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REVIEW ARTICLE

MANAGEMENT OF SEVERE ALCOHOLIC HEPATITIS-STEROID OR PENTOXIPHYLLINE?

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ABSTRACT

Alcohol use is common worldwide. Although used as a pleasurable substance, it has been associated with both acute and chronic diseases. Alcoholic hepatitis is a major life-threatening illness caused by chronic alcohol intake. Corticosteroids remain the mainstay of treatment in severe alcoholic hepatitis. Pentoxiphylline is used as an alternative drug where corticosteroids are contraindicated. In this review, we attempted to evaluate the largest multi-centric trial, "STOPAH", which focused on possible treatment modalities for severe alcoholic hepatitis. This trial used a factorial design to evaluate the efficacy of corticosteroid and pentoxiphylline in alcoholic hepatitis management. In this article, the STOPAH trial is summarised in the first section, followed by comments which enumerates strengths, limitations and utility of trial results.

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INTRODUCTION

Alcohol has been widely used in many cultures for millennia. Globally, in 2012, 5.9% of all deaths were attributable to alcohol consumption. (Management of substance abuse, 2015) Chronic excessive use of alcohol can lead to gastrointestinal diseases like fatty liver, alcoholic hepatitis, alcoholic cirrhosis, liver cancer, etc. The short-term mortality is about 40%-50% in the case of severe alcoholic hepatitis. (Lucey *et al*., 2009) Mainstay of treatment in alcoholic hepatitis is steroids. Corticosteroids act by reducing inflammatory cytokines such as tumour necrosis factor-α (TNF-α), intercellular adhesion molecule 1, interleukins (IL-6 and IL-8). (Spahr *et al*., 2001; Taïeb *et al*., 2000) Inflammation is a major component of alcoholic hepatitis pathogenesis and hence corticosteroids constitute the main treatment option. The drug is given orally in a dose of 40-60 mg/day for a total duration of 4 weeks. Pentoxiphylline is also used in the management of alcoholic hepatitis. (Akriviadis *et al*., 2000) Pentoxiphylline is effective in cases where corticosteroids use is contraindicated. (Reuter and Wallace, 1999) Corticosteroids are effective only in reducing short term mortality and their efficacy varies based on the clinical profile of the patients. (Imperiale and McCullough, 1990) Neutralization of TNF-α or regulating cyclic nucleotide levels may explain the protective effect of pentoxiphylline in alcoholic hepatitis by preventing hepato-renal syndrome although the exact mechanism of action is not clear. (Akriviadis *et al*., 2000; Lebrec *et al*., 2010) Pentoxiphylline is given orally at a dose of 400 mg three times a day for a total duration of 28 days. Though both prednisolone and pentoxiphylline are recommended for the treatment of severe alcoholic hepatitis, their benefits are still not proven beyond doubt.

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SUMMARY

Steroids or Pentoxiphylline for Alcoholic Hepatitis (STOPAH) trial was done to assess the effectiveness of administering steroids or pentoxiphylline in reducing the short-term (at 28 days) and medium-term (at 90 days and 1year) mortality among the hospitalised patients with severe alcoholic hepatitis. STOPAH was a multicentric, randomized, double-blind factorial trial. The patients were recruited from 65 hospitals of United Kingdom during January 2011 to February 2014. Inclusion criteria were age of 18 years or older, clinical diagnosis of alcoholic hepatitis, average alcohol consumption>80 g per day for men and >60 g per day for women, serum bilirubin level > 80 μmol/L (4.7 mg/dl), and a

discriminant function ≥32. Patients, who had jaundice for >3 months, cessation of alcohol consumption for >2 months, presence of other liver diseases, serum AST level >500 IU/L or ALT level >300 IU/L and previous entry into the study in last 6 months were excluded.

Taking power as 90%, with effect size of 9% (reduction of 28 days mortality from 30% to 21%) with two-sided significance level of 5% and loss to follow up of 10%, the study aimed to recruit 1200 participants. A total of 1103 eligible patients after stratification with geographic area and disease severity were randomised equally to four treatment groups using block randomisation with block size of four. Four treatment groups were- pentoxiphylline matched placebo and prednisolone matched placebo, pentoxiphylline with prednisolone matched placebo, prednisolone with pentoxiphylline matched placebo, and prednisolone with pentoxiphylline. Ethical approval was obtained from the Wales Research Ethics Committee and clinical trial authorization was received from the Medicines and Healthcare Products Regulatory Agency. Written informed consent was obtained from the patients. However relatives provided consent when patients were in a compromised mental state of health. Baseline characteristics were comparable. Follow up was done for 12 months or until the time of death or liver transplant except for those who were enrolled at the end of trial. Loss to follow up was 1% at 28 days, 5% at 90 days and 8% at 1 year. Intention to treat analysis was done. Primary end point of the trial was mortality assessment at 28 days and secondary end points were mortality or liver transplantation at 90 days and at 1 year. No significant treatment interaction was present between prednisolone and pentoxiphylline. In univariate analysis, the odds of mortality at 28 days among patients who received pentoxiphylline as compared to patients who did not receive was 1.07 (95% CI, 0.77 to 1.49; P = 0.69), and among patients who received prednisolone as compared to the patients who did not receive was 0.72 (95% CI, 0.52 to 1.01; P = 0.06). In multivariate analysis, prednisolone was effective [OR 0.61 (95% CI, 0.41-0.91, p=0.02)] at reducing short-term mortality (28 days) but no association was found for medium-term (at 90 days and 1year) mortality in severe alcoholic hepatitis after adjusting for age, presence of encephalopathy, white-cell count, prothrombin time, serum bilirubin, creatinine, and urea. Serious adverse effects were present among 42% of the patients and equally distributed among all the treatment groups. STOPAH trial concluded that the treatment with pentoxiphylline in severe alcoholic hepatitis did not improve mortality, and treatment with 40mg of prednisolone in severe alcoholic hepatitis improves only short term mortality.

COMMENTS

STOPAH trial was the largest trial to study the effects of possible treatment options in alcoholic hepatitis. The factorial design used in the study is rightly justified as it had shown the effects of prednisolone and pentoxiphylline independently and in combination, thus exploring the different possible treatment options in severe alcoholic hepatitis. This trial studied the effects of prednisolone and pentoxiphylline in short-term (at 28 days) or medium-term (at 90 days and 1year) mortality, thus paving the way for comprehensive understanding of the management of this disease. In this trial, 1103 patients were randomised to one of the four treatment groups. However data from 1053 participants were used for analysis of the outcome at 28 days. Similarly, only 968 and 747 participants were taken for 90 days and 1 year follow-up analysis respectively. This violates the essence of intention to treat (ITT) analysis (Wertz 1995), mentioned to have been done in this study. Back calculation of the power reveals the study to be underpowered for the expected results. For assessing the effect of prednisolone, actual power of the study was 41.8%, 2.4%, and 1.5% for the analysis at 28 days, 90 days and 1 year, respectively. For pentoxiphylline, calculated power was 2.4%, 2.8% and 1.8% for analysis at 28 days, 90 days and 1 year, respectively. Therefore, there is definite possibility of a type II error in the study. (Trout *et al*., 2007) We suggest that the results of this study need to be interpreted with caution.

INDIAN CONTEXT

Death due to liver disease is the tenth most common cause of death in India which accounts for 2.24% of total deaths. (http://www.worldlifeexpectancy.com/india-liver-disease) Alcohol-related problems contribute to 20-30% of the hospital admissions in India. (Benegal *et al*., 2002) According to the national survey done by Government of India, there were 62.5 million alcohol users in the country. (Ray *et al*., 2004) In the end, understanding the management of severe alcoholic hepatitis is crucial and its application in relation to the Indian context needs to be explored.

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