A randomised, double blind, placebo-controlled trial of a two-week course of dexamethasone for adult patients with a symptomatic Chronic Subdural Haematoma (Dex-CSDH trial)

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Disclosure of interests

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Scientific summary

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Background

Chronic subdural haematoma (CSDH) is a common neurological disorder predominantly affecting older people, affecting approximately 5000 people aged over 65 years in the UK each year. Its incidence is increasing owing to an ageing population, alongside the growing use of antithrombotic agents.

The majority of CSDHs do not cause symptoms and are managed conservatively. In those that do cause symptoms, surgical evacuation remains the mainstay of management, which achieves a good recovery in approximately 80% of patients. The remaining 10–20% of patients may suffer a recurrence, requiring further surgery.

Additional and alternative measures to surgery are sought to improve outcomes in this patient group. Inflammation has been implicated in the pathogenesis of CSDHs, which suggests a role for anti-inflammatory medications, such as steroids. Therefore, steroids may serve as a useful adjunct or even alternative to surgery. However, to date, there is a lack of high-quality evidence in the form of a randomised clinical trial or meta-analysis. This trial investigates the clinical effectiveness of a steroid, dexamethasone, in patients with symptomatic CSDH.

Objectives

Primary objective

The primary objective of the trial was to determine the clinical effectiveness of a 2-week course of dexamethasone for adult patients with a symptomatic CSDH, assessed by comparing the rate of favourable outcomes [defined as a Modified Rankin Scale (mRS) score of 0–3] at 6 months after randomisation between the treatment and the control arm. This outcome was reviewed centrally by a clinically trained investigator blinded to treatment allocation.

Secondary objectives

The secondary objectives were to compare the following outcomes between the treatment and the control arm of the trial:

- number of CSDH-related surgical interventions undertaken during the index admission
- number of CSDH-related surgical interventions undertaken during subsequent admissions in the follow-up period
- Glasgow Coma Scale (GCS) score at discharge from the neurosurgical unit (NSU) and at 6 months
- Modified Rankin Scale score at discharge from the NSU and at 3 months
- Barthel Index score at discharge from the NSU and at 3 and 6 months
- mortality (30 days and 6 months)
- EuroQol-5 Dimensions, five-level version (EQ-5D-5L), utility index at discharge from the NSU and at 3 and 6 months
- length of stay in the NSU
- discharge destination from the NSU
- length of stay in secondary care
- rates of adverse events (AEs).

An economic evaluation was also undertaken to estimate the cost-effectiveness of dexamethasone compared with placebo.

Tertiary objectives

Postoperative recurrence is a tertiary outcome measure and is defined as a symptomatic recurrence requiring reoperation of a previously evacuated ipsilateral CSDH.

Methods

Trial design

The Dex-CSDH (DEXamethasone in Chronic SubDural Haematoma) trial is a multicentre, pragmatic, clinical phase III, randomised, double-blind, placebo-controlled trial of a tapering 2-week course of dexamethasone in patients with a symptomatic CSDH. The pragmatic design meant that the trial ran in parallel with standard clinical care, with the only difference being the addition of the trial drug (dexamethasone) or placebo.

Intervention

Two-week tapering course of dexamethasone (with matching placebo as the control).

Participants

Participants were screened for eligibility from 23 NSUs across the UK, with the admitting neurosurgical team determining eligibility for participation. Participants were adult patients aged ≥ 18 years with a symptomatic CSDH confirmed on cranial imaging (computerised tomography or magnetic resonance imaging of the brain). The patient or their legal representative had to provide informed consent. In the absence of a legal representative, an independent healthcare professional provided authorisation for enrolment.

Patients were excluded in the presence of any of the following criteria:

- presence of a condition for which steroids are clearly contraindicated
- patients who are (or within 1 month of) receiving regular oral or intravenous glucocorticoid steroids (this did not include inhaled or topical steroids, nor did it include those receiving a single intraoperative dose of dexamethasone for anti-emesis)
- previous enrolment in this trial for a prior episode
- time interval from time of admission to the NSU to first dose of trial medication exceeded 72 hours
- chronic subdural haematoma in the presence of a cerebrospinal fluid shunt
- severe lactose intolerance or a known hypersensitivity to dexamethasone or other excipients
- a history of psychotic disorders
- unwillingness to take products containing gelatine.

Patients who were screened but not included in the study were recorded on a screening log and reported centrally, with both the number of failures and the reasons for failure to recruit to the trial documented.

Trial procedures

Patients were managed in NSUs in accordance with standard practice. In the UK, this typically includes burr hole evacuation with the use of a subdural drain for most symptomatic patients. The decision for surgery or active monitoring was made on an individual patient basis by the blinded admitting clinical team in conjunction with the patient, in keeping with the pragmatic nature of the trial. Enrolment in the trial took place irrespective of the decision to operate and the timing of surgical intervention.

Patients were randomised in 1 : 1 allocation using a computer-generated randomisation schedule, stratified by site using permuted blocks of random sizes (two or four). An interactive web-based response system was used to allocate treatment packs of 62 overencapsulated 2-mg dexamethasone tablets or 62 identical placebo capsules.

The enrolled participants, clinical and research team and outcome assessors were blinded to the treatment allocation. The assigned treatment was administered as part of the routine drug round by the ward nurses. Oral administration was the preferred option, but administration via a nasogastric tube was offered to those unable to swallow. The latter method required opening of the capsules for crushing of the contents, allowing potential unblinding of the ward nurse. Therefore, the content of any opened capsules was not documented in the patient notes to maintain the blinding of the neurosurgeons and research staff. Trial drug compliance was recorded through inpatient drug charts during admission or by completion of a medication diary.

Data were collected at baseline (on admission to the neurosurgical department) as part of routine standard of care, on discharge from the acute NSU, at 30 days, at 3 months and at 6 months. Patients were monitored in line with routine clinical practice until discharge, and at 3 and 6 months, to score clinical outcomes.

Sample size

This sample size was calculated with the following assumptions: a favourable outcome rate of 80–85% in the control arm and allowing for up to 15% loss to follow-up. A target sample size of 750 patients was needed to detect an increase in favourable outcome rate from 80–85% to 88–93%, with a power of 81–92% at the 5% significance level (two sided). An 8% increase in the rate of favourable outcome (mRS score of 0–3) at 6 months represents a clinically important treatment effect.

Statistical analysis

Data were analysed in accordance with the prespecified statistical analysis plan that was agreed prior to unblinding of data. Outcome data were analysed using a modified intention-to-treat analysis (all patients were included as randomised, except for those who withdrew consent for participation in the trial and those lost to follow-up).

The primary outcome (mRS score at 6 months) was dichotomised into favourable (0–3) or unfavourable (4–6) outcomes. Primary analysis estimated the absolute difference between the intervention arm and the control arm in the proportions achieving a favourable outcome. A normal approximation was used to produce 95% confidence intervals (CIs) and a two-sided *p*-value testing the null hypothesis of no difference.

Secondary analysis included a logistic regression and proportional odds logistic regression of the original mRS score adjusting for baseline covariates of age and Glasgow Coma Scale (GCS) score.

Economic evaluation

In the base-case analysis, costs were estimated over the 6-month trial period from an NHS and a Personal Social Services perspective. Outcomes were quality-adjusted life-years (QALYs) derived from the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at NSU discharge and at the 3- and 6-month follow-ups. Analyses were undertaken to estimate the mean incremental cost and effect, and enable the net monetary benefit (NMB) (a negative score indicates that the intervention is not estimated to be cost-effective) to be calculated, along with the cost-effectiveness acceptability curve (CEAC) (probability that dexamethasone was cost-effective). NMB and CEAC values at a willingness-to-pay threshold of £20,000 per QALY are reported.

Results

Primary outcome

An outcome of mRS score of 0–3 occurred in 286 out of 341 patients (83.9%) in the dexamethasone arm and 306 out of 339 patients (90.3%) in the placebo arm at 6 months (difference −6.4%, 95% CI −11.4% to −1.4%; $p = 0.01$).

After adjustment for prespecified covariates (age > 70 years and GCS score on admission), the odds ratio (OR) of a favourable outcome with dexamethasone was 0.55 (95% CI 0.33 to 0.91; $p = 0.022$), favouring placebo.

Secondary outcomes

Modified Rankin Scale at discharge and 3 months

At 3 months, 268 out of 322 patients (83.2%) in the dexamethasone arm and 298 out of 326 patients (91.4%) in the placebo arm had a favourable outcome, for a between-group difference of −8.2% (95% CI −13.3% to −3.1%) in favour of the placebo arm.

There was no significant difference in mRS score between the two arms at discharge [255/318 (80.2%) in the dexamethasone arm and 263/316 (83.2%) in the placebo arm for a difference of −3.0% (95% CI −9.1% to 3.0%)].

Mortality

At discharge, 8 out of 375 patients (2.1%) in the dexamethasone arm and 2 out of 373 patients (0.5%) in the placebo arm had died (OR 4.08, 95% CI 1.01 to 27.2). At 6 months, 30 out of 341 patients (8.8%) in the dexamethasone arm and 17 out of 339 patients (5.0%) in the placebo arm had died (OR 1.83, 95% CI 0.99 to 3.45).

Number of chronic subdural haematoma-related surgical interventions undertaken

The number of surgical interventions undertaken during the index admission or during subsequent admissions during the follow-up period was similar in both arms. However, in the subset of patients who received surgery, repeat surgery for recurrence of the CSDH was performed in 6 out of 349 patients (1.7%) in the dexamethasone arm and in 25 out of 350 patients (7.1%) in the placebo arm.

EuroQol-5 Dimensions, five-level version, utility index (at discharge and at 3 and 6 months)

The mean EQ-5D-5L, utility index scores were compared. At discharge, the difference was −0.03 (95% CI −0.07 to 0.01), favouring placebo. At 3 months, the difference was −0.07 (95% CI −0.12 to −0.02), favouring placebo. At 6 months, the difference was −0.03 (95% CI −0.09 to 0.02), favouring placebo.

Glasgow Coma Scale (at discharge and at 6 months)

Glasgow Coma Scale was grouped into scores of 9–12 and 13–15. The percentage of patients with a score of 13–15 was similar at discharge (99.7% in the placebo arm vs. 99.2% in the dexamethasone arm). Insufficient data at 6 months prevented analysis.

Barthel Index (at discharge and at 3 and 6 months)

No significant difference was seen between the placebo arm and the dexamethasone arm at discharge, 3 months or 6 months.

Length of stay in the neurosurgical unit

The mean length of stay was 9.03 days in the placebo arm and 9.32 days in the dexamethasone arm.

Length of stay in secondary care

The mean length of stay was 13.0 days in the dexamethasone arm and 13.7 days in the placebo arm, with no significant difference between the two arms (0.95, 95% CI 0.835 to 1.09; $p = 0.467$).

Discharge destination from the neurosurgical unit

No significant difference was observed between the placebo arm and the dexamethasone arm when comparing discharge destinations.

Rates of adverse events

The odds of an adverse event of special interest were greater in the dexamethasone arm than in the placebo arm (OR 3.40, 95% CI 1.81 to 6.85). Similarly, the odds of a serious adverse event occurring were greater in the dexamethasone arm than in the placebo arm (OR 2.49, 95% CI 1.54 to 4.15).

Economic evaluation

The mean incremental cost for dexamethasone was estimated to be −£143.73 (95% CI −£1793 to £1505), with a QALY of −0.012 (95% CI −0.027 to 0.003), compared with placebo. The associated NMB of dexamethasone compared with placebo was −£97.19, with an estimated 46% probability of being cost-effective.

Conclusions

Implications for healthcare

Dexamethasone for the treatment of symptomatic CSDH resulted in a lower proportion of favourable outcomes, as measured with the mRS, and a larger number of AEs than placebo. This treatment regime was also not estimated to be cost-effective (based on the NMB). Therefore, dexamethasone is not recommended in the treatment of CSDH.

Implications for research

The results of our literature review indicate that this study is the first multicentre randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of dexamethasone in the management of symptomatic CSDH. It provides evidence to inform the role of dexamethasone in this condition.

Trial registration

This trial is registered as ISRCTN80782810.

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