The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2 × 2 factorial randomised controlled trial

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Scientific summary

The STOPAH trial

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Scientific summary

Background

Alcoholic hepatitis (AH) is a florid manifestation of alcohol-related liver disease with a 1-month mortality of 20–30% for those with severe disease [Maddrey's discriminant function (DF) ≥ 32]. It is characterised by the onset of jaundice in the context of excessive alcohol misuse and is a major cause of acute-on-chronic liver failure. Despite the serious nature of this illness there is controversy regarding the most effective medical therapy. Although there are numerous trials on this topic, there is still debate about the role of corticosteroids, with advocates citing significant improvement in the short- to medium-term mortality, while detractors raise concerns about the risks of sepsis and gastrointestinal (GI) haemorrhage. Pentoxifylline (PTX) has also been suggested as a treatment but meta-analyses to date have been inconclusive. Therefore, optimal medical treatment of AH is unclear and its management inconsistent.

Objectives

We aimed to evaluate whether or not prednisolone or PTX administered for 28 days improved short- and medium-term mortality in patients admitted with severe AH. We also aimed to assess their relative cost-effectiveness. The primary outcome measure was mortality at 28 days, with mortality at 90 days and 1 year being secondary outcomes. In addition, we aimed to assess the outcome relative to the Glasgow Alcoholic Hepatitis Score (GAHS), the model for end-stage liver disease (MELD) score and the Lille score, all of which have been advocated as methods of assessing disease severity and identifying patients for treatment.

Methods

Study design

The study design was a multicentre, double-blind, factorial (2 × 2) trial in which patients were randomised to one of four arms:

1. arm A – placebo/placebo
2. arm B – placebo/prednisolone
3. arm C – PTX/placebo
4. arm D – PTX/prednisolone.

Participants

Patients ≥ 18 years with a clinical diagnosis of AH on admission to hospital were considered for inclusion. Eligibility criteria were age ≥ 18 years; alcohol consumption > 80 g/day for males and 60 g/day for females to within 2 months of randomisation; serum bilirubin > 80 µmol/l; and DF ≥ 32. Key exclusion criteria were: duration of jaundice > 3 months; other causes of liver disease present; aspartate aminotransferase > 500 IU/ml or alanine aminotransferase > 300 IU/ml; previous entry to the study; previous use of prednisolone or PTX within 6 weeks of admission; renal failure (creatinine > 500 µmol/l or requiring renal replacement therapy); active GI bleeding; untreated sepsis; and patients requiring inotropic support. As the trial was conducted in 65 hospitals across the UK, and many of which do not have access to transjugular liver biopsy, it was decided not to make liver histology an entry criterion. Patients with GI bleeding, renal impairment or sepsis during the admission were allowed specific treatment for up to 7 days and randomised if the condition had been stabilised.

Main outcome measures

The primary end point was mortality at 28 days; this time point represents the end of the peak period of mortality for AH and is consistent with other trials in the field. Secondary end points looked at mortality or liver transplant at 90 days and 1 year, outcome relative to other prognostic scores (GAHS, MELD and Lille score), rates of recidivism, hospital readmission rates for liver or non-liver-related events, rates of GI haemorrhage and sepsis, and rates of new or recurrent renal failure (serum creatinine greater than 500 µmol/l or requiring renal support).

Study procedures

Potential patients for the trial were identified on admission to hospital with suspected AH. After clinical assessment, suitable candidates were given a patient information sheet and were given at least 24 hours to consider the study and ask questions, after which they (or their legal representatives) were asked to give written informed consent. Special arrangements were in place to ensure that the interests of patients with hepatic encephalopathy were protected. After enrolment, patients were registered via Trans European Network for clinical trials services, a web-based registration and randomisation system. If eligible for the study, patients were randomised to a study treatment arm, which was blinded to the site staff and the patient by means of a unique four-digit patient pack number.

Randomisation was performed using the following two stratification factors:

1. geographic region (28 in total)
2. risk group: either high or intermediate risk (high risk was defined as either sepsis or history of GI bleeding in the previous 7 days, or creatinine > 150 µmol/l, or any combination of the these; intermediate risk was defined as no sepsis and no history of GI bleeding in the previous 7 days, and creatinine ≤ 150 µmol/l).

All patients were given one capsule containing 400 mg of PTX (or identical placebo) three times per day, plus one capsule containing 40 mg of prednisolone (or identical placebo) once daily. Both medications were administered for 28 days.

Patients were evaluated on treatment days 7, 14, 21 and 28, and at each time point recordings were made of vital signs, World Health Organization performance status, concomitant medication and adverse events. Blood samples were taken for liver function tests, prothrombin time, full blood count, urea and creatinine. Patients were assessed for the presence of hepatic encephalopathy and the occurrence of GI bleed or sepsis in the past 7 days. If patients were discharged from hospital before the end of the 28-day treatment period, assessments were made at 28 days by telephone interview.

After discharge from hospital, patients were similarly evaluated at 90 days and at 1 year.

Statistical methods

A power calculation was performed to estimate sample sizes using the following parameters:

- power = 90%
- significance = 5%
- estimated mortality in placebo-treated group = 35%
- estimated mortality in prednisolone-treated group = 25%
- estimated mortality in PTX-treated group = 25%
- estimated mortality in prednisolone- and PTX- treated group = 17% (estimated assuming no interaction).

Based on a reduction in the 28-day mortality rate from 30% to 21%, a sample size of 513 per group of single agent versus no single agent was required. Thus, in total, the trial required 1026 patients. We allowed for a ≈ 10% withdrawal/lost to follow-up rate and therefore aimed to recruit 1200 patients to the study, with patients being evenly allocated to each treatment arm.

Analysis was on the basis of intention to treat. In order to determine the efficacy of prednisolone, the 28-day mortality rate in the prednisolone-treated group (arms B and D) was compared with the mortality rate in the control group (arms A and C). Similarly, PTX efficacy was assessed by comparing the 28-day mortality rate in the PTX-treated group (arms C and D) with the mortality rate in the control groups (arms A and B).

The impact of pre-treatment variables such as GI bleeding, sepsis or renal impairment on admission was estimated by adding these covariates to the logistic regression analysis. Mortality rates at 90 days and 1 year were compared using the same strategy.

Economic analysis

Within-trial cost-effectiveness and model-based cost–utility analyses were conducted. The economic evaluation was conducted from the perspective of the UK NHS and all costs were reported in 2014 UK pounds. The results of the cost-effectiveness analysis are reported as the incremental cost per additional survivor at 28 days and the results of the cost–utility analysis were reported as the incremental cost per quality-adjusted life-year (QALY) gained at 1 year and the patient's lifetime. QALYs were derived from responses to the European Quality of Life-5 Dimensions administered at baseline, 90 days and 1 year. Costs were based on the use of primary and secondary care services over the trial follow-up and cost using routine sources and study-specific estimates.

Results

Main trial results

Between January 2011 and February 2014, 5234 patients were screened for the trial and after applying eligibility criteria, 1103 patients were randomly allocated to the four treatment arms: 276 to placebo/placebo; 277 to placebo/prednisolone; 276 to PTX/placebo; and 274 to PTX/prednisolone. Patients were followed for 1 year or up until the time of their death with the exception of the final 223 patients recruited, when early cessation of follow-up meant that the trial was completed prior to them reaching this time point. The four arms were well matched with regard to their baseline characteristics and laboratory variables. At day 28, 16% of patients had died, 1% had been lost to follow-up and 2% had withdrawn from the study. At 90 days, 285 of 968 (29%) patients had died, 5% were lost to follow-up and 7% had withdrawn (including 4% owing to early cessation of follow-up). At 1 year, 421 of 747 (56%) patients had died or had a liver transplantation ($n = 3$), 8% were lost to follow-up and 24% of patients had withdrawn (including 20% owing to early cessation of follow-up).

At 28 days in the placebo/placebo arm, 45 of 269 (16.7%) patients had died, in the placebo/prednisolone arm 38 of 266 (14.3%) patients had died, in the PTX/placebo arm 50 of 258 (19.4%) patients had died and in the PTX/prednisolone arm 35 of 260 (13.5%) had died. There was no significant interaction between prednisolone and PTX. In the logistic regression analysis, the odds ratio for 28-day mortality in the PTX-treated group versus no-PTX-treated group was 1.07 [95% confidence interval (CI) 0.77 to 1.49; $p = 0.686$] and for the prednisolone-treated group versus no-prednisolone-treated group, the odds ratio was 0.72 (95% CI 0.52 to 1.01; $p = 0.056$). Although this result is of borderline significance, any effect of the steroid in the first month is rapidly lost: neither prednisolone nor PTX were found to influence mortality at 90 days and 1 year. At 90 days, 29.8% of patients treated with prednisolone had died, compared with 29.1% who did not receive this drug (odds ratio 1.02, 95% CI 0.77 to 1.35). At 90 days, 29.1% of patients treated with PTX had died, compared with 29.8% who did not receive this drug (odds ratio 0.97, 95% CI 0.73 to 1.28). At 1 year, 56.6% of patients treated with prednisolone had died, compared with 56.1% who did not receive this drug (odds ratio 1.01, 95% CI 0.76 to 1.35). At 1 year, 56.2% of patients treated with PTX had died, compared with 56.5% who did not receive this drug (odds ratio 0.99, 95% CI 0.74 to 1.33).

Baseline variables were assessed to establish whether or not prednisolone or PTX influenced (i.e. statistical significant at 5% level) 28-day mortality. In the univariate analysis, DF, GAHS, MELD, Lille score, age, encephalopathy, white blood cell (WBC) count, prothrombin ratio, serum bilirubin, urea and creatinine were all significant. In the multivariate analysis, age, encephalopathy, WBC count, urea, creatinine and prothrombin ratio remained significant. Using the multivariate logistic regression model to take into account these prognostic variables, we found that the odds ratio for 28-day mortality in the prednisolone-treated group versus no-prednisolone-treated group was 0.61 (95% CI 0.41 to 0.91; $p = 0.015$). However, the odds ratio for mortality in the prednisolone-treated group compared with the group not treated with prednisolone at 90 days was 1.00 (95% CI 0.73 to 1.36; $p = 0.976$) and at 1 year was 1.01 (95% CI 0.74 to 1.39; $p = 0.942$) remained statistically non-significant. This may indicate that minor variation in baseline factors influenced the result at 28 days. However, even if there is a benefit of steroid use at this early time point, it does not translate into long-term benefit.

In the univariate analysis, each of the four existing scoring systems provided prognostic information on patient survival at 28 days, 90 days and 1 year with p-values < 0.001. MELD had a slightly greater area under the receiver operating characteristic curve compared with the other scoring systems, although the GAHS had the higher odds ratio on logistic regression analysis at day 28. However, the prognostic value of each scoring system diminished with increased duration of follow-up. When the Lille score was studied as an indicator of corticosteroid response using cox proportional hazards regression modelling, Lille non-responders (≥ 0.45) had a higher overall mortality of 51.9% (70/135) compared with 24.6% (49/199) for responders (< 0.45) (hazard ratio 2.66, 95% CI 1.95 to 4.05; $p < 0.001$).

Serious adverse events (SAEs) were reported in 42% of patients with an equal distribution in each treatment arm and 29% of all SAEs resulted in deaths. Infection occurred in 74 of 547 (13.5%) patients in the prednisolone-treated group compared with 43 of 545 (7.9%) patients who did not receive prednisolone ($p = 0.003$). Acute kidney injury occurred in 9 of 546 (1.65%) patients who received PTX and 14 of 546 (2.56%) who did not receive this drug ($p = 0.4$).

Economic analysis

In terms of incremental cost per additional survivor at 28 days, prednisolone was the most likely treatment to be cost-effective. In the model-based analysis prednisolone was, on average, associated with an incremental cost per QALY that society may be willing to pay. No other treatment has an incremental cost per QALY of $<$ £30,000. However, the cautious assumptions made and limited longer-term data available means that there is considerable imprecision around estimates of cost-effectiveness, so that definitive conclusions cannot be drawn.

Conclusions

In this study we are able to show a reduction in the 28-day mortality in the prednisolone-treated group on logistic regression model analysis, but there was not clear evidence of benefit sustained beyond this point. In contrast there is no evidence of survival benefit for PTX either alone or in combination with steroids, at any measured time point.

The GAHS, MELD and Lille score performed similarly in assessing overall prognosis, but a high Lille score did not effectively identify a severe group of patients who may benefit from transplantation, as has been suggested previously.

Prednisolone use was associated with an increased rate of sepsis, which probably negated some of the benefits. There was no significant reduction in renal impairment with PTX use; however, there was a low rate of acute kidney injury in this trial, making a definitive conclusion about renal protection inappropriate.

Prednisolone was the most likely treatment to be considered cost-effective at 28 days and the results are suggestive of an incremental cost per QALY of < £30,000 at 1 year and over a lifetime, but remain tentative owing to limited longer-term data.

Recommendations for future research

1. Development of disease severity scores that allow identification of those most likely to benefit from corticosteroid use and to identify those for whom other treatment should be considered.
2. To address whether or not additional measures such as the addition of *N*-acetylcysteine or granulocyte colony stimulating factor to corticosteroids could reduce the rate of sepsis and improve outcome beyond 28 days.
3. To investigate methods to improve rates of abstinence after discharge from hospital.

Trial registration

This trial is registered as EudraCT 2009-013897-42 and ISRCTN88782125.

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