The ADRENAL study protocol: ADjunctive corticosteroid tREatment iN criticAlly ilL patients with septic shock

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ABSTRACT

Background: There is considerable global uncertainty on the role of low-dose corticosteroids in septic shock, which translates into variations in prescribing practices.

Objective: To describe the protocol for a large-scale multicentre randomised controlled trial in critically ill patients with septic shock, comparing the effects of hydrocortisone and placebo (in addition to standard treatment) on 90-day mortality and other outcomes such as shock reversal, duration of mechanical ventilation and quality of life.

Methods: We will recruit 3800 critically ill patients with septic shock treated in an intensive care unit, to concealed, randomised, parallel assignment of hydrocortisone or placebo. The primary outcome will be all-cause mortality at 90 days postrandomisation. Secondary outcomes will include ICU and hospital mortality, length of ICU stay and quality of life at 6 months. Subgroup analyses will be conducted in two predefined subgroups. All analyses will be conducted on an intention-to-treat basis.

Results and conclusions: The run-in phase has been completed and the main trial commenced in February 2013. The trial should generate results that will inform and influence prescribing of corticosteroids in septic shock.

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Globally, septic shock is a major cause of mortality and its incidence continues to increase.[1] Mortality rates in the control arms of randomised controlled trials (RCTs) of septic shock range from 33%–53%.[2-5] The accepted principles of therapy for septic shock include prompt resuscitation and administration of antibiotics, source control, intravenous (IV) fluid therapy and organ system support with vasopressor drugs, mechanical ventilation and renal replacement therapy as required. The role of low-dose corticosteroids (LDC) in septic shock remains controversial. Evidence from RCTs in the late 1980s showed that high-dose methylprednisolone (30 mg/kg), although effective in reversing shock, did not reduce mortality in patients with sepsis and that treatment with high-dose corticosteroids was associated with increased risk of death from superinfection.[6-9]

More recent RCTs have consistently shown that treatment with lower doses of corticosteroids, typically hydrocortisone 200 mg every 24 hours, results in more rapid reversal of shock.[10,11] This finding has been reported in all RCTs of low-dose hydrocortisone in patients with septic shock.[12] Concomitant with these findings was the observation that patients with a reduced cortisol response to an exogenous stimulation test with synthetic adrenocorticotrophic hormone (ACTH) (non-responders) had a higher mortality in severe sepsis.[13] This gave rise to the concept of relative adrenal insufficiency (RAI) that may be contributory to adverse outcomes.[14]

Effect of corticosteroids on mortality in septic shock

The findings of improved vasopressor responsiveness and a trend towards lower mortality with supplemental corticosteroids, coupled with the potential adverse effects of RAI, provided justification for trials examining the effect of corticosteroids on mortality of patients with septic shock. Two international multicentre RCTs produced divergent results.[10,15] The French study ($n = 299$)[10] found that shock was reversed more rapidly in patients receiving hydrocortisone and, although overall landmark mortality was not reduced, the investigators reported improved survival in patients with a reduced response to corticotrophin (non-responders) (mortality, 63% versus 53%; 95% CI, 0.47–0.95; $P = 0.02$). However, etomidate was used in at least 24% of the patients. Etomidate is a short-acting IV anaesthetic agent that selectively inhibits adrenal corticosteroid synthesis due to a concentration-dependent blockade of the two mitochondrial cytochrome P450-dependent enzymes, cholesterol side chain cleavage enzyme and 11 beta-hydroxylase.[16,17] Its use may explain the unexpectedly high number of patients who did not respond to corticotropin, and whether the trial results apply in health care systems such as Australia, where etomidate is not licensed or its availability for use is not known. Moreover, patients assigned to receive hydrocortisone also received fludrocortisone. The role of this additional mineralocorticoid was unclear.

The Pan-European multicentre Corticosteroid Therapy of Septic Shock study (CORTICUS) examined the efficacy of

Table 1. Inclusion and exclusion criteria for enrolment in the ADRENAL* study

Inclusion criteria

Patients receiving treatment in the intensive care unit are eligible for recruitment if they meet all the following criteria:

1. Patient is aged 18 years or older
2. Patient has a documented infection site or there is a strong suspicion of infection
3. Two of the four clinical signs of the systemic inflammatory response syndrome are present:
   - core temperature > 38°C or < 36°C
   - heart rate > 90 beats per minute
   - respiratory rate > 20 breaths per minute, or $PaCO_2$ < 32 mmHg, or mechanical ventilation
   - white cell count > 12×10^9/L or < 4×10^9/L or > 10% immature neutrophils.
4. Patient is being treated with mechanical ventilation at the time of randomisation (including non-invasive ventilation modes such as bilevel positive airway pressure or continuous positive airway pressure)
5. Patient is being treated with continuous vasopressors or inotropes to maintain systolic blood pressure > 90 mmHg, or mean arterial blood pressure (MAP) > 60 mmHg, or a MAP target set by the treating clinician for maintaining perfusion
6. Administration of vasopressors or inotropes for ⩾ 4 hours and at the time of randomisation.

Exclusion criteria

Patients are excluded from the study if they meet one or more of the following exclusion criteria:

1. Patient met all inclusion criteria > 24 hours ago
2. Clinician expects to prescribe systemic corticosteroids for an indication other than septic shock (not including nebulised or inhaled corticosteroid)
3. Patients treated with etomidate
4. Patient is receiving treatment with amphotericin B for systemic fungal infections at time of randomisation
5. Patient has documented cerebral malaria at the time of randomisation
6. Patient has documented strongyloides infection at the time of randomisation
7. Death is deemed inevitable or imminent during this admission and the attending doctor, patient or legally recognised surrogates are not committed to active treatment
8. Death from underlying disease is likely within 90 days
9. Patient has been previously enrolled in the ADRENAL study.

* ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock.

low-dose hydrocortisone (200 mg/day) compared with placebo in 499 patients with septic shock.[15] The study did not find a significant difference in mortality in patients assigned to the steroid versus placebo groups (34% versus 31%). An important limitation shared by both studies was that they were powered on the basis of large effect sizes. They consequently lacked adequate statistical power to demonstrate a smaller realistic difference attributable to the therapy being tested.

A meta-analysis[12] of 17 trials with 2138 patients reported reduced mortality in patients with septic shock treated with hydrocortisone. The 28-day mortality was 388 of 1099 versus 400 of 1039 (35.3% versus 38.5%; relative risk [RR], 0.84; 95% CI, 0.71–1.00; $P = 0.05$). Subgroup analysis of the 12 randomised trials investigating low-dose corticosteroid treatment ($n = 1228$) published between 1998 and 2009 reported that 28-day mortality for treated patients versus control patients was 236 of 629 versus 264 of 599 (37.5% versus 44.1%; RR, 0.84; 95% CI, 0.72–0.97; $P = 0.02$). Trends in smaller studies and meta-analyses point to reduced mortality in patients with septic shock treated with corticosteroids, but the uncertainty engendered by the two largest RCTs to date has led to a lack of consensus among intensive care specialists about the role of hydrocortisone in the treatment of patients with septic shock.

This uncertainty directly translates into variations in prescribing practices, which mainly concern the duration of treatment and the dose of corticosteroids. The PROGRESS (Promoting Global Research Excellence in Severe Sepsis) registry[18] highlighted the regional variation in LDC treatment for septic shock (23% in the Oceania region; 51% in Europe). Subsequent articles presented similar "heterogeneous" results. Consequently, use of and withholding of LDC are both currently accepted as standards of care in septic shock, thus highlighting the urgent need for a definite trial with adequate power to resolve the current uncertainty.[19,20]

To address this uncertainty and clarify the efficacy of corticosteroids in septic shock, we, on behalf of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the George Institute for Global Health, will conduct a trial to examine the impact of hydrocortisone therapy on mortality in intensive care unit patients with septic shock. This report describes the trial protocol and has been supported by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand. The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12611001042932) and with ClinicalTrials.gov (NCT01448109).

Methods

Study design and participants

The ADRENAL trial (ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock) is an international, prospective, multicentre, double-blinded, concealed, randomised, placebo-controlled trial to determine whether hydrocortisone therapy reduces 90-day all-cause mortality

in patients treated in an ICU with septic shock. It is anticipated that the study will enrol 3800 critically ill adult patients with septic shock from 60 ICUs in Australia, New Zealand, Europe, India and Saudi Arabia over 48 months.

Adult patients who are critically ill with septic shock requiring vasopressor and mechanical ventilatory support will be eligible for enrolment. The inclusion and exclusion criteria are summarised in Table 1. Patients will be excluded if they are not enrolled within 24 hours of meeting all inclusion criteria, require concomitant treatment with systemic steroids for a cause other than sepsis, have been treated with etomidate, have been previously enrolled in the ADRENAL trial, or if death is deemed imminent and inevitable. Corticotropin testing will not be part of the protocol due to problems with reliability,[21,22] and an absence of any differential treatment effect.[17]

Outcomes

The primary end point of the study is 90-day mortality. Secondary outcomes will include 28-day and 6-month mortality, lengths of ICU stay and hospital stay, duration of mechanical ventilation and renal replacement therapy, new bacteraemias, and the need for blood transfusion (Table 2). This study will also include an assessment of quality of life and functional capacity using the EQ-5D-5L quality-of-life questionnaire at the 6-month follow-up. Predefined subgroups will include the following categories:

- operative (admitted to ICU from operating theatre or recovery room) versus non-operative admission
- dose of adrenaline or noradrenaline at randomisation: $\leqslant 15$ μg/minute versus > 15 μg/minute.[2]

Treatments

The treatments to be compared in this study are either IV hydrocortisone 200 mg/day or placebo. The hydrocortisone sodium succinate sterile powder (equivalent to hydrocortisone 100 mg) has been sourced from the manufacturer of the registered product and is supplied in a plain glass vial. The placebo is a matching, sterile, air-filled vial. The hydrocortisone and placebo vials will be completely covered in blinding label and labelled according to good manufacturing practice requirements with the appropriate medication kit number. The bedside nurse will prepare the study drug aseptically by reconstituting a study drug vial with sterile water 2 mL. The vial will be agitated for 20 seconds and then rested for 3 minutes (these figures are based on bench studies to determine optimal mixing and dissolution times [own unpublished observations]). The reconstituted solution will be added to an IV infusion bag of either 0.9% sodium chloride 100 mL or 5% glucose 100 mL, and will be administered as a continuous IV infusion over 12 hours. Once reconstituted and added to a bag of IV fluid, the solution is stable for 24 hours. Study treatments will be administered daily as a continuous infusion for up to 7 days, or until discharge from ICU if discharge occurs less than 7 days after randomisation

Open-label steroids will not be administered for patients with refractory shock but may be permissible if other clinical indications arise, such as bronchospasm. Study treatment may be permanently discontinued if a definite indication for, or contraindication to, hydrocortisone becomes apparent during the study treatment period. Regardless of whether the full study treatment is continued or not, the follow-up schedule will continue unchanged for all randomised participants.

Table 2. Study outcomes

Primary outcome

All-cause mortality at 90 days after randomisation.

Secondary outcomes

1. All-cause mortality at 28 days and 6 months after randomisation
2. Time to resolution of shock, defined as "time taken to achieve a clinician-prescribed mean arterial pressure goal for > 24 hours without vasopressors or inotropes"[11]
3. Recurrence of shock, defined as a new episode of shock after reversal of the initial episode[23]
4. Duration of intensive care unit stay
5. Duration of hospital stay
6. Frequency and duration of mechanical ventilation
7. Duration of renal replacement therapy
8. Development of bacteraemia 2–14 days after randomisation
9. Bleeding requiring blood transfusions received in the ICU
10. Quality-of-life assessment at 6 months.

Drug distribution and logistics

Management of the drug distribution will be coordinated by the George database solution (GDS), including an interactive web-based randomisation system. The GDS has full drug inventory tracking capabilities, tracking initial orders to sites and reordering when stock is low, allocating of study drug at randomisation and reconciliation of used and unused study drug. The GDS allows the coordinating centre to monitor study drug at any point in time.

Randomisation and allocation concealment

Randomisation will be achieved using a minimisation algorithm via a password-protected, encrypted, web-based interface available 24 hours a day, 7 days a week. Trained staff at participating sites will randomise patients by entering their demographic details and responses to all eligibility criteria into this system. Randomisation will be stratified according to participating site and operative or non-operative admission to the ICU. Following successful randomisa-

tion, each patient will be assigned a unique patient study number, and a medication kit will be allocated from available kits at the site. Each medication kit contains 14 blinded study drug vials. The unique medication kit number is matched to blinded study drug with sufficient supply to last a 7-day course of treatment.

The allocation of medication kits is determined by the GDS randomisation system. The information on which codes correspond to what treatment is maintained in a secure location at the coordinating centre and the pharmacy preparation unit. Apart from nominated senior information technology employees programming the GDS, and two selected statisticians (who will carry out the interim analyses), all staff at the participating sites and the coordinating centre will be blinded to the treatment allocation. Further detailed instructions regarding study treatment are provided in the study operations manual. Study treatment is labelled, stored, tracked and reconciled as for the standard operating procedures of the coordinating centre. Standard operating procedures will also be in place for potential unblinding which may become necessary for reasons of patient safety and management.

Data collection and management

Data collection will be conducted by trained staff at each participating site and will be entered into the GDS electronic case report forms. Information collected will include eligibility criteria at randomisation; baseline patient demographic and medical information (such as ICU diagnoses and Acute Physiology and Chronic Health Evaluation [APACHE] II scores[24]) to evaluate the balance of randomisation; and information to categorise patients into the a-priori subgroups of interest (medical admissions, surgical admissions and vasopressor requirements). During the first 14 days while the patient is in the ICU, information on daily physiological parameters will be collected to measure secondary outcomes and ensure protocol compliance. At 90 days after randomisation, information on vital status will be obtained. At 6 months after randomisation, quality of life will be measured using the EQ-5D-5L score.[25] The GDS system allows for ad-hoc and automatic validation and consistency checks as well as immediate query resolution. This will facilitate accuracy and completeness of data and allow timely access to "clean" data for analytical purposes. Finally, a screening log will be maintained at each participating site to record patients who were admitted with septic shock but were considered ineligible.

Statistical methods

Sample size

The planned sample size is 3800 patients. The sample size has been calculated assuming that recruitment of 3800 participants will provide 90% power to detect a 15% reduction in RR, corresponding to a 5% absolute risk reduction (ARR) from an estimated baseline mortality rate of 33%. The corresponding sample size for 80% power is 2790 patients. The 33% mortality rate in the control population is based on data from sepsis surveys performed in Australia and New Zealand by ANZICS CTG;[26] recent international trials of septic shock;[4] and the catecholamine comparison trial (CAT).[23] These mortality rates are also consistent with the mortality rates in the control arms of RCTs of septic shock globally. Given that hydrocortisone is cheap and may confer a substantive mortality benefit, a 5% ARR (which corresponds to the ARR reported in the meta-analysis) would be considered clinically important and likely to influence practice. The sample size of 3800 patients also allows for a potential withdrawal rate of 1%–2% and loss-to-follow-up (LTFU) rate of 29% at 90% power, and a 29% LTFU at 80% power. Consideration will be given to increasing the sample size to accommodate a larger LTFU rate if this were to be the case during the monitoring process and interim analysis.

Statistical analysis

All analyses will be conducted on an intention-to-treat basis, using standard statistical methods for categorical and continuous data. Analyses will also be conducted in predefined subgroup pairs. As was done for other studies, a formal statistical analysis plan will be agreed on and placed in the public domain before the study database is locked for the analysis of the primary outcome.[27-29]

A formal interim analysis will be conducted when 1900 patients have been followed for 90 days. The purpose of this interim analysis is to test for the difference in mortality between the two study groups, to check for potential safety issues, and to assess early efficacy. Any additional reviews of the data may be performed at the discretion of the study's independent data and safety monitoring committee (DSMC). The DSMC will reveal the unblinded results to the management committee if, taking into account statistical and clinical issues and exercising their best clinical and statistical judgement, the unblinded results provide sufficient evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients. "Stopping rules" will be based on efficacy or safety (in accordance with other large-scale ICU trials[27-29]), and will be according to the following:

> a three standard deviation difference in mortality would constitute such evidence, unless the data monitoring committee should itself decide in the circumstances of the trial that other data constitutes evidence beyond reasonable doubt.

Ethical issues

All participating sites will obtain local ethics approvals to conduct the trial. In sites where it is approved by the local human research ethics committee, and if it is not possible to obtain prior informed consent from the patient or a legally recognised substitute decisionmaker in a timely manner to allow initiation of treatment with the study drug, delayed consent will be obtained as soon as reasonably possible. Patients who are enrolled with delayed consent will be entered in the study and will receive the study drug, and as soon as is practical, they or their surrogate will be asked to provide consent to continue in the study. The patient or their surrogate will also be given the opportunity to withdraw from the study at any time. When local ethics committees do not allow delayed consent, consent must be obtained from the patient or their legally recognised surrogate before recruitment. All included patient data will be as approved by local ethics committees.

Monitoring

The DSMC will review all unblinded serious adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC. The DSMC is independent of the coordinating centre and investigators, and will perform an ongoing review of predefined safety parameters, study outcomes and overall study conduct. A detailed charter between the DSMC and study management committee outlining roles, responsibilities, processes for stopping rules, reporting and communication has been signed. The DSMC comprises Duncan Young, Chair (Oxford University, United Kingdom), John Marshall (University of Toronto, Canada) and Ian Roberts (London School of Hygiene and Tropical Medicine, UK).

The coordinating centre monitor will visit each study site on several occasions during the recruitment phase to ensure compliance with the protocol, good clinical practice guidelines and relevant regional regulatory requirements. The study may also be audited by local or national regulatory authorities. Source documents and other study files will be made available at all study sites for monitoring and auditing purposes. Source data verification by trained monitors for all consents and for the primary outcome, and then of secondary end points and study compliance on 20% of all patients, will be carried out. The coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

Close out

At completion of the study, the monitor will ensure that there are plans for long-term storage of all relevant data and source documentation for 15 years. The study drug will be reconciled and destroyed according to local standard procedures.

Current status

A run-in phase of the study was commenced in June 2012 to test the web-based randomisation process and data collection tools in a few centres. The study commenced at all other sites in February 2013.

Summary

Septic shock is a common and increasing cause of major morbidity and mortality worldwide. Whether treatment with corticosteroids is beneficial or harmful in this setting has long been debated and remains unclear. This uncertainty can only be resolved by a large-scale pragmatic trial of the nature outlined in this article. As corticosteroids may produce either benefit or harm, there is a scientific, ethical and health economic imperative to conduct such a trial. A 3800-participant trial (nearly twice as many patients as those included in the most recent meta-analysis of trials of corticosteroids in septic shock[14]) is designed to answer a fundamental clinical question that has challenged clinicians caring for critically ill patients for the past 40 years. This study will be the largest of its kind to date and will provide data to inform policy and practice in the intended patient population.

Competing interests

None declared.

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