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CORTICOSTEROIDS AND ALCOHOLIC HEPATITIS


EDITOR’S ABSTRACT

The purpose of the study was to determine whether corticosteroids affect short-term mortality from alcoholic hepatitis. A metanalysis was conducted using studies identified through a MEDLINE computer search from 1966 to 1989 and extensive manual searches of associated bibliographies. Eleven randomized studies that assessed mortality in hospitalized patients diagnosed with alcoholic hepatitis and treated with corticosteroids were evaluated. Overall, the protective efficacy of corticosteroids was 37% (95% confidence interval 20% to 50%). Protective efficacy was higher among those trials with higher quality scores and in trials that excluded subjects with active gastrointestinal bleeding in patients with hepatic encephalopathy, protective efficacy was 34% overall (confidence interval 15% to 48%). In subjects without hepatic encephalopathy, corticosteroids were not believed to have a protective effect; this lack of efficacy was noted across all trial subgroups. Results of the metanalysis suggest that corticosteroids reduce short-term mortality in patients with acute alcoholic hepatitis who have hepatic encephalopathy. The protective effect is dependent on exclusion of patients with acute gastrointestinal bleeding.

COMMENTS

This important metanalysis responds, at least temporally, to an editorial published in the same journal almost a year earlier calling for a metanalysis of the benefit of corticosteroids in the treatment of alcoholic hepatitis (1). The most widely accepted therapy for acute alcoholic hepatitis is general supportive care. Research into the mechanism of liver injury from alcohol has lead to the treatment of alcoholic hepatitis with a number of agents, including propylthiouracil, anabolic steroids and corticosteroids. The latter has been the most intensively studied, starting with a report in 1971 of a randomized controlled study terminated early by the investigators because of the overwhelming protective effect found for corticosteroid use in encephalopathic patients with alcoholic hepatitis (2). A succession of randomized controlled trials followed, two of which showed significant improvement in survival with steroids and seven of which did not. In 1989 a multicenter trial found a substantial benefit from steroid treatment in a population of patients selected for encephalopathy or high prothrombin times and bilirubin levels (3).

Combining results from multiple trials allows a metanalysis to achieve large sample sizes and statistically significant results where individual trials have failed to do so. Accumulating a large sample size in this manner is easy relative to the difficulty of conducting a large clinical trial. However, to prevent the sample size from giving the reader false confidence in the results of the analysis, the methodology of the metanalysis assumes an even greater significance for both authors and readers. Imperiale and McCullough carefully follow the emerging standards for the performance of a metanalysis by specifying the literature-search methods, supplying a list of rejected trials, describing the criteria for the quality review of the articles and describing standards for deciding if the trials may be appropriately aggregated.

Although the authors adhere to many of the standards of metanalysis methodology, in a few areas their methodology could be more rigorously described. It is very important for a metanalysis to use all available studies done on the research question. Imperiale and McCullough describe their use of a computerized database, textbook references and references from the articles retrieved by the first two methods. A more complete search would have specified the use of a professional librarian to perform the computer search, as skill in using these databases varies widely. Other sources for finding references recommended in the literature on metanalysis include Current Contents, databases of unpublished material and polls of senior researchers in the field (4). The latter two sources are important for addressing the issue of publication bias or the selective appearance in the published literature of trials with positive results. The authors’ case for the lack of publication bias, on the grounds that a large proportion of the studies found no significant difference in the study groups, is not compelling. Although the question of how to include unpublished studies in a pooled analysis is complicated, a simple sensitivity analysis can be done to determine how many unpublished negative trials (of good quality) would be required to render the result of the pooled analysis statistically insignificant.
Rosenthal (5) in 1980 suggested an equation based on the Z scores of the pooled studies that, when applied to this metanalysis, would suggest that more than 50 insignificant unpublished studies would be required to raise the p value of the primary result over 0.05. Thus the confidence of the reader in the completeness of a search can usually be improved by a more detailed description of sources used and application of sensitivity analysis to the issue of publication bias.

Also missing from the description of the design of this metanalysis is mention of whether the people selecting a paper for inclusion and assessing its quality were blinded to the authors and the journal in which it appeared. Additionally, no information is presented on the reliability of the data extraction step. Finally, the pooled studies do not consistently use an intention-to-treat analysis. For example, a number of deaths were withdrawn from analysis by the authors of the original trials, either because the deaths occurred early in the course of the experimental treatment or because the subjects did not complete the treatment protocol. Some of these deaths are retained in the results of the studies and some are excluded. The methods section of the metanalysis does not address this issue. These are important sources of potential bias.

The fundamental question addressed in a metanalysis is whether the conflicting findings of different experiments represent a chance event or the application of a treatment to more than one population. In evaluating the homogeneity of the treatment populations the authors very appropriately rely first on graphic methods. We have reproduced their graph of mortality rates in the control vs. treatment group with an enhancement using the area of the data points to represent the sample size of each of the pooled experiments. A line representing the average protective efficacy of prednisone (37% protective efficacy) reported in the paper is superimposed over the data points (Fig. 1). Using a graphic presentation of the data gives the reader much more information than does the summary measure of treatment effect. In fact, one can see that graphically, two populations might be present; one consisting of seven studies lying close to the no-treatment effect line and four studies lying along a line of much steeper slope close to the y axis. If underlying differences in the methodology, study population or treatment intervention supported this division, one might decide not to pool all 11 studies. The other available information about these studies, in fact, does not support this division. The graphic outlier, rather, is also found to have an extremely low methodological quality score. When it is removed, the remaining studies satisfy a statistical test of homogeneity, which is the second step in the analysis. In metanalyses of small numbers of studies, the power to reject the null hypothesis of homogeneity is low; thus graphic methods are stressed as a way of searching for possible heterogeneity in study populations (4, 6).

This metaanalysis is particularly strengthened by its secondary analyses. The presence of hepatic encephalopathy was hypothesized to predict treatment efficacy and a separate analysis of subjects who have encephalopathy found that virtually all treatment benefit was confined to this group (Fig. 2). Likewise, study-level hypotheses predicted that studies that did not exclude subjects with gastrointestinal bleeding and were of lower quality would show less of a treatment effect. These hypotheses were also borne out by the subgroup analysis. This consistency in the distribution of treatment effects is very compelling evidence supporting the authors' conclusions.
The authors present strong support for the use of corticosteroids for the treatment of alcoholic hepatitis in patients with hepatic encephalopathy if the goal is to improve 30-day survival. The significance of these findings is lessened by two factors. First, this is a relatively select group of patients. In the 1989 multicenter trial mentioned above, it was estimated that each participating academic medical center would only admit five or six such patients per year. Second, the long-term survival of these patients is unknown. Several of the pooled studies described late deaths (at 1 to 3 mo) that might well have been steroid complications. Thus, late complications of therapy or an overall poor prognosis could eliminate the treatment benefit of steroids if a longer survival period was stipulated.

The authors have made an important contribution to the question of corticosteroid use in alcoholic hepatitis. They have both described the state of the experimental literature in a structured way and have quantified a treatment effect in a particular subgroup. The priority for future research is to work on refining the definition of the subgroup(s) that benefit from corticosteroids and to determine whether the treatment effect persists for a reasonable length of time beyond 1 mo.

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