSTRACT

Background

Dengue shock syndrome is the most severe from of dengue haemorrhagic fever, one of the leading causes of death in children. Observational studies have suggested corticosteroids may benefit people with dengue shock syndrome.

Objectives

To compare corticosteroids with placebo or no corticosteroids for treating dengue shock syndrome.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register (August 2009), CENTRAL (*The Cochrane Library* 2009, Issue 2), MEDLINE (1966 to August 2009), EMBASE, (1974 to August 2009), LILACS (1982 to August 2009), and reference lists. We also contacted researchers.

Selection criteria

Randomized and quasi-randomized controlled trials comparing corticosteroids with no corticosteroids or placebo in people diagnosed with dengue shock syndrome.

Data collection and analysis

Two authors independently applied the inclusion criteria, extracted data, and assessed methodological quality. We calculated the risk ratio (RR) for dichotomous data and mean difference for continuous data, and presented them with 95% confidence intervals (CI).

Main results

Four trials involving 284 participants met the inclusion criteria. Corticosteroids were no more effective than placebo or no treatment for reducing the number of deaths (RR 0.68, 95% CI 0.42 to 1.11; 284 participants, 4 trials), the need for blood transfusion (RR 1.08, 0.52 to 2.24; 89 participants, 2 trials), or the number of serious complications (convulsions and pulmonary haemorrhage) as reported in one trial (63 participants).

Authors' conclusions

There is insufficient evidence to justify the use of corticosteroids in managing dengue shock syndrome. As corticosteroids can potentially do harm, clinicians should not use them unless they are participating in a randomized controlled trial comparing corticosteroids with placebo.

PLAIN LANGUAGE SUMMARY

No good evidence that corticosteroids are helpful in dengue shock syndrome

The dengue virus is transmitted by mosquitoes and can cause either a mild illness with fever or a more severe illness with fever and bleeding (dengue haemorrhagic fever). The bleeding is generally seen as tiny red spots on the skin but can occasionally be more severe affecting the nose, gums, and gut. In its most severe form it can cause shock, collapse, and sometimes death (dengue shock syndrome). The current treatment for dengue shock syndrome is to give fluids directly into the bloodstream, but corticosteroids have been suggested as drugs that may help due to their anti-inflammatory properties. This review of trials found only four small trials (with 284 participants) that were not of good quality and which showed no benefit overall. Further trials would be needed before this drug were used in these patients, as there is the potential for adverse effects due to the drugs' properties of suppressing the immune system and potentially leaving people open to other infections.

BACKGROUND

Definition

Dengue virus is an arbovirus transmitted to humans by two species of mosquito, *Aedes aegypti* and *A. albopictus*. The four serotypes of dengue virus can cause a wide range of symptoms from mild febrile illness to severe haemorrhagic fever, which leads to dengue shock syndrome. Dengue haemorrhagic fever is said to be present when patients have high fever for two to seven days, bleeding, enlargement of the liver, and insufficient circulation (Nimmanitya 1993). Bleeding usually occurs and frequently presents as tiny, scattered, red spots in the skin (petechiae). Bleeding from the nose, gums, and gastrointestinal tract is less common but may be severe. There are four grades dengue haemorrhagic fever according to the level of shock or bleeding: grades I and II are non-shock dengue haemorrhagic fever, and grades III and IV are cases with shock (dengue shock syndrome) (WHO 1997).

Epidemiology

Dengue haemorrhagic fever was first recognized in South-East Asia in the 1950s when outbreaks occurred in Philippines, Thailand, and Vietnam. The incidence of dengue haemorrhagic fever has increased in several countries in Asia and is one of the leading causes of death in children (Thongcharoen 1993). It is currently estimated that the majority of the 100 million cases of dengue infection that occur annually are in South-East Asia (Kautner 1997). Dengue haemorrhagic fever is also endemic in some parts of the Americas. Twenty-five countries in the Americas reported 42,246 cases of dengue haemorrhagic fever and 582 deaths between 1981 and 1996 (Pinheiro 1997), and an epidemic occurred in Cuba in 1981. There are increasing numbers of imported cases of dengue infection among travellers returning from these endemic areas (Kautner 1997).

Pathogenesis

It is unclear how dengue infection causes bleeding and shock. Immune responses seem to play an important role in causing illness. Infection with one of the four serotypes of dengue virus provides lifelong immunity to that serotype. Secondary infection with another serotype of dengue virus can form a 'virus-antibody complex' by combining with existing antibody from previous dengue infection. The virus-antibody complex promotes the growth of the virus in mononuclear cells and activates the complement system (Halstead 1993). In another hypothesis, genetic changes in the virus genome increase viral replication, virulence, and epidemic potential of the dengue virus (Gubler 1998). Capillary damage and increased permeability of vessel walls cause plasma to flow into extravascular spaces and increase the blood concentration. A depletion of plasma volume can cause low blood pressure and lead to shock in severe cases. Bleeding in dengue haemorrhagic fever

is related to platelet depletion (thrombocytopenia, ≤ 100,000 platelets/mm^3), which results from the depression of megakaryocyte function and increased destruction of mature platelets. It may also be involved with microvascular injury, platelet dysfunction, and clotting defect in blood vessels (disseminated intravascular coagulation) (Nelson 1964; Mitrakul 1979). Complications such as encephalopathy, hepatic failure, and renal failure can occur but are unusual.

Management

The standard treatment of dengue shock syndrome is to immediately administer intravenous fluids to expand plasma volume. People are at particular risk of circulatory problems when their fever resolves. Plasma leakage is thought to be self limiting and rarely lasts longer than 48 hours, so clinicians prevent shock by replacing the plasma volume as soon as the haematocrit concentration starts to rise (Nimmanitya 1993). Clinicians give blood if patients are bleeding. There are no drugs available specifically for the treatment of dengue haemorrhagic fever. Although carbazochrome sodium sulfonate (AC-17) was tested in clinical trials because it is thought to be protective against vascular damage and decrease the severity of plasma leakage, the authors of one study concluded no benefit was shown (Tassniyom 1997).

Corticosteroids are potent anti-inflammatory agents that have a wide range of effects on immunological processes and have found use in a broad spectrum of diseases (Kehrl 1983). The use of corticosteroids in the management of dengue haemorrhagic fever and dengue shock syndrome is under debate. The World Health Organization does not mention corticosteroids in the treatment guidelines for dengue shock syndrome (WHO 1997). Observational studies in Thailand have shown a marked decline in case-mortality rate without any use of corticosteroids; this was attributed to both close observation of the patients for signs of shock during the critical period and early replacement of plasma loss (Cohen 1964; Nimmanitya 1978). Corticosteroids are used in some countries, particularly those in South-East Asia for managing dengue shock syndrome. They are thought to be effective for stabilizing capillary permeability and have been used in addition to fluid replacement (Sumarmo 1987). This systematic review examines the best available evidence on the effects of corticosteroids on death in dengue shock syndrome.

OBJECTIVES

To compare corticosteroids with placebo or no corticosteroids for treating dengue shock syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

People diagnosed with dengue shock syndrome, as defined by the trial authors.

Types of interventions

Intervention

Corticosteroids (methylprednisolone, hydrocortisone, dexamethasone).

Control

Placebo or no corticosteroids.

Types of outcome measures

Primary

Death.

Secondary

- Time to regain normal blood pressure.
- Intravenous fluid requirement during the period of shock.
- Blood transfusion.
- Severe complications, including pulmonary oedema, renal failure, hepatic failure, pulmonary haemorrhage and convulsion.
- Days in hospital.
- Adverse events.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (August 2009); Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (2009, Issue 2); MEDLINE (1966 to August 2009); EMBASE (1974 to August 2009); and LILACS (1982 to August 2009).

Researchers

We contacted individual researchers working in the field for unpublished trials.

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Two authors independently screened the results of the literature search for potentially relevant trials. We used an eligibility form to assess these trials for inclusion in the review; the reasons for excluding studies are in the 'Characteristics of excluded studies'.

Data extraction and management

We used data extraction forms to collect information on the participants, methods, interventions, and outcomes. The first two authors independently extracted data. Where there were differences, we referred to the original papers. We checked the data sources to avoid extracting data from multiple publications based on the same data set.

Assessment of risk of bias in included studies

Two authors independently assessed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear (Jüni 2001). We also described who was blinded, and assessed the inclusion of all randomized participants in the final analysis to be adequate if 90% or more.

Data synthesis

We used Review Manager 5 for data analysis. We combined dichotomous data using risk ratio (RR) and combined continuous data using mean difference (MD), both with 95% confidence intervals (CI).

We assessed heterogeneity by visually examining the forest plots and by using the chi-squared test for heterogeneity with a 10% level of statistical significance. The I^2 statistic was also used to measure inconsistency results among trials (Higgins 2003). We intended to explore disease severity and corticosteroid dose and type as potential sources of heterogeneity, but there were too few trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Four randomized controlled trials involving 284 participants met the inclusion criteria (*see* 'Characteristics of included studies') and four were excluded (*see* 'Characteristics of excluded studies').

Trial location and participants

Two trials were conducted in Thailand (Pongpanich 1973; Tassniyom 1993), one in Burma (now known as Myanmar) (Min 1975), and one in Indonesia (Sumarmo 1982). Participants were children aged less than 15 years with serologically confirmed dengue and shock.

Interventions

Three trials compared intravenous hydrocortisone hemisuccinate with no corticosteroids or placebo (Pongpanich 1973; Min 1975; Sumarmo 1982), and one compared methyl prednisolone with placebo (Tassniyom 1993).

Outcomes

All four trials reported on death (Pongpanich 1973; Min 1975; Sumarmo 1982; Tassniyom 1993), two reported the number needing a blood transfusion (Pongpanich 1973; Tassniyom 1993), and one reported the duration of hospitalization (Tassniyom 1993).

Risk of bias in included studies

Also see Table 1 *and the* 'Characteristics of included studies'.

Generation of allocation sequence was adequate in one trial. No trials described allocation concealment, three trials used double blinding, and the same three trials were adequate for the number of randomized participants included in the analysis.

Effects of interventions

Death

Death was an outcome in all four trials, but only three reported deaths (Min 1975; Sumarmo 1982; Tassniyom 1993). Overall no benefit of corticosteroids was demonstrated, but the number of participants in the analysis was small (284 participants, Analysis 1.1).

Blood transfusion

There was no statistically significant difference in the number of participants needing blood transfusion (89 participants, 2 trials, Analysis 1.2) (Pongpanich 1973; Tassniyom 1993).

Complications

Tassniyom 1993 reported no statistically significant difference between the corticosteroids and placebo for convulsions and pulmonary haemorrhage (63 participants, Analysis 1.3).

Days in hospital

Tassniyom 1993 reported an average stay of 6.2 days in the placebo group and 7.3 days in the corticosteroid group (63 participants, Analysis 1.4).

DISCUSSION

Trials in people with a life-threatening illness are not easy to conduct, and the authors of these trials did their best to ensure an unbiased comparison. However, the trials were conducted some time ago and methods have become more advanced and more stringent. In the context of current standards, these trials have potential for bias, as allocation was not clearly concealed in any of them. Four trials were included in the review and the results showed no benefits of corticosteroids in reducing death in dengue shock syndrome.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to justify the use of corticosteroids in managing dengue shock syndrome. They should not be used in dengue shock syndrome outside the context of carefully conducted randomized controlled trials.

Implications for research

Large, randomized controlled trials that carefully conceal allocation and measure death as an outcome are required. Types, dose, and duration of corticosteroids should also be studied.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Min 1975 *{published data only}*
Min M, U T, Aye M, Shwe TN, Swe T. Hydrocortisone in the management of dengue shock syndrome. *Southeast Asian Journal of Tropical Medicine and Public Health* 1975;**6**(4):573–9.

Pongpanich 1973 *{published data only}*
Pongpanich B, Bhanchet P, Phanichyakarn P, Valyasevi A. Studies on dengue hemorrhagic fever: An evaluation of steroids as a treatment. *Journal of Medical Association of Thailand* 1973;**56**(1):6–14.

Sumarmo 1982 *{published data only}*
Sumarmo, Talogo W, Asrin A, Isnuhandojo B, Sahudi A. Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics* 1982;**69**(1):45–9.

Tassniyom 1993 *{published data only}*
Tassniyom S, Vasanawathana S, Chirawathul A, Rojanasuphot S. Failure of high-dose methylpredisolon in established dengue shock syndrome: A placebo-controlled, double-blind study. *Pediatrics* 1993;**92**(1):111–5.

References to studies excluded from this review

Futrakul 1981 *{published data only}*
Futrakul P, Vasanauthana S, Poshyachinda M, Mitrakul C, Cherdboonchart V, Kanthirat V. Pulse therapy in severe form of dengue shock syndrome. *Journal of Medical Association of Thailand* 1981;**64**(10):485–90.

Futrakul 1987 *{published data only}*
Futrakul P, Poshyachinda M, Mitrakul C, Kwakpetoon S, Unchumchoke P, Teranaparin C. Hemodynamic response to high-dose methyl prednisolone an mannitol in severe dengue-shock patients unresponsive to fluid replacement. *Southeast Asian Journal of Tropical Medicine and Public Health* 1987;**18**(3):373–9.

Sumarmo 1975 *{published data only}*
Widya MS, Martoatmodjo. Clinical observations on dengue shock syndrome (an evaluation of steroid treatment). *Paediatrica Indonesiana* 1975;**15**(5-6):151–60.

Sumarmo 1987 *{published data only}*
Sumarmo. The role of steroids in dengue shock syndrome. *Southeast Asian Journal of Tropical Medicine and Public Health* 1987;**18**(3):383–9.

Additional references

Cohen 1964
Cohen SN, Halstead SB. Shock associated with dengue infection. *Tropical Pediatrics* 1964;**68**(3):448–56.

Gubler 1998
Gubler DJ. Dengue and dengue hemorrhagic fever. *Clinical Microbiology Reviews* 1998;**11**(3):480–96.

Halstead 1993
Halstead SB. Pathophysiology and pathogenesis of dengue haemorrhagic fever. *Monograph on dengue/dengue haemorrhagic fever*. New Delhi: World Health Organization Regional Office for South-East Asia, 1993:80–103.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2005
Higgins JPT, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 updated May 2005; Appendix 5b. www.cochrane.org/resources/handbook/hbook.htm (accessed 9 January 2006).

Jüni 2001
Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42–6.

Kautner 1997
Kautner I, Robinson MJ, Kuhnle U. Dengue virus infection: epidemiology, pathogenesis, clinical presentation, diagnosis, and prevention. *Journal of Pediatrics* 1997;**131**(4):516–24.

Kehrl 1983
Kehrl JH, Fauci AS. The clinical uses of glucocorticoids. *Annals of Allergy, Asthma, and Immunology* 1983;**50**(1):2–8.

Mitrakul 1979
Mitrakul C. Bleeding diathesis in dengue haemorrhagic fever. *Southeast Asian Journal of Tropical Medicine and Public Health* 1979;**10**(3):434–7.

Nelson 1964
Nelson ER, Bierman HR. Dengue fever: a thrombocytopenic disease?. *JAMA* 1964;**190**:99–103.

Nimmanitya 1978
Nimmanitya S. Management of dengue hemorrhagic fever. *Asian Journal of Infectious Diseases* 1978;**2**:67.

Nimmanitya 1993
Nimmanitya S. Clinical manifestations of dengue/dengue haemorrhagic fever. *Monograph on dengue/dengue haemorrhagic fever*. New Delhi: World Health Organization Regional Office for South-East Asia, 1993:48–54.

Pinheiro 1997
Pinheiro FP, Corber SJ. Global situation of dengue and dengue haemorrhagic fever, and its emergence in the Americas. *World Health Statistics Quarterly* 1997;**50**(3-4): 161–9.

Review Manager 5
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Tassniyom 1997
Tassniyom S, Vasanawathana S, Dhiensiri T, Nisalak A, Chirawatkul A. Failure of carbazochrome sodium sulfonate (AC-17) to prevent dengue vascular permeability or shock: a randomized, controlled trial. *Journal of Pediatrics* 1997; **131**(4):525–8.

Thongcharoen 1993
Thongcharoen P, Jatanasen S. Epidemiology of dengue and dengue haemorrhagic fever. *Monograph on dengue/dengue haemorrhagic fever*. New Delhi: World Health Organization, 1993:1–8.

WHO 1997
World Health Organization. *Dengue haemorrhagic fever: diagnosis, treatment, prevention and control*. 2nd Edition. Geneva: World Health Organization, 1997.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Min 1975

Methods	Generation of allocation sequence: participants were randomly selected after matching for age and sex Allocation concealment: unclear Blinding: "double blind" Inclusion of randomized participants in analysis: "complete follow up"
Participants	98 children diagnosed with dengue shock syndrome using serological confirmation
Interventions	1. Hydrocortisone hemisuccinate (Solucortef): intravenous in a single dose of 25 mg/kg on day 1, 15 mg/kg on day 2, and 10 mg/kg on day 3 in addition to fluid replacement; 48 participants 2. Fluid replacement only: 50 participants Fluid replacement included normal saline, Ringer lactate solution, plasma, and blood products
Outcomes	1. Death 2. Duration of shock
Notes	Location: children's hospital in Rangoon, Burma (now known as Myanmar) Date: 1973-4 Haemagglutination inhibition test and complement fixation test performed on paired sera; positive result was a 4-fold rise in titre or a fixed level at 1:640 or more

Pongpanich 1973

Methods	Generation of allocation sequence: "a card was drawn" to decide which treatment programme participants entered; numbers recruited were unbalanced Allocation concealment: inadequate Blinding: none Inclusion of randomized participants in analysis: "complete follow up"
Participants	26 children diagnosed with dengue shock syndrome using serological confirmation
Interventions	1. Hydrocortisone hemisuccinate: intravenous 25 mg/kg/day; 5 mg/kg at start, rest given in divided doses every 4 to 6 h in addition to fluid replacement; 7 participants 2. Fluid replacement only: 19 participants Fluid replacement included normal saline, albumin, dextrans, plasma, and blood products
Outcomes	1. Death 2. Duration of shock 3. Requirement of fluid replacement
Notes	Location: Ramathibodi Hospital, Thailand Date: 1969-71 Haemagglutination inhibition test and complement fixation test performed on paired sera; positive result was a 4-fold rise in titre or a fixed level at 1:640 or more

Sumarmo 1982

Methods	Generation of allocation sequence: a "simple random assignment" Allocation concealment: unclear Blinding: "double blind" Inclusion of randomized participants in analysis: "complete follow up"
Participants	97 children diagnosed with dengue shock syndrome using serological confirmation
Interventions	1. Hydrocortisone hemisuccinate: 50 mg/kg, single intravenous dose in addition to fluid replacement; 47 participants 2. Fluid replacement with a placebo: sodium chloride 0.9% with same colour and turbidity; 50 participants
Outcomes	1. Death 2. Duration of shock
Notes	Location: Indonesia Date: 1978-9

Tassniyom 1993

Methods	Block randomization Generation of allocation sequence: generated by statistician and running number put on drug package Allocation concealment: unclear Blinding: "double blind" Inclusion of randomized participants in analysis: "complete follow up"
Participants	63 children diagnosed with dengue shock syndrome using World Health Organization clinical criteria and serological confirmation
Interventions	1. Methyl-prednisolone sodium succinate (Solu-medrol, Upjohn): single dose of 30 mg/kg in addition to fluid replacement; 32 participants 2. Fluid replacement with a placebo: 5% dextrose in normal saline solution; 31 participants
Outcomes	1. Death 2. Number of needing transfusion 3. Number of complication 4. Duration of hospitalization
Notes	Location: Khon Kaen, Thailand Date: 1987-8 Haemagglutination inhibition test and enzyme-linked immunosorbent assay

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

Study	Reason for exclusion
Futrakul 1981	Not a randomized controlled trial
Futrakul 1987	Not a randomized controlled trial
Sumarmo 1975	Not a randomized controlled trial
Sumarmo 1987	Review of studies on the role of steroids on dengue shock syndrome

DATA AND ANALYSES

Comparison 1. Corticosteroids versus no corticosteroids or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4	284	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.42, 1.11]
2 Blood transfusion	2	89	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.52, 2.24]
3 Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Pulmonary haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Convulsions	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Days in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 1 Death.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 1 Death

Study or subgroup	Corticosteroid n/N	No steroid/placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Min 1975	9/48	19/50		0.49 [0.25, 0.98]
Pongpanich 1973	0/7	0/19		0.0 [0.0, 0.0]
Sumarmo 1982	8/47	9/50		0.95 [0.40, 2.25]
Tassniyom 1993	4/32	4/31		0.97 [0.27, 3.54]
Total (95% CI)	**134**	**150**		**0.68 [0.42, 1.11]**

Total events: 21 (Corticosteroid), 32 (No steroid/placebo)

Heterogeneity: Chi^2 = 1.68, df = 2 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 1.54 (P = 0.12)

Analysis 1.2. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 2 Blood transfusion.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 2 Blood transfusion

Study or subgroup	Corticosteroid n/N	No steroid/placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pongpanich 1973	0/7	4/19		24.0 %	0.28 [0.02, 4.59]
Tassniyom 1993	11/32	8/31		76.0 %	1.33 [0.62, 2.86]
Total (95% CI)	**39**	**50**		**100.0 %**	**1.08 [0.52, 2.24]**

Total events: 11 (Corticosteroid), 12 (No steroid/placebo)

Heterogeneity: $Chi^2 = 1.19$, df = 1 (P = 0.28); $I^2 = 16\%$

Test for overall effect: Z = 0.20 (P = 0.84)

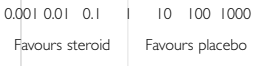
Analysis 1.3. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 3 Complications.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 3 Complications

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Pulmonary haemorrhage				
Tassniyom 1993	1/32	1/31		0.97 [0.06, 14.82]
2 Convulsions				
Tassniyom 1993	3/32	0/31		6.79 [0.36, 126.24]

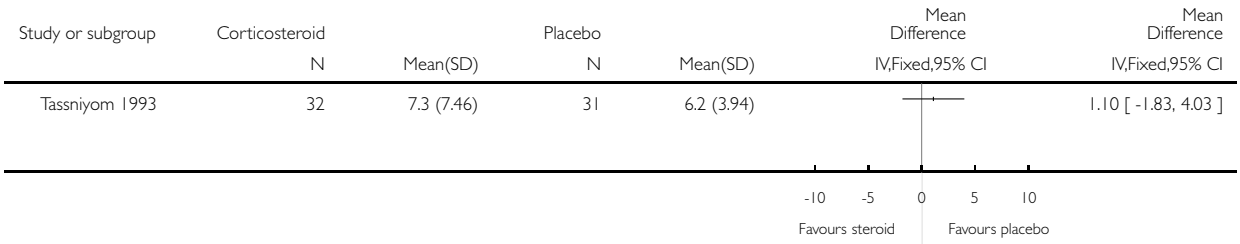


Analysis 1.4. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 4 Days in hospital.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 4 Days in hospital



ADDITIONAL TABLES

Table 1. Risk of bias assessment

Trial	Allocation sequence generation	Allocation concealment	Blinding	Inclusion[a]
Min 1975	Unclear	Unclear	"double blind"	Adequate
Pongpanich 1973	Unclear	Inadequate	None	Inadequate
Sumarmo 1982	Unclear	Unclear	"double blind"	Adequate
Tassniyom 1993	Adequate	Unclear	"double blind"	Adequate

[a] Inclusion of all randomized participants in the final analysis.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	adrenal cortex hormone	adrenal cortex hormone	exp DENGUE	exp DENGUE	dengue
2	corticosteroids	corticosteroids	dengue	dengue	corticosteroids
3	hydrocortisone	hydrocortisone	HEMORRAGIC FEVER	HEMORRAGIC FEVER	dexamethasone
4	dexamethasone	dexamethasone	hemorrhagic fever	hemorrhagic fever	prednisolone
5	methylprednisolone	methylprednisolone	('break-bone fever'). ti,ab	('break-bone fever'). ti,ab	2 or 3 or 4
6	prednisolone	prednisolone	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	1 and 5
7	hemorrhagic fever	hemorrhagic fever	ADRENAL CORTEX HORMONES	adrenal cortex hormones	-
8	dengue fever	dengue fever	corticosteroids	corticosteroids	-
9	-	-	steroid*	steroid$	-
10	-	-	cortisol*	cortisol$	-
11	-	-	HYDROCORTISONE	HYDROCORTISONE	-
12	-	-	hydrocortisone	hydrocortisone	-
13	-	-	DEXAMETHASONE	DEXAMETHASONE	-
14	-	-	dexamethasone	dexamethasone	-
15	-	-	METHYLPREDNISOLONE	METHYLPREDNISOLONE	-
16	-	-	methylprednisolone	methylprednisolone	-
17	-	-	PREDNISOLONE	PREDNISOLONE	-
18	-	-	prednisolone	prednisolone	-

(*Continued*)

19	-	-	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	-
20	-	-	6 and 19	6 and 19	-
21	-	-	Limit 20 to human	Limit 20 to human	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005; upper case: MeSH or EMTREE heading; lower case: free text term.

WHAT'S NEW

Last assessed as up-to-date: 8 January 2006.

Date	Event	Description
12 August 2009	New search has been performed	New search conducted; no new trials for inclusion

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2006

Date	Event	Description
19 September 2008	Amended	Converted to new review format with minor editing.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the review, extraction of the data, analysis, and interpretation of the results.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Chiang Mai University, Thailand.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The intravenous fluid requirement during the period of shock and blood transfusion were added as secondary outcomes measures as they are important supportive treatments in both groups. The amounts of fluids and blood requirements should be compared if they reported.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Blood Transfusion [utilization]; Dengue Hemorrhagic Fever [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans