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BRIEF ARTICLE

Early mortality of alcoholic hepatitis: A review of data from placebo-controlled clinical trials

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Abstract

AIM: To investigate the early mortality of placebo-treated alcoholic hepatitis patients.

METHODS: Mortality data about alcoholic hepatitis patients who participated in randomized placebo-controlled trials were searched from PubMed, EMBASE, and Cochrane Library, extracted and analyzed.

RESULTS: A total of 661 placebo-treated patients in 19 trials were included. The overall mortality rate was 34.19% with a median observation time of 160 d (range 21-720 d). Hepatic failure, gastrointestinal bleeding and infection were the three main causes of death, accounting for 55.47%, 21.17% and 7.30% of all deaths, respectively. One-month mortality data about 324 placebo-treated alcoholic hepatitis patients in 10 trials were reported with a pooled mortality rate of 20.37%. The one-month mortality rate of patients with moderate to severe alcoholic hepatitis tended to be higher than that of general patients (22.69% *vs* 10.93%, $P < 0.05$), whereas no significant difference was observed between the patients from North America or Europe (22.43% *vs* 18.45%, $P > 0.05$), neither any difference was found between the studies published before and after 1990 (18.18% *vs* 21.88%, $P > 0.05$).

CONCLUSION: Alcoholic hepatitis is a severe liver disease with a high mortality rate, and hepatic failure, gastrointestinal bleeding and infection are the three main causes of death.

Key words: Alcoholic hepatitis; Mortality; Placebo

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INTRODUCTION

Alcohol abuse causes a variety of liver diseases including alcoholic steatosis, alcoholic hepatitis, liver fibrosis and cirrhosis[1,2]. Generally, alcoholic steatosis is a benign lesion with a favorable prognosis if the patient abstains from alcohol use, whereas alcoholic hepatitis, which is observed in approximately 20% of heavy drinkers, is much more serious and requires treatment[3]. With increasing alcohol consumption worldwide, alcoholic liver disease has become a significant global health concern[4,5].

Alcoholic hepatitis is characterized by the development of hepatocellular necrosis and inflammation in

alcoholic patients[6]. Its pathogenesis is a multifactorial process involving metabolism of alcohol to toxic products, Kupffer cell stimulation by endotoxin and nutritional impairment lead to liver injury and inflammation[7]. The treatment of alcoholic hepatitis is still mostly symptomatic or empirical at best. Abstinence and supportive care are the two critical principles for the treatment of alcoholic hepatitis[7]. Several clinical trials have shown that corticosteroids can improve the short-term survival of patients with severe alcoholic hepatitis[8]. Recent evidence also suggests that inhibiting tumor necrosis factor-alpha release is beneficial for alcoholic hepatitis[9].

Since most studies on alcoholic hepatitis have focused either on its pathogenesis or on its potential therapies[7-9], its natural history has not been clearly defined. One possible explanation for this is that many alcoholic hepatitis patients are treated with available therapies immediately upon its diagnosis. Active therapies may significantly influence its natural progression and it is inappropriate to withdraw the treatment for studying its natural history. An understanding of the progression of alcoholic hepatitis would contribute to its prevention and treatment.

Randomized placebo-controlled clinical trials are considered the gold standard for evaluating the efficacy of medical interventions on the disease[10]. Data from placebo-controlled trials may also provide valuable information about its natural history. Since the use of placebo has very little effect on the progression of alcoholic hepatitis[11], placebo-treated patients may be the most suitable subjects for studying its natural history. Since a number of randomized placebo-controlled clinical trials are available on evaluating the treatment of alcoholic hepatitis worldwide[9], it has become feasible to study its natural history by extracting data from these studies.

In this study, we conducted a pooled analysis of data about alcoholic hepatitis patients who were treated with placebo in the eligible randomized placebo-controlled trials, in an attempt to evaluate the early mortality of such patients.

MATERIALS AND METHODS

Systematic literature search

English literature on alcoholic hepatitis patients in randomized placebo-controlled trials was searched from PubMed (1966 - March 2009), EMbase (1974 - March 2009), and Cochrane Library (2009, Issue 1) by two independent investigators using the search terms "alcoholic hepatitis", "alcoholic steatohepatitis", "alcoholic liver disease", "placebo" and "randomized controlled trial". Editorial or letter or comment or review was excluded. Reference lists of the retrieved relevant articles were also searched for additional trials.

Study selection

Two investigators independently performed the study selection. Search findings were screened for potentially eligible trials and full-text articles were obtained for their detail evaluation. Disagreements between the two investigators regarding studies included were solved by consensus.

Studies fulfilling the following criteria were included: studies of a randomized placebo-controlled clinical trial in alcoholic hepatitis patients, studies with enrollment, treatment and analysis of patients well-defined, and studies with more than 15 patients involved in the placebo arm, since we believed that they would not generate enough meaningful data to allow quality assessment. Trials were excluded if relevant data were not extractable or if the case-mix included unclassified alcoholic liver disease patients. Alcoholic hepatitis patients in the placebo arms that received basic active treatment with drugs such as steroids were also excluded.

Data extraction and quality assessment

Data extracted from the studies included name of the first author, publication year, study design, location(s), sample size, randomized method, and gender, mean age and disease severity of patients, description of active therapy, duration of therapy, duration of follow-up, mortality data and causes of death. Data extraction was performed by two independent reviewers. Sections of METHODS and RESULTS were coded to blind reviewers to the above information. Primary investigators were contacted if data were incomplete. The methodological quality of studies included was assessed using a validated quality checklist[12] with a maximum score of 32. A score of 12 (38%) or greater was considered to have acceptable quality[13].

Statistical analysis

Pooled estimate of each variable of interest was calculated and presented as a mean. The cumulative rate of each outcome of interest was calculated in the placebo arm of eligible studies. χ^2 test was used to compare qualitative variables. $P < 0.05$ (2-tailed test) was considered statistically significant.

RESULTS

Description of trials

We identified 892 potentially relevant articles and excluded 845 articles describing studies that obviously did not fulfill the inclusion criteria in this study by reviewing their titles and abstracts. Of the 47 studies selected for full-text review, 19 were excluded because they were not designed as placebo-controlled trials, 3 were excluded because the patients received other active medications[14-16], 4 were excluded because less than 15 patients received placebo[17-20], 1 was excluded because detailed survival data were not available[21], and 1[22] sharing the same placebo with a previous patient[23] was also excluded. Thus, only 19 studies fulfilled the inclusion criteria in this study (Figure 1).

Of these 19 clinical trials, 9 were single center studies, 10 were multi-center studies. A total of 661 patients with a mean age of 46.4 years served as placebo controls. Detailed information and summarized information about the studies included are shown in Tables 1 and 2, respectively.

Pooled mortality

Of the 661 patients, 226 (34.19%) died during a median

Table 1 Description of studies included in pooled analysis

Study	Country	Study type	Severity of alcoholic hepatitis	Placebo size	Mean age	Gender (M/F)	Active therapy	Therapeutic time	Follow-up time	Death (1-mo/ overall)
Helman *et al*[24], 1971	US	Single center	Unclassified	17	47.7	NA	Prednisolone	4 wk	3 mo	NA/6
Blitzer *et al*[25], 1977	US	Single center	Unclassified	16	48.4	NA	Prednisolone	26 d	9 wk	NA/5
Maddrey *et al*[26], 1978	US	Single center	Moderate to severe	31	42.3	23/8	Prednisolone	28-32 d	4 wk	6/6
Baker *et al*[27], 1981	US	Single center	Unclassified	25	41.0	13/12	Insulin/glucagon	3 wk	3 wk	NA/6
Hallé *et al*[28], 1982	US	Single center	Severe	36	38.9	32/4	Propylthiouracil	6 wk	8 wk	7/7
Mendenhall *et al*[29], 1984	US	Multi-center	Moderate to severe	88	50.4	NA	Oxandrolone and prednisolone	1 mo	2 yr	NA/50
Fehér *et al*[30], 1987	Hungary and Spain	Multi-center	Unclassified	33	46.0	18/15	Insulin/glucagon	3 wk	3 wk	NA/14
Carithers *et al*[31], 1989	US	Multi-center	Severe	31	44.4	21/10	Methylprednisolone	4 wk	4 wk	11/11
Trinchet *et al*[32], 1989	Belgique	Multi-center	Unclassified	34	52.0	17/17	Colchicine	6 mo	6 mo	0/0
Akriviadis *et al*[33], 1990	US	Single center	Severe	36	40.8	25/11	Colchicine	1 mo	4 mo	6/8
Panos *et al*[34], 1990	UK	Single center	Unclassified	51	49.3	22/29	Polyunsaturated phosphatidyl choline	2 yr	2 yr	NA/20
Bird *et al*[35], 1991	UK	Single center	Severe	43	51.0	16/14	Insulin/glucagon	3 wk	6 mo	14/15
Mezey *et al*[36], 1991	Spain	Multi-center	Severe	26	43.7	12/14	Amino acid suppl.	3 wk	23 mo	5/16
Ramond *et al*[23], 1992	France	Multi-center	Severe	29	48.2	9/20	Prednisolone	4 wk	6 mo	NA/16
Trinchet *et al*[37], 1992	France	Multi-center	Severe	35	48.0	17/18	Insulin/glucagon	3 wk	1 mo	5/5
Bird *et al*[38], 1998	UK	Multi-center	Unclassified	30	51.0	16/14	Amlodipine	4 wk	4 wk	7/7
Akriviadis *et al*[9], 2000	US	Single center	Severe	52	40.8	40/17	Pentoxifylline	4 wk	160 d	NA/24
Mezey *et al*[39], 2004	US and Spain	Multi-center	Unclassified	26	49.0	16/10	Vitamin E	3 mo	1 yr	NA/5
Boetticher *et al*[40], 2008	US	Multi-center	Moderate to severe	22	49.1	17/5	Etanercept	3 wk	6 mo	5/5

NA: Not available.

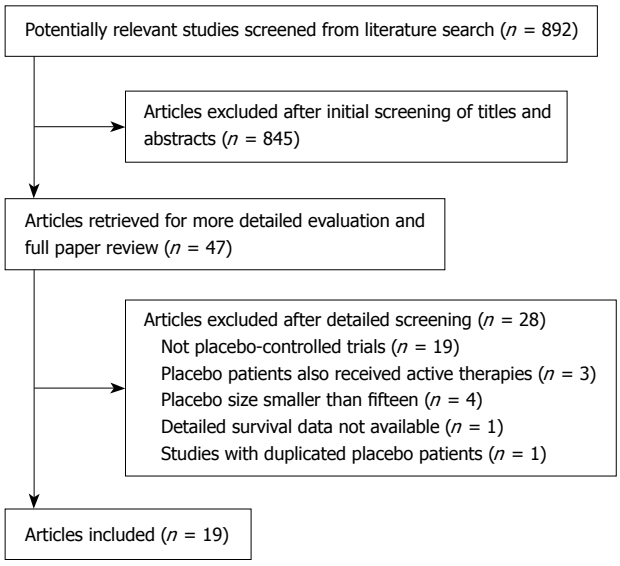

Figure 1 Schema for literature search and study inclusion.

observation time of 160 d (range 21-720 d). Detailed causes of 137 deaths were available from 13 of the studies. Hepatic failure, gastrointestinal bleeding and sepsis were the three main causes of death, accounting for 55.47%, 21.17% and 7.30% of all deaths, respectively. One-month mortality data were available in 10 studies and the pooled mortality rate for these patients was 20.37% (66/324).

Subgroup analysis

Since the observation time was different among the studies included, we did not directly compare the overall mortality rate of alcoholic patients. In subgroup analysis, we compared the one-month mortality rate of alcoholic patients based on the data extracted from 10 studies.

Of the 10 studies selected for comparison, 2 were performed in moderate to severe alcoholic hepatitis patients, 6 in severe alcoholic hepatitis patients, 2 in unclassified alcoholic hepatitis patients. The pooled one-month mortality rate of such patients tended to increase with increasing severity of the disease. The pooled mortality rate of unclassified, moderate to severe and severe alcoholic hepatitis patients was 10.94% (7/64), 20.75% (11/53), and 23.19% (48/207), respectively (Table 2).

Of the 10 studies, 5 were conducted in the United States and 5 in Europe (UK, France, Belgium and Spain) showing a pooled mortality rate of 22.44% (35/156) and 18.45% (31/168), respectively. No significant difference was found in pooled mortality rate between the patients from North America or Europe ($\chi^2 = 0.791$, $P = 0.409$) (Table 2).

Of the 10 studies, 5 were published before December 31, 1990, showing a pooled total mortality rate of 17.86% (30/168), 5 were published after January 1, 1991, showing a pooled mortality rate of 23.08% (36/156). No significant difference was observed in pooled mortality rate between the publication time ($\chi^2 = 1.359$, $P = 0.244$) (Table 2).

DISCUSSION

In this study, we extracted data about alcoholic hepatitis patients in randomized placebo-controlled trials and

Table 2 Comparison of pooled one-month mortality by different variables

	Studies (*n*)	Placebo-treated patients (*n*)	Gender (M/F)	One-month death (*n*)	One-month mortality rate (%)	χ^2	*P* value
Severity of disease							
Unclassified	2	64	33/31	7	10.94	4.375	0.038
Moderate to severe	8	260	171/89	59	22.69		
Geographical area(s)							
US	5	156	119/37	35	22.44	0.791	0.409
Europe	5	168	85/83	31	18.45		
Publication year							
Before 1990	5	168	118/50	30	17.86	1.359	0.271
After 1991	5	156	86/70	36	23.08		

analyzed their mortality, showing that the mortality rate of alcoholic hepatitis patients is positively correlated with the severity of the disease. Our pooled analysis also showed that hepatic failure, gastrointestinal bleeding and infection were the three main causes of early death of alcoholic hepatitis patients, which may be of great importance in clinical practice.

Unlike nonalcoholic hepatitis, a chronic form of liver disease associated with obesity, alcoholic hepatitis is an acute and potentially life-threatening form of liver disease[41]. The cause of its early mortality is not clear since it is difficult to evaluate a sufficient number of such patients without prompt treatment upon diagnosis. In this study, the data about 661 placebo-treated patients extracted from 19 placebo-controlled trials were evaluated, showing that the mortality rate of alcohol hepatitis patients is 34.19% with a pooled one-month mortality rate of 20.37%, which increases with increasing disease severity. These findings suggest that alcoholic hepatitis patients should be treated promptly upon diagnosis.

Recognizing the causes of death in alcoholic hepatitis patients contributes to the treatment of alcoholic hepatitis. Hepatic failure, gastrointestinal bleeding and infection are the three main causes of early death in alcoholic hepatitis patients. Hepatic failure can be prevented by avoiding exposure to certain hepatotoxic drugs, such as acetaminophen, carbon tetrachloride and galactosamine. Corticosteroid therapy is effective against alcoholic hepatitis[8], but it may result in complications such as gastrointestinal bleeding. It is, therefore, necessary to evaluate the risks and benefits of corticosteroid therapy for alcoholic hepatitis before it is used.

Due to the limited available data, there are some limitations in this study. First, we did not analyze the factors predicating the early mortality rate of alcoholic hepatitis patients since necessary data could not be extracted from the studies included. However, our pooled analysis provided the main causes of death, which may be of importance in clinical practice. Second, we did not clarify whether the mortality rate of alcoholic hepatitis patients varies between males and females. Since females are reported to be more sensitive to alcohol abuse[7], it would be of interest to compare mortality rates of both genders. Third, we did not analyze the potential heterogeneity due to the relative small number of placebo patients. We grouped all the patients irrespective of their age, gender, ethnic distinction, or severity of disease. The pooled analysis of all these cases provided a clearer general picture of early mortality rate in a relatively large sample of alcoholic hepatitis patients.

In summary, alcoholic hepatitis is a severe liver disease with a high early mortality, especially among those with moderate to severe alcoholic hepatitis. Hepatic failure, gastrointestinal bleeding and infection are the three main causes of early death in alcoholic hepatitis patients.

COMMENTS

Background

Alcoholic hepatitis is a potentially life-threatening complication of alcohol use, but its natural history has not been clarified so far.

Research frontiers

This study investigated the early mortality of placebo-treated alcoholic hepatitis patients.

Innovations and breakthroughs

This study has confirmed that alcoholic hepatitis is a severe liver disease with a high early mortality, especially among those with moderate to severe disease.

Applications

The results of this study suggest that hepatic failure, gastrointestinal bleeding and infection should be treated in order to prevent early death of alcoholic hepatitis patients.

Terminology

Alcoholic hepatitis is a disease resulting from hepatocellular necrosis and inflammation in alcoholic patients. Its pathogenesis is a multifactorial process involving metabolism of alcohol to toxic products. Kupffer cell stimulation by endotoxin and nutritional impairment lead to liver injury and inflammation, *etc*.

Peer review

This is an interesting review of data concerning the early mortality of alcoholic hepatitis. The authors critically discussed the limitation of their survey.

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