Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial

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Summary

Background **Corticosteroids have been used to treat head injuries for more than 30 years. In 1997, findings of a systematic review suggested that these drugs reduce risk of death by 1–2%. The CRASH trial—a multicentre international collaboration—aimed to confirm or refute such an effect by recruiting 20 000 patients. In May, 2004, the data monitoring committee disclosed the unmasked results to the steering committee, which stopped recruitment.**

Methods **10 008 adults with head injury and a Glasgow coma score (GCS) of 14 or less within 8 h of injury were randomly allocated 48 h infusion of corticosteroids (methylprednisolone) or placebo. Primary outcomes were death within 2 weeks of injury and death or disability at 6 months. Prespecified subgroup analyses were based on injury severity (GCS) at randomisation and on time from injury to randomisation. Analysis was by intention to treat. Effects on outcomes within 2 weeks of randomisation are presented in this report. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN74459797.**

Findings **Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21·1%] *vs* 893 [17·9%] deaths; relative risk 1·18 [95% CI 1·09–1·27]; p=0·0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0·22) or time since injury (p=0·05).**

Interpretation **Our results show there is no reduction in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear.**

Introduction

Every year, millions of people worldwide are treated for head injury. A substantial proportion die or are permanently disabled. Although much damage is done at the time of injury, post-traumatic inflammatory changes are believed to contribute to neuronal degeneration.[1,2] Corticosteroids have been used to treat head injury for more than 30 years. A survey of UK neurosurgical intensive-care units in 1996 showed that these drugs were used in 14% of units to treat head injuries,[3] and a survey of intensive-care management of patients with a head injury in the USA reported that corticosteroids were used in 64% of trauma centres.[4] Corticosteroids are also used for management of head injury in Asia.[5]

Previous randomised trials of corticosteroids in head injury have included no more than a few hundred patients, and altogether only about 2000 patients have been studied. In 1997, a systematic review of available trials suggested that the absolute risk of death in the corticosteroid-treated group was about 1–2% lower than in controls, but the 95% CI was from 6% fewer to 2% more deaths.[6]

The second US National Acute Spinal Cord Injury Study (NASCIS-2) compared 24 h of methylprednisolone with placebo in 333 patients with acute spinal-cord injury.[7] At 6 months, people receiving methylprednisolone within 8 h of injury seemed to have greater improvement in motor function and sensation to pinprick and touch than did those given placebo. Similar results were reported in a Japanese trial of the same regimen.[8] Results of NASCIS-3 indicated slightly more neurological recovery with 48 h of treatment than with 24 h.[9] Use of corticosteroids to treat acute spinal-cord injury led to renewed interest in their role in the treatment of head injury.[10]

The CRASH trial (corticosteroid randomisation after significant head injury) is a large, international, randomised placebo-controlled trial of the effect of early administration of 48 h infusion of methylprednisolone on risk of death and disability after head injury. The trial aimed to inform clinical decision-making in an area of increasing global health importance. Reliable demonstration of even a small absolute benefit from corticosteroids would have the potential to avoid thousands of deaths and disabilities. Similarly, because corticosteroids are widely used to treat head injury, reliable refutation of any benefit would protect thousands of patients from possible side-effects and avoid unnecessary cost.

Patients and methods

The protocol for the CRASH trial has been published elsewhere (http://www.crash.lshtm.ac.uk). All collaborating investigators were required to secure local ethics or research committee approval before recruitment could begin. Patients with clinically significant head injury are

unable to give valid informed consent. Local ethics committees set consent procedures for participating hospitals. Some allowed consent waiver and others consent from a legal representative. We always adhered to these requirements.

Patients

Adults (age 16 years or older) with head injury were screened for inclusion in the study if they were within 8 h of injury and were noted in hospital to have a Glasgow coma score (GCS) of 14 or less (maximum score 15).[11] Such patients were eligible if, after assessment, the treating doctor was substantially uncertain whether or not to treat with corticosteroids—ie, the uncertainty principle. Thus, if we noted a clear indication for corticosteroids, the patient was not randomised. Likewise, those we judged to have a clear contraindication were not randomised.

Procedures

We randomised patients in one of two ways. If the hospital had reliable telephone access and the recruiting doctor could provide baseline data and receive the treatment allocation in English then they used the central telephone randomisation service provided by the clinical trial service unit (CTSU) in Oxford, UK. During the call, which lasted 2–3 min, we obtained and recorded baseline data on the central computer. Data were checked for range and consistency and only after they were complete did the computer generate a treatment allocation. The allocation was balanced for sex, age (16–24 years, 25–34 years, 35 years and older), time since injury (≤1 h, >1 to ≤3 h, >3 to ≤8 h), GCS (severe 3–8, moderate 9–12, mild 13–14), pupil reactiveness, and country.[12] The allocated treatment pack number was then given to the recruiting doctor and recorded on the trial entry form.

Hospitals at which use of this central randomisation was not feasible used a local pack system. We obtained baseline information on the trial entry form and the next consecutively numbered treatment pack was taken from a box of eight packs—with an allocation sequence based on a block size of eight, also generated by CTSU. The pack number was recorded on the form, which was then sent by fax or as an encrypted e-mail attachment to the trial coordinating centre in London. We then entered data into the central computer at CTSU. Once the pack number was recorded, the patient was included in the trial whether or not the pack was opened or the allocated treatment started.

An independent clinical trial supply company (DHP Clinical Supplies, Abergavenny, UK) prepared the treatment packs. We randomly allocated patients to 48 h infusion of either methylprednisolone or placebo. Every participant was assigned a uniquely numbered treatment pack, containing 11 vials of either methylprednisolone or placebo, one 20 mL ampoule of sterile water, one 100 mL bag of 0·9% NaCl (for use with the loading dose), CRASH trial stickers to attach to the infusion bags and patient's notes, a patient's information leaflet in the appropriate language, and two copies of the form for collection of early outcome data. We translated the stickers and early outcome forms into local languages if needed. The loading dose was 2 g methylprednisolone (or placebo) over 1 h in a 100 mL infusion. The maintenance dose was 0·4 g methylprednisolone (or placebo) per h for 48 h in a 20 mL per h infusion. The methylprednisolone and placebo vials were identical and the solutions looked the same. This treatment regimen was based on that used in the NASCIS trials,[9] but fixed doses were used to simplify procedures. Emergency unmasking of treatment allocation was possible by telephoning the randomisation service in Oxford or via a call to the 24 h emergency pager.

Primary outcome measures were death from any cause within 2 weeks of injury and death or disability at 6 months. We obtained mortality data within 2 weeks of injury from the early outcome form that was completed at death, discharge, or at 2 weeks, whichever happened first. These data were obtained electronically (with electronic data forms and the CRASH-Net website [http://crashnet.lshtm.ac.uk]) and by fax and post. The early outcome form included patient's contact details, cause of injury, short-term outcome, management and complications, results from the first computerised tomography (CT) scan, and adherence to trial treatment. Data on management and complications included number of days in intensive care and occurrence of seizure, haematemesis or melaena requiring transfusion, wound infection with pus, pneumonia treated with antibiotics, use of antibiotics for other reasons, whether the patient had a neurosurgical operation, and whether they had sustained major extracranial injury. Events were recorded if they arose while the patient was still in hospital and within 14 days of randomisation. Non-fatal events happening after discharge but within 14 days of randomisation were not recorded.

We assessed disability at 6 months with a questionnaire that was mailed to patients or their carers, administered by telephone interview, or undertaken during a home visit or hospital appointment. Before the start of the trial, a simple questionnaire version of the Glasgow outcome scale was developed and shown to be both reliable and valid.[13,14] The questionnaire was translated into relevant languages for use in every country, with back-translation into English to ensure accuracy. Completed questionnaires were sent to the coordinating centre in London to be entered into the trial database.

With respect to prespecified subgroup analyses, we planned to report the effects of treatment subdivided by two main baseline characteristics of patients: time from injury to randomisation (≤1 h, >1 to ≤3 h, >3 to ≤8 h)

and severity of head injury based on the GCS at randomisation (severe 3–8, moderate 9–12, mild 13–14).

Statistical analysis

We initially estimated that risk of death in patients allocated to placebo might be around 15%. Because even a 2% survival difference would be clinically important, the trial had to be large enough to detect a difference of this size. A trial of 20 000 patients would have a good chance of showing a 2% survival difference at convincing levels of significance—ie, more than 90% power to achieve $p<0\cdot01$. All analyses were undertaken on an intention-to-treat basis, that is, patients were analysed on the basis of the group to which they were randomised, irrespective of whether they actually received their allocated treatment. Effect measures were relative risk and absolute risk reduction. Precision was quantified with 95% CIs for overall risk and 99% CIs for subgroup results. We assessed homogeneity in treatment effects within subgroups by the χ^2 test at a 5% significance level.

During the study, interim analyses of in-hospital mortality, complications, and 6-month outcome were supplied at least once a year to the independent data monitoring and ethics committee. This committee had responsibility for deciding whether, while randomisation was in progress, the unmasked results should be revealed to the trial steering committee. The data monitoring and ethics committee terms of reference stated that they would unmask results only if the randomised comparisons in the trial provided both (1) proof beyond reasonable doubt of a difference in outcome between the study and control groups and (2) evidence that would be expected to alter substantially the choice of treatment for patients whose doctors were, in view of data from other randomised controlled trials, substantially uncertain whether to give corticosteroids to patients with head injury.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN74459797. The protocol for this study was peer-reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer-review the primary clinical manuscript.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled in 239 hospitals from 49 countries: 2141 (21%) were enrolled by central telephone randomisation and 7867 (79%) were non-centrally randomised. The first patient was enrolled in

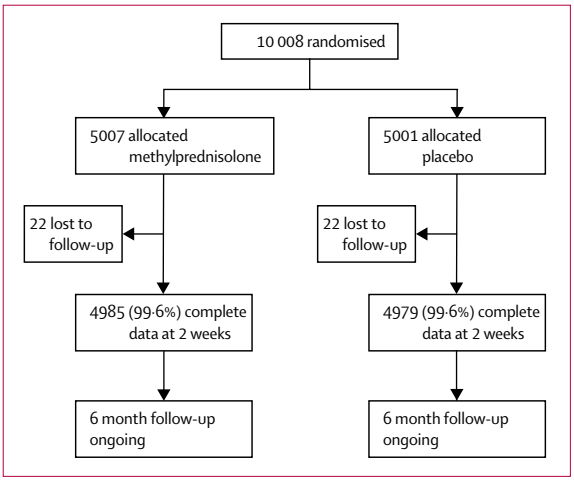

Figure 1: **Trial profile**
The number of people screeened before randomisation and excluded because of a clear contraindication or indication for corticosteroids is unknown, because these data were not available from every hospital.

	Corticosteroid (n=5007)	Placebo (n=5001)
Age at randomisation (years)		
<25	1481 (30%)	1450 (29%)
25–34	1151 (23%)	1217 (24%)
35–54	1554 (31%)	1485 (30%)
⩾55	821 (16%)	849 (17%)
Men	4075 (81%)	4029 (81%)
GCS		
Severe (3–8)	1985 (40%)	1981 (39%)
Moderate (9–12)	1557 (31%)	1483 (30%)
Mild (13–14)	1465 (29%)	1537 (31%)
Time since injury (h)		
⩽1	1350 (27%)	1347 (27%)
>1 to ⩽3	1532 (31%)	1567 (31%)
>3 to ⩽8*	2125 (42%)	2087 (42%)
Both pupils reactive to light		
No	722 (14%)	728 (15%)
Yes	4285 (86%)	4273 (85%)
Major extracranial injury	1134 (23%)	1082 (22%)
Cause of head injury		
Road traffic crash	3249 (65%)	3169 (63%)
Fall >2 m	608 (12%)	699 (14%)
Other	1085 (22%)	1053 (21%)
Not known	65 (1%)	80 (2%)
Head CT scan done		
Yes	3916 (78%)	3896 (78%)
No/not known	1091 (22%)	1105 (22%)
CT scan results†		
Normal	897 (23%)	878 (22%)
One or more petechial haemorrhages within the brain	1139 (29%)	1098 (28%)
Obliteration of the third ventricle or basal cisterns	906 (23%)	920 (24%)
Subarachnoid bleed	1226 (31%)	1231 (32%)
Midline shift >5 mm	556 (14%)	579 (15%)
Non-evacuated haematoma	1061 (27%)	1050 (27%)
Evacuated haematoma	486 (12%)	500 (13%)
Cortical contusion >1 cm in diameter‡	869 (22%)	886 (23%)

*Includes 21 patients randomised more than 8 h after injury. †Percentages shown are of patients who had a CT scan; patients may have more than one result. ‡Cortical contusion as a CT-reporting category was introduced after randomisation started.

Table: **Baseline characteristics**

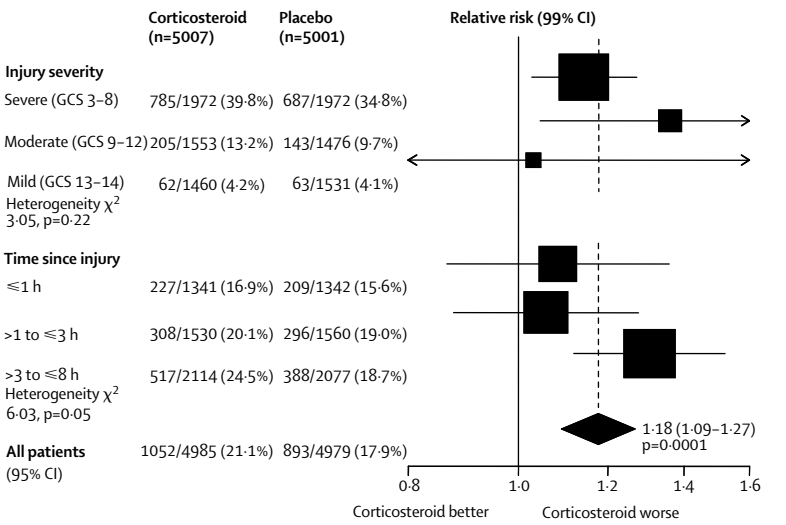

Figure 2: **Effects of corticosteroid allocation on deaths from all causes within 2 weeks, by injury severity (based on GCS at randomisation) and time since injury**

April, 1999. In May, 2004, the data monitoring and ethics committee disclosed the unmasked results to the trial steering committee, which then stopped recruitment. 10 008 patients were randomised to corticosteroid or placebo infusions (figure 1): 62 were subsequently found to be younger than 16 years of age, 21 were enrolled more than 8 h after injury, and the trial infusion was stopped in three at the request of a relative. All these patients are included in the analysis.

The table shows baseline data for all patients randomised. Mean age of participants was 37 years (SD 17) and median time from injury to randomisation was 3 h (IQR 1–5). Treatment groups were balanced with respect to patients' characteristics and presence of major extracranial injuries, cause of injury, and head CT scan results.

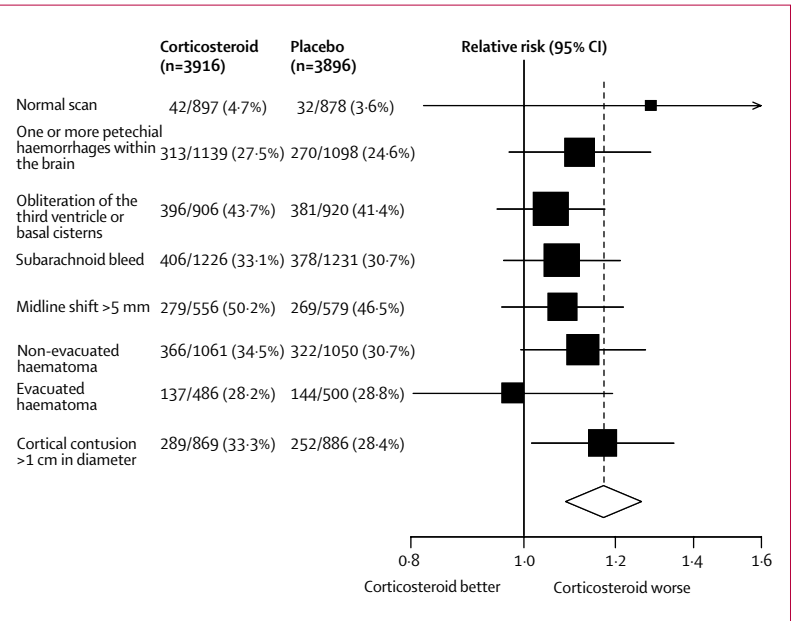

Figure 3: **Effects of corticosteroid allocation on deaths from all causes within 2 weeks, by head CT scan results**
Subgroups are not mutually exclusive because some patients are included in more than one category.

Adherence to treatment was known for 9848 (98%) patients, of whom 9748 (99%) received the full loading dose. Although some patients died or were discharged from hospital before completion of the full 48 h maintenance dose, 8286 (83%) patients received at least 24 h of treatment.

Mortality data during the first 2 weeks were obtained for 9964 patients. Of 4985 patients allocated corticosteroids whose outcomes were known, 1052 (21%) died within 2 weeks of randomisation, compared with 893 (18%) of 4979 allocated placebo. Thus, the relative risk of death from all causes within 2 weeks in patients allocated corticosteroids compared with placebo was 1·18 (95% CI 1·09–1·27; p=0·0001; figure 2). The relative risk of death at 2 weeks did not differ by injury severity (p=0·22) or time since injury (p=0·05; figure 2).

7812 (78%) patients had a head CT scan. The relative risk of death at 2 weeks was not different in any of the eight CT scan diagnosis subgroups examined (figure 3). Furthermore, the relative risk of death within 2 weeks did not differ in patients with (321/1134 [28%] corticosteroid *vs* 244/1082 [23%] placebo) and without (731/3851 [19%] *vs* 649/3897 [17%]; p=0·27) major extracranial injury. We did not record an increase in complications with corticosteroid allocation (figure 4).

Treatment allocation was unmasked for 24 (0·2%) patients (15 corticosteroid, nine placebo). The usual reason for emergency unmasking was that patients were subsequently found to have a disorder that the doctor wished to treat with corticosteroids.

Discussion

The results of the MRC CRASH trial of methylprednisolone treatment reliably refute any reduction in mortality in the 2 weeks after head injury: this treatment was associated with a significant rise in risk of death within 2 weeks. The apparent increase in mortality did not differ in the prespecified subgroups, although the hazard might be enhanced in patients presenting at a later time. Although the apparent hazard could be a statistical artifact, due in part to the data-dependent stopping of the trial,[15] we believe that our results provide evidence that could substantially alter the choice of treatment for patients with head injury. For this reason, we opted for early publication of the 2-week outcome data. The effect of corticosteroids on disability at 6 months will be reported later.

Our study has many strengths. Our randomisation methods ensured that participating clinicians could not have foreknowledge of treatment allocation and that baseline prognostic factors were well balanced between treatment groups. Data on the primary outcome of death

from any cause within 2 weeks were available for more than 99% of randomised patients, and all analyses were undertaken on an intention-to-treat basis. The CRASH trial had sufficient power to reliably detect modest but nevertheless clinically important treatment benefits or harms. It was undertaken in more than 200 hospitals in 49 countries. The patients included would have undergone several concurrent interventions that would have varied between hospitals. We did not obtain data on all concurrent interventions, but similar numbers of patients in every hospital were allocated corticosteroids or placebo. Furthermore, because doctors were unaware of treatment allocation, use of concomitant therapies would not have been influenced.

The CRASH trial had one limitation. To establish the main cause of death is difficult when multiple factors relating to trauma are present, so we did not ask participating clinicians what they judged to be the cause of death. We saw no evidence of a large rise in risk of infectious complications or gastrointestinal bleeding from corticosteroid treatment. We are still unsure of the mechanism of the increased mortality with corticosteroids.

Before starting the CRASH trial, a systematic review and meta-analysis of the existing trials of corticosteroids in head injury was done. When all previous trials were combined, risk of death in the corticosteroid-treated group seemed lower than in the control group (relative risk 0·96 [95% CI 0·85–1·08]; figure 5). When this meta-analysis is updated to include the findings of the CRASH trial, risk of death in the corticosteroid-treated group seems to be higher than in the control group (1·12 [1·05–1·20]). The CRASH trial result, judged either separately or in combination with previous trials, clearly refutes any material reduction in mortality with corticosteroids, although the size of the CRASH trial has a major influence on the result of the meta-analysis. We noted some statistical heterogeneity in the updated meta-analysis that might be accounted for by the data-dependent stopping of the trial.[15]

Our early results show that corticosteroids should not be used routinely to treat head injury, whatever the severity. By clearly refuting a mortality benefit from corticosteroids in head injury, the CRASH trial results should protect many thousands of patients from any increased risk of death associated with these drugs. However, our results could also have implications for use of corticosteroids in spinal-cord injury. After publication of NASCIS-2,[7] in which some evidence of neurological benefit was seen in the subgroup of patients with spinal-cord injury treated within 8 h, corticosteroids have been widely used to treat this type of injury, although this approach is controversial.[16,17] Because trials of corticosteroids in spinal-cord injury have been small (even when combined they include about 500 patients),[18] and because of the emphasis on subgroup effects, use of corticosteroids in spinal-cord injury should remain an area for debate.

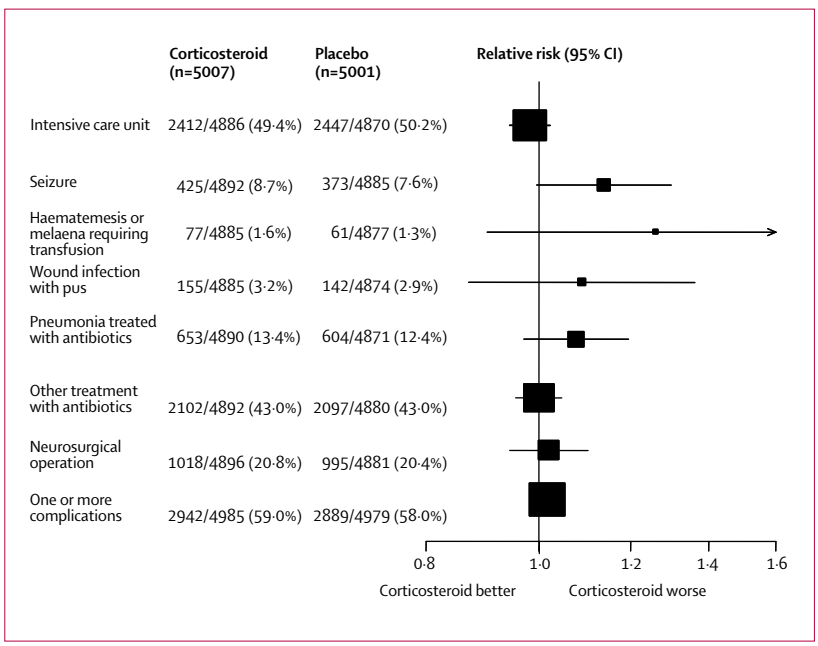

Figure 4: **Effects of corticosteroid allocation on early management and complications in hospital within 2 weeks**
Denominators vary because of different levels of data completeness for every event.

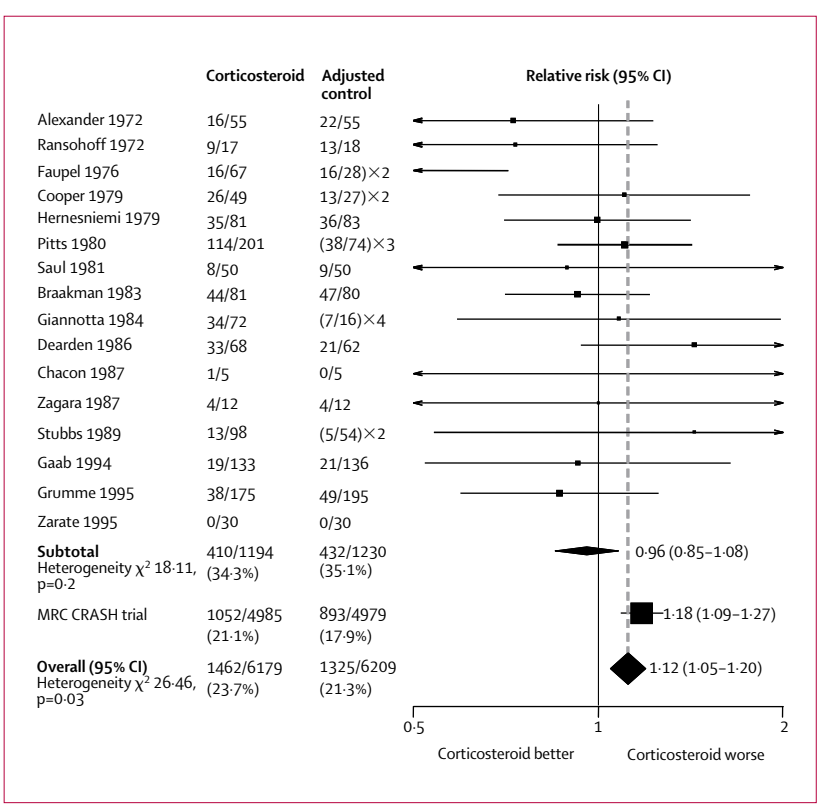

Figure 5: **Updated meta-analysis of effect of corticosteroids on death after head injury**
In five trials there was an imbalance in the numbers of patients allocated corticosteroids compared with those allocated placebo. The control group data for these trials have therefore been adjusted so that when combined with the other trials, the overall estimate of risk of death is comparable with that in the corticosteroid-allocated group. References of trials included in this meta-analysis are available at http://image.thelancet.com/extras/04art9140webreferences.pdf.

The effect of corticosteroid treatment on disability 6 months after head injury will be reported as soon as these data are available. Many other treatments of uncertain effectiveness for head injury are in widespread use,[19] and further large-scale randomised trials are needed. The CRASH trial has shown that we can enrol many trauma patients into clinical trials in the emergency setting. Every year, about 3 million people worldwide die from trauma, many after reaching hospital.[20] Of those who do survive to reach hospital, blood loss accounts for nearly half of in-hospital trauma deaths.[21] Hypotension from such loss is one of the strongest predictors of poor outcome after head injury that is amenable to therapeutic modification.[22] A large placebo-controlled trial of the effects of an antifibrinolytic drug on death and transfusion requirements in patients with clinically significant haemorrhage after trauma is in progress (http://www.crash2.lshtm.ac.uk).

Conflict of interest statement

We declare that we have no conflict of interest.

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Indonesia (238)—Sanglah General Hospital (222): Nyoman Golden NC, Sri Maliawan; Sidoarjo General Hospital (14): Achmad Fauzi, Umar Farouk.

Iran (233)—Naghavi University Hospital (110): Esmaeel Fakharian, Amir Aramesh; Fatemeh Zahra Hospital (85): Maasoumeh Eghtedari, Farhad Ahmadzadeh, Alireza Gholami; Social Security Hospital (38): Maasoumeh Eghtedari, Farhad Ahmadzadeh.

Ireland (113)—St James's Hospital (113): Patrick Plunkett, Catherine Redican, Geraldine McMahon.

Italy (9)—Università Cattolica del Sacro Cuore (4): Maria Giuseppina Annetta; Università di Firenze (3): Homère Mouchaty; Ospedale San Martino (2): Eros Bruzzone.

Ivory Coast (3)—CHU de Cocody (3): Béatrice Harding.

Kenya (2)—Aga Khan Hospital (2): Mahmood Qureshi.

Malaysia (176)—Hospital University Science Malaysia (162): Zamzuri Idris, Jafri Abdullah NC, Ghazaime Ghazali, Abdul Rahman Izaini Ghani; Ipoh Specialist Hospital (14): Fadzli Cheah.

Mexico (17)—Alfredo Cabrera NC; Hospital General Regional no 1 (12): José Luis Mejía González; Hospital General de Queretaro (4): José Luis Mejía González; Hospital General Regional no 25 (1): Jorge Loría-Castellanos.

New Zealand (43)—Dunedin Hospital (43): Suzanne Jackson, Robyn Hutchinson.

Nigeria (180)—Obafemi Awolowo University Teaching Hospitals (77): Edward Komolafe NC, Augustine Adeolu, Morenikeji Komolafe; Lagos University Teaching Hospital (43): Olusanya Adeyemi-Doro, Femi Bankole; Usmanu Danfodiyo University Teaching Hospital (36): Bello Shehu, Victoria Danlami; University of Ilorin Teaching Hospital (15): Olugbenga Odebode; Lautech Teaching Hospital (7): Kehinde Oluwadiya; Lagos State University Teaching Hospital (1): Ahmed Sanni; Seventh Day Adventist Hospital (1): Herb Giebel; St Stephen's Hospital (1): Sushil Kumar.

Pakistan (17)—Jinnah Postgraduate Medical Centre (17): Rashid Jooma.

Panama (7)—Complejo Hospitalario M A Guerrero (7): Jose Edmundo Mezquita.

Paraguay (10)—Instituto de Prevision Social (10): Carlos Ortiz Ovelar.

Peru (8)—Hospital Nacional "Dos de Mayo" (6): Marco Gonzales-Portillo; Hospital Nacional Arzobispo Loayza (2): Diana Rodriguez NC.

Romania (319)—Spitalul Clinic de Urgenţă Bucureşti (282): Laura Balica NC, Bogdan Oprita, Mircea Sklerniacof, Luiza Steflea, Laura Bandut; Sfantum Pantelimon Hospital (28): Adam Danil, Remus Iliescu; Prof Dr D Bagdasar Clinical Emergency Hospital (9): Jean Ciurea.

Saudi Arabia (32)—King Khalid University Hospital (24): Abdelazeem El-Dawlatly, Sherif Alwatidy; King Khalid National Guard Hospital (8): Walid Al-Yafi; Megahid El-Dawlatly.

Serbia (23)—Klinicki Centar Srbije (23): Ranka Krunic-Protic, Vesna Janosevic.

Singapore (23)—National Neuroscience Institute (21): James Tan NC; Changi General Hospital (2): Charles Seah.

Slovakia (179)—Reiman Hospital (71): Štefan Trenkler NC, Matuš Humenansky, Tatiana Stajančová; NsP Poprad (39): Ivan Schwendt, Anton Laincz; Nemocnica Bojnice (25): Zeman Julius, Stano Maros; FNsP Kosice (12): Jozef Firment; NsP Trebisov (11): Maria Cifraničova; Faculty Hospital in Martin (10): Beata Sániová; NsP Ruzinov (4): Karol Kalig; NsP Nové Zámky (3): Soňa Medekova; NsP Liptovsky Mikulas (2): Radovan Wiszt; NsP F D Roosevelt (1); NsP Zilina (1): Ivan Mačuga.

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Spain (259)—Hospital Universitario Virgen del Rocio (133): Angeles Muñoz-Sánchez NC, Francisco Murillo-Cabezas NC, Juan Flores-Cordero, Dolores Rincón-Ferrari; Hospital Torrecárdenas (37): Martin Rubi, Lopez Caler; Hospital Universitario Germans Trias i Pujol (32): Maite Misis del Campo, Luisa Bordejé Laguna; Hospital Mútua de Terrassa (20): Juan Manuel Nava; Hospital Universitario de Girona Dr Josep Trueta (12): Miguel Arruego Minguillón; Hospital Carlos Haya (10): Alfonso Muñoz Lopez; Hospital General de La Palma (6): Luis Ramos-Gómez; Hospital Universitario Virgen de la Victoria (5): Victoria de la Torre-Prados; Hospital General Yagüe (4): Romero Pellejero.

Sri Lanka (132)—Batticaloa General Hospital-Médecins Sans Frontières (84): Véronique Laloë NC, Bernhard Mandrella, Suganthan; National Hospital of Sri Lanka (39): Sunil Perera; Point-Pedro Base Hospital (9): Véronique Laloë, Kanapathipillai Mahendran.

Switzerland (160)—University Hospital of Zurich (133): Reto Stocker NC, Silke Ludwig NC; University Hospital Bern (15): Heinz Zimmermann; Kantonsspital Schaffhausen (12): Urs Denzler.

Thailand (579)—Khon Kaen Regional Hospital (535): Surakrant Yutthakasemsunt NC, Warawut Kittiwattanagul; Parnumas Piyavechvirat; Pojana Tapsai; Ajchara Namuang-jan; Chiangrai Prachanuko Hospital (12): Upapat Chantapimpa; Rayong Hospital (11): Chanothai Watanachai, Pusit Subsompon; Krabi Hospital (10): Wipurat Pussanakawatin, Pensri Khunjan; Suratthani Hospital (8): Sakchai Tangchitvittaya, Somsak Nilapong; Roi-Et Hospital (2): Tanagorn Klangsang, Wibul Taechakosol; Lampang Hospital (1): Atirat Srinat.

Tunisia (63)—Hospital Habib Thameur (63): Zouheir Jerbi NC, Nebiha Borsali-Falfoul, Monia Rezgui.

Turkey (2)—Istanbul Medical Faculty (2): Nahit Cakar.

Uganda (43)—Makerere Medical School (43): Hussein Ssenyonjo, Olive Kobusingye.

UK (1391)—Hope Hospital (209): Gabrielle Lomas, David Yates, Fiona Lecky; Birmingham Heartlands Hospital (123): Anthony Bleetman, Alan Baldwin, Emma Jenkinson, Shiela Pantrini; North Manchester General Hospital (85): James Stewart, Nasreen Contractor, Trudy Roberts, Jim Butler; Royal Albert Edward Infirmary (83): Alan Pinto, Diane Lee; Colchester General Hospital (79): Nigel Brayley, Karly Robbshaw, Clare Dix; Whiston Hospital (69): Sarah Graham, Sue Pye; Selly Oak Hospital (61): Marcus Green, Annie Kellins; Royal Bolton Hospital (51): Chris Moulton, Barbara Fogg; Eastbourne District General Hospital (50): Rowland Cottingham, Sam Funnell, Utham Shanker; Trafford General Hospital (41): Claire Summers, Louise Malek; Royal Sussex County Hospital (38): Rowland Cottingham NC, Christopher Ashcroft, Jacky Powell; Countess of Chester Hospital (36): Steve Moore, Stephanie Buckley; Worthing Hospital (34): Mandy Grocutt, Steve Chambers; Medway Maritime Hospital (29): Amanda Morrice, Helen Marshall; Chelsea and Westminster Hospital (28): Julia Harris, Wendy Matthews, Jane Tippet; Furness General Hospital (27): Simon Mardell, Fiona MacMillan, Anita Shaw; Royal Oldham Hospital (26): Pramod Luthra, Gill Dixon; Stepping Hill Hospital (26): Mohammed Ahmed, John Butler, Mike Young; Northern General Hospital (25): Sue Mason, Ian Loveday; Blackburn Royal Infirmary (23): Christine Clark, Sam Taylor; Cheltenham General Hospital (23): Paul Wilson; Fairfield General Hospital (23): Kassim Ali, Stuart Greenwood; Queen Elizabeth the Queen Mother Hospital (21): Martin White, Rosa Perez; Ninewells Hospital and Medical School (19): Sam Eljamel; Queen Elizabeth Hospital Birmingham (18):

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NC=national coordinator. RC=regional coordinator.

CRASH trial coordination

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