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Systematic review: glucocorticosteroids for alcoholic hepatitis – a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials

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SUMMARY

Background
Glucocorticosteroids versus placebo or no intervention for patients with alcoholic hepatitis have been evaluated for more than 35 years. However, the results of randomized trials and meta-analyses differ substantially.

Aim
To review all randomized clinical trials of glucocorticosteroids vs. placebo or no intervention for patients with alcoholic hepatitis.

Methods
We searched for randomized trials published before July 2007. The trials were assessed for risk of bias.

Results
We included 15 trials with a total of 721 randomized patients. The overall mortality rate was 39.5%. Twelve of the fifteen trials were at risk of bias. Glucocorticosteroids did not statistically reduce mortality compared with placebo or no intervention (relative risk 0.83, 95% CI 0.63–1.11). Glucocorticosteroids significantly reduced mortality in the subgroup of trials with patients with Maddrey's score of at least 32 or hepatic encephalopathy and with low-bias risk. In all analyses, heterogeneity was significant and substantial. Trial sequential analyses using heterogeneity-adjusted information size demonstrated no significant effect of glucocorticosteroids on mortality. Weighted logistic regression analyses taking prognostic factors at randomization into consideration found no significant effect of glucocorticosteroids on mortality.

Conclusions
The current evidence base of mainly heterogeneous with high bias risk trials does not support the use of glucocorticosteroids in alcoholic hepatitis. Large, low-bias risk placebo-controlled randomized trials are needed.

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INTRODUCTION

Alcoholic hepatitis is often accompanied by cirrhosis and associated with high mortality. Glucocorticosteroid for alcoholic hepatitis has gained some acceptance in clinical practice. In 1992, 2% of European gastroenterology specialists always used it as standard of care, and 66% used it sometimes.[1] However, there are discrepancies in the literature as several randomized trials and meta-analyses have reached contradictory results.[2, 3] Glucocorticosteroids for patients with alcoholic hepatitis continue to be advocated.[4–6] These recommendations are based on selected parts of the evidence.[2, 3, 7, 8]

We have been unable to identify systematic reviews on the topic. Therefore, we conducted a Cochrane systematic review, including meta-analyses of randomized trials, to evaluate both beneficial and harmful effects of glucocorticosteroids for patients with alcoholic hepatitis. Meta-analyses may overestimate treatment effect because of systematic errors ('bias').[9–11] To avoid systematic errors, we considered the bias risks in our analysis.[9–11] Meta-analyses may also overestimate treatment effect because of random errors ('play of chance').[12–15] Especially, randomized trials and meta-analyses with few participants or outcomes are at risk of producing random errors.[12–15] To avoid random errors, we calculated an information size (i.e., a required meta-analysis sample size) as large as that of an adequately powered randomized trial and quantified the precision of the available evidence accordingly.[12] At least 11 meta-analyses have previously been published on glucocorticosteroids for alcoholic hepatitis.[3] None of them met the requirements expected of reliable meta-analyses, i.e., none of them was conducted as part of a systematic review.[3, 15] Nevertheless, results from clinical trials have been looked at, analysed, and presented repeatedly. In this regard, it is inevitable that statistical tests were performed on 'statistical significance' of the results. The repeated testing of accumulating data in cumulative meta-analyses are analogous to what is known as 'repeated significance testing' or multiplicity, a problem that is well known in data monitoring of clinical trials. Repeated significance testing on accumulating data, if not adjusted, increases the type I error, that is, the risk of falsely obtaining a 'positive result'. Therefore, we sought to control the risk of type I error in our primary meta-analyses by utilizing the methodology of trial sequential analysis.[12]

METHODS

Data extraction

We applied The Cochrane Collaboration methodology and followed our peer-reviewed, published Cochrane protocol.[16] Only randomized trials were included. Patients with severe, clinically overt alcoholic hepatitis diagnosed through clinical and biochemical criteria according to the diagnostic work-up used in the trial were included. Our primary outcome measure was the number of deaths.[16] Secondary outcomes were liver-related mortality, clinical symptoms and complications, liver biochemistry, liver histology, and adverse events. The interventions were peroral or parenteral administration of glucocorticosteroids at any dose vs. placebo or no intervention. Additional interventions were allowed, as long as intervention groups in the individual trial received the additional intervention equally.

We identified the randomized trials by searching The Cochrane Hepato-Biliary Group Controlled Trials Register (July 2007), The Cochrane Central Register of Controlled Trials in The Cochrane Library (Issue 2, 2007), MEDLINE (1950 to July 2007), EMBASE (1980 to July 2007), Science Citation Index EXPANDED (http://isi3.isiknowledge.com/portal.cgi from 1945 to July 2007), and LILACS (1982 to July 2007).

We evaluated the risk of bias in the trials by assessing the adequacy of the generation of the allocation sequence, allocation concealment, blinding, and follow-up to identify trials with low bias risk.[9–11, 15]

We extracted data on the diagnostic procedures and participants' age, gender, severity of liver disease according to Maddrey's score,[17] and hepatic encephalopathy. We extracted data on glucocorticosteroid dosage, duration of therapy, and route of administration, as well as intervention in the control group and any co-intervention.

Statistical analyses

All analyses on mortality were performed according to intention-to-treat method, i.e. we included all randomized patients.[15] RevMan Analyses was used for random-effects model relative risk (RR) meta-analyses.[15] This model was chosen as the trials included patients with varying definitions of alcoholic

hepatitis over many years. Furthermore, the model choice was justified by the apparent statistical heterogeneity. We estimated heterogeneity by I^2 and considered it significant if $P < 0.1$.[15, 18] I^2 describes variance between trials rather than sampling error.[15, 18] I^2 lies between 0% (no heterogeneity) and 100% (maximal heterogeneity). In case significant heterogeneity was found, the potential causes were explored by performing subgroup analyses with test of interaction according to severity of alcoholic hepatitis at inclusion, risk of bias, and year of publication.

A funnel plot in which a trial's RR is plotted against the standard error (S.E.) to the log RR explored presence of bias. If the plot is symmetric, like an inverted V, bias is unlikely. If the plot is asymmetric, bias is possible.[15]

All the included trials were small. Meta-analysis of such trials are at risk of producing random errors because repetitive testing of accumulating data in cumulative meta-analysis raises the risk of random errors and the sample size requirement, analogous to that of a single optimally powered clinical trial, may not be met.[12] Therefore, to avoid random errors, we calculated the required information size (i.e. the meta-analysis information size needed to detect or reject a certain intervention effect).[12] Information size calculation also accounted for the heterogeneity present in the meta-analyses as proposed by Wetterslev *et al.*[12] Information size calculation was based on the assumption of a plausible relative risk reduction of 0.20 or on the relative risk reduction observed in trials with low bias risk.[12] The underlying assumption for our trial sequential analysis is that significant testing is performed each time a new trial is published.[12] The trial sequential analysis was performed with a desire to maintain an overall 5% of type I error (which is standard in most meta-analyses and systematic reviews). Trial sequential analysis depends on the quantification of the required information size. In this context, the smaller the required information size, the more lenient the trial sequential analysis, thus the more lenient the criteria for statistical significance.[12]

Weighted logistic regression analysis was applied using the summarized data (e.g. proportion with encephalopathy, mean bilirubin value) of the treatment and control groups of the trials that provided this information.[2]

RESULTS

Description of trials

Through electronic searches up to July 2007, we identified 372 publications potentially on glucocorticosteroids for patients with alcoholic hepatitis. We excluded 330 publications that were either duplicates or had different objectives from those in our review. A total of 42 publications were further assessed; 22 publications describing 19 studies were excluded (see Appendix with list of excluded studies).[19]

Fifteen trials (Table 1) randomizing a total of 721 patients described in 20 publications were included.[17, 20–33] The smallest trial included 20 patients[21] and the largest 178 patients.[29] Tables 1–3 show the characteristics of included trials.

All the patients had alcoholic hepatitis. Patients with gastrointestinal bleeding or bacterial infection were excluded from the trials. The patients had varying degrees of alcoholic hepatitis, assessed by Maddrey's score of at least 32 or spontaneous hepatic encephalopathy (six trials, 249 patients) or other criteria (liver biochemistry or histology) (eight trials, 404 patients, with part of Helman's patients contributing[20]), or had less severe forms of alcoholic hepatitis (two trials, 68 patients) (Table 2). The Galambos trial[24] is an unpublished trial quoted by Conn.[34] As specified in our protocol, such trials should also be included.[16] We identified one further unpublished trial, but have been unable to obtain any data from it.[35]

Mortality

Overall, 285/721 (39.5%) patients died. Combining all trials failed to show a statistically significant effect of glucocorticosteroids on mortality with 130/360 (36.1%) deaths in the glucocorticosteroid group vs. 155/361 (42.9%) deaths in the placebo or no intervention group (RR 0.83; 95% CI 0.63–1.11). There was statistically significant heterogeneity (I^2 = 49.7%; $P < 0.05$) (Figure 1).

Subgroup analyses based on bias risk of the trials, severity of alcoholic hepatitis and year of publication

In the subgroup analysis of three trials with low bias risk, we found a significant mortality reduction in

Table 1. Methodological quality of randomized clinical trials comparing glucocorticosteroids vs. placebo or no intervention

Trial	Generation of the allocation sequence	Allocation concealment	Blinding	Follow-up	Sample size calculation	Intention -to-treat analysis	Methological quality*
Helman *et al.*[20]	Unclear	Adequate	Unclear	Adequate	No	Yes	Low
Porter *et al.*[21]	Adequate	Adequate	Adequate	Adequate	No	No	High
Campra *et al.*[22]	Adequate	Adequate	Inadequate	Adequate	No	No	Low
Blitzer *et al.*[23]	Adequate	Adequate	Unclear	Adequate	No	No	Low
Galambos [24]	Unclear	Unclear	Unclear	Unclear	No	No	Low
Mendenhall and Goldberg [25]	Unclear	Unclear	Unclear	Unclear	No	Yes	Low
Maddrey *et al.*[17]	Adequate	Unclear	Adequate	Adequate	No	No	Low
Shumaker *et al.*[26]	Unclear	Adequate	Unclear	Adequate	No	Yes	Low
Depew *et al.*[27]	Unclear	Unclear	Adequate	Adequate	Yes	Yes	Low
Theodossi *et al.*[28]	Unclear	Adequate	Inadequate	Adequate	No	No	Low
Mendenhall *et al.*[29]	Unclear	Adequate	Unclear	Adequate	No	Yes	Low
Bories *et al.*[30]	Adequate	Unclear	Inadequate	Adequate	No	Yes	Low
Carithers *et al.*[31]	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Ramond *et al.*[32]	Adequate	Adequate	Adequate	Adequate	Yes	No	High
Richardet *et al.*[33]	Unclear	Unclear	Inadequate	Inadequate	No	No	Low

* Based on adequacy of generation of the allocation sequence, allocation concealment, blinding, and follow-up. When methodological quality is low bias risk is high.

patients who were administered glucocorticosteroids vs. the control group (RR 0.33, 95% CI 0.11–0.97). This analysis was associated with a significant heterogeneity (I^2 = 73.4%; P = 0.04) and included only 46 deaths in 147 patients (Figure 1).

In the subgroup of six trials including patients with Maddrey's score of at least 32 or spontaneous hepatic encephalopathy, glucocorticosteroids were associated with a statistically significant reduction in mortality vs. the control group (RR 0.37, 95% CI 0.16–0.86). There was again statistically significant heterogeneity (I^2 = 66.1%) and the analysis included only 64 deaths in 249 patients (Figure 2).

Combining the other trials, including patients with severe alcoholic hepatitis, showed no significant effect of glucocorticosteroids on mortality (RR 1.06, 95% CI 0.89–1.26) and there was no heterogeity (I^2 = 0). The mortality in the control arm of these trials was higher than the trials requiring a Maddrey's score of at least 32 or hepatic encephalopathy for inclusion (49.3% compared to 37.7%).

Subgroup analyses based on year of publication of the trial (before 1980 compared to 1980 or later) did not demonstrate significant differences in intervention effect.[19] Subgroup analyses of the trials based on the comparison group did not demonstrate a significant reduction in mortality in the trials with placebo or no intervention.[19]

We found no significant effect of glucocorticosteroids on mortality after excluding trials that were only reported as abstracts.[19]

Trial sequential analyses

Figure 3 shows the trial sequential analyses based on the information size adjusting for the presence of heterogeneity among all the 15 trials. The required heterogeneity-adjusted information size using 5% risk of type I error (risk of obtaining a false 'positive' result) and 20% risk of type II error (risk of obtaining false 'negative' result) and an anticipated RR = 0.80 (i.e. a relative risk reduction in mortality by glucocorticosteroids of 20%) is 1307 patients. The required information size using 1% risk of type I error instead is 1944 patients. The analyses did not yield any sign of statistical significance whatsoever.

We also conducted trial sequential analyses using heterogeneity-adjusted information size based on the relative risk observed in trials with low risk of bias, i.e. a relative risk of 0.31, of all the 15 trials

Table 2. Characteristics of included trials comparing glucocorticosteroids vs. placebo or no intervention

Trial	Inclusion criteria of alcoholic hepatitis	Numbers of patients		Glucocorticosteroids group intervention	Control group	Duration of trial mean
		Steroid	Control			
Helman *et al.*[20]	Various degrees of alcoholic hepatitis	20	17	Prednisolone (40 mg)	Placebo	4 months
Porter *et al.*[21]	Severe	11	9	Methyl-prednisolone (40 mg)	Placebo	8 weeks
Campra et al.[22]	Severe	20	25	Prednisone (0.5 mg/kg)	No intervention	6 weeks
Blitzer et al.[23]	Severe	17	16	Prednisolone (40 mg)	Placebo	8 weeks
Galambos [24]	Severe	8	9	Not stated	Not stated	Not stated
Mendenhall and Goldberg[25]	Severe	12	17	Prednisolone (60 mg)	Placebo	3 weeks
Maddrey *et al.*[17]	Maddrey score at least 32, or hepatic encephalopathy	25	32	Prednisolone (40 mg)	Placebo	4 weeks
Shumaker *et al.*[26]	Severe	12	15	Methyl-prednisolone (80 mg)	Placebo	4 weeks
Depew *et al.*[27]	Maddrey score at least 32, or hepatic encephalopathy	15	13	Prednisolone (40 mg)	Placebo	6 weeks
Theodossi *et al.*[28]	Severe	28	32	Methyl-prednisolone (1 g)	No intervention	1½ weeks
Mendenhall *et al.*[29]	Severe	90	88	Prednisolone (60 mg)	Placebo	1 year
Bories *et al.*[30]	Less severe	24	21	Prednisolone (40 mg)	No intervention	3 months
Carithers *et al.*[31]	Maddrey score at least 32, or hepatic encephalopathy	35	31	Methyl-prednisolone (32 mg)	Placebo	4 weeks
Ramond *et al.*[32]	Maddrey score at least 32, or hepatic encephalopathy	33	32	Prednisolone (40 mg)	Placebo	6 months
Richardet *et al.*[33]	Maddrey score at least 32, or hepatic encephalopathy	12	11	Prednisolone (40 mg)	Placebo	8 days

(Figure S1, please see http://ctu.rh.dk). The low bias, heterogeneity-adjusted information size (LBHIS) using 5% of type I error and 20% risk of type II error is 95 patients. The LBHIS using 1% risk of type I error is 142 patients. The 721 patients randomized have long surpassed this information size. None of the chosen trial sequential monitoring boundaries was reached or crossed. Accordingly, we are able to reject an intervention effect of this size. Trial sequential analyses of the three low-bias risk trials alone revealed no sign of statistical significance.[19]

We also conducted the trial sequential analyses using heterogeneity-adjusted information size based on the six trials including patients with Maddrey's score of at least 32 or spontaneous hepatic encephalopathy (Figure S2, please see http://ctu.rh.dk). The heterogeneity-adjusted information size using 5% risk type I error, 20% risk of type II error, and a RR = 0.80 is 1627 patients. The information size using 1% risk of type I error is 2420 patients. These information sizes are far from reached with only 249 patients randomized in these six conducted trials. As shown (Figure S2, please see http://ctu.rh.dk), the obtained *z* score did not cross the trial sequential monitoring boundaries.

Funnel plot asymmetry

The funnel plot suggested asymmetry with small trials finding larger intervention effects (Figure S3, please see http://ctu.rh.dk).

Table 3. Characteristics of included trials comparing glucocorticosteroids vs. placebo or no intervention in each arm of the trial, with proportion of men, mean age (years), proportion with encephalopathy, proportion with ascites, mean serum bilirubin (mg/100 mL), and mean plasma albumin (g/100 mL), and additional treatment

Trial	Men (%)	Age (years)	Encephalopathy (%)	Ascites (%)	Bilirubin (mg/100 mL)	Albumin (g/100 mL)	Patients in both groups received
Helman *et al.*[20]							
Steroid*	32	47.8	40.5	73	10.8	2.99	High protein and calorie diet plus vitamins
Control	32	47.8	40.5	73	10.8	2.99	
Porter *et al.*[21]							
Steroid*	64	44.6	64	82	24.6	2.69	Patients got no additional treatment
Control	67	49.5	89	100	24.3	2.39	
Campra *et al.*[22]							
Steroid*	40	43.1	40	65	18.5	2.2	When encephalopathy protein intake was reduced
Control	35	42.7	40	48	17.8	2.5	
Blitzer *et al.*[23]							
Steroid*	100	47.2	25	66	25.4	2.3	Hospital diet 2.600 kg calories
Control	100	48.4	12	81	15.4	2.2	
Mendenhall and Goldberg[25]							
Steroid*	100	No data	No data	No data	17	2.7	Supportive care
Control	100	No data	No data	No data	17	2.7	
Maddrey 1978[17]							
Steroid*	50	40	21	67	11.8	2.6	3.000 kg calories diet
Control	74	42.3	32	58	11.2	2.4	
Shumaker *et al.*[26]							
Steroid*	42	46	33	No data	22.4	2.4	Patients got no additional treatment
Control	46.4	44.2	47	No data	18.6	2.5	
Depew *et al.*[27]							
Steroid*	67	49.8	100	87	24.7	2.4	Supportive care plus vitamins
Control	46	48.2	100	92	26.2	2.4	
Theodossi *et al.*[28]							
Steroid*	70	No data	74	93	11	2.5	Standard diet, while in too ill patients supportive care
Control	43	No data	50	71	17.5	2.8	
Mendenhall *et al.*[29]							
Steroid*	100	51.5	67	93	16.1	2.6	Supportive care
Control	100	50.4	70	86	15.4	2.5	
Bories *et al.*[30]							
Steroid*	67	41.3	16.7	50	8.8	3.1	1.500 kg calories and 50 g protein per day
Control	52	49.2	18.8	57	9.7	2.9	
Carithers *et al.*[31]							
Steroid*	57	43.1	40	71	16.8	2.4	3.000 kg calories diet plus vitamins
Control	68	44.4	61	65	17.9	2.45	
Ramond *et al.*[32]							
Steroid*	31	48.1	28	75	12.5	2.7	3.000 kg calories diet plus vitamins
Control	31	48.2	34	86.2	16.6	2.6	

Helman *et al.*[20] and Mendenhall and Goldberg[25] only present the overall average for the trial of the descriptive values. These total average values are applied for the treatment and control groups in this analysis. Galambos[24] and Richardet *et al.*[33] are not included, as no descriptive variables are available from them.

* Steroid is the short form for glucocorticosteroid.

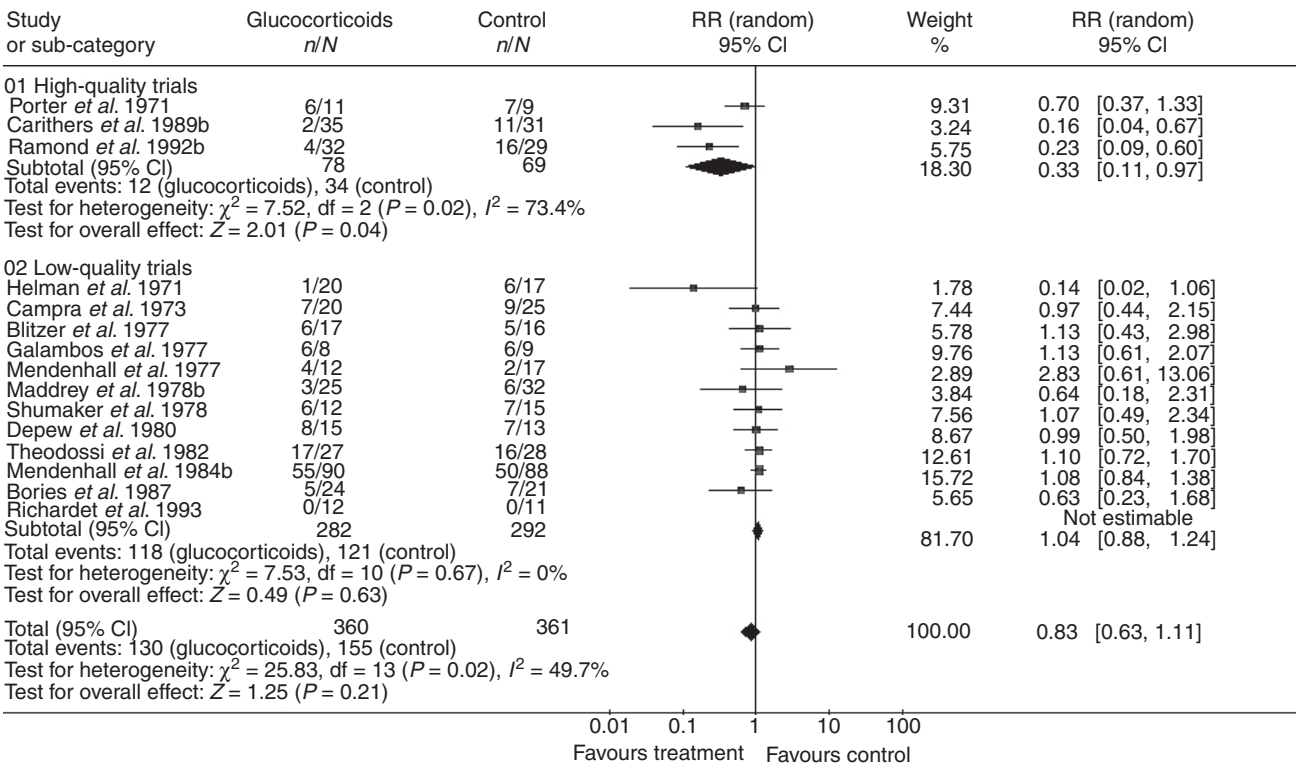

Figure 1. Mortality of patients with alcoholic hepatitis randomized to glucocorticosteroids vs. placebo or no intervention. Subgroup analysis stratifying the randomized clinical trials according to the risk of bias [trials having all four components adequate vs. other trials (see Methods)].
n/N, number of patients who died/number of patients randomized; RR,relative risks; CI, confidence interval.

Sensitivity analysis including trials using nutrition as control intervention and analyses taking prognostic factors at randomization into consideration

Sensitivity analysis including two excluded trials using nutrition as control intervention[36, 37] did not noticeably change the results (RR 0.84, 95% CI 0.64–1.10). Heterogeneity was significant (I^2 = 52.9%).[19]

Univariate meta-regression analysis (Table 3) of all trials providing data showed a significant prognostic influence of mean age, mean serum bilirubin, and proportion with ascites, encephalopathy, and male gender. Therapy and serum albumin concentration did not interact. The final multivariate meta-regression analysis is shown in Table 4. The effect of therapy is close to zero when adjusted for imbalance in the significant prognostic variables like age and serum bilirubin (adjusted log death risk (glucocorticosteroid vs. control) −0.098, 95% CI −0.50 to 0.31); adjusted relative death risk (glucocorticosteroid vs. control) 0.91, 95% CI 0.60–1.36).

We observed similar findings including the 15 trials comparing glucocorticosteroids vs. placebo or no intervention (data not shown).

Other outcome measures

Combining the results of eight trials reporting liver-related mortality demonstrated no significant effect of glucocorticosteroids vs. placebo or no intervention (RR 0.65, 95% CI 0.37–1.12). There was significant heterogeneity (I^2 = 53.3%). In the glucocorticosteroid group 39/180 (21.7%) patients died vs. 60/181 (33.1%) patients in the control group.[19]

Combining the results of four trials providing data demonstrated no significant effects of glucocorticosteroids on ascites, variceal bleeding, hepatic encephalopathy, and hepatocellular carcinoma.[19]

Combining the results of the eight trials reporting adverse events[17, 20, 21, 23, 29, 30, 32] demonstrated a significantly higher proportion of patients with adverse events in the glucocorticosteroid group (RR

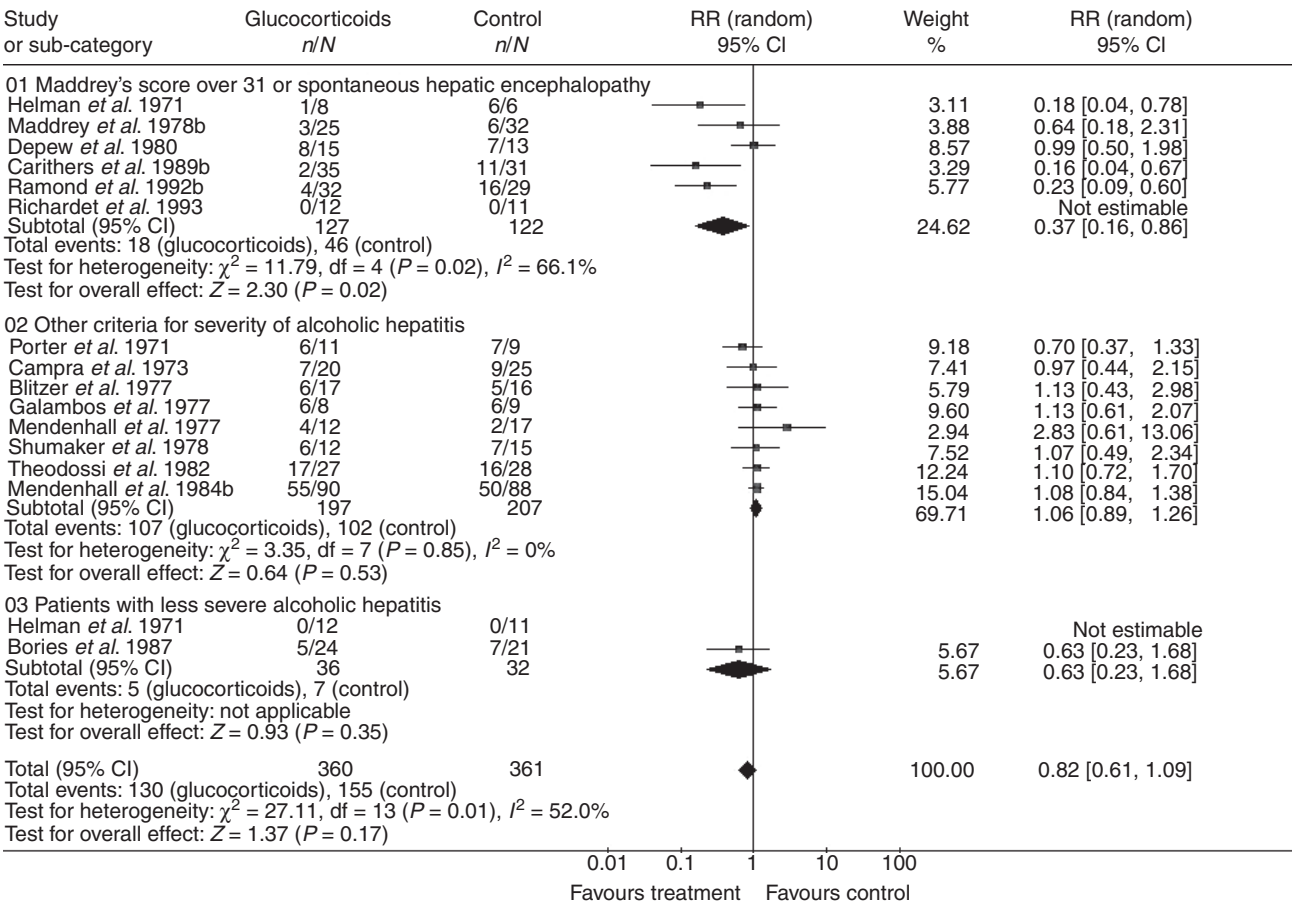

Figure 2. Mortality of patients with alcoholic hepatitis randomized to glucocorticosteroids vs. placebo or no intervention. Subgroup analysis stratifying the randomized clinical trials according to the severity of alcoholic hepatitis (see Methods). *n/N*, number of patients who died/number of patients randomized; RR, relative risks; CI, confidence interval.

3.63, 95% CI 1.95–6.76). In the glucocorticosteroids group, 40/239 (16.7%) patients (23 diabetes mellitus, 10 Cushing's syndrome, five infection, one suspicious of gastro-intestinal bleeding, one suspicious of gastric ulcer) had adverse events vs. 9/237 (3.8%) control patients (five diabetes mellitus, four Cushing's syndrome).

DISCUSSION

Our systematic review demonstrates that there is insufficient evidence to recommend or refute glucocorticosteroids for patients with alcoholic hepatitis or for any subgroup of patients with alcoholic hepatitis. We are not able to reach any conclusion after 721 patients with alcoholic hepatitis have been randomized during the past 35 years. Even if 2000 patients had been randomized, estimates of intervention effects may change substantially.[38]

Our overall analyses regarding mortality and liver-related mortality showed no significant beneficial effects of glucocorticosteroids, but heterogeneity was substantial. It may be misleading to quote an average value for the treatment effect when data are that heterogeneous.[15] To unravel the reason for the heterogeneity, we conducted subgroup analyses. They demonstrated that it was low-bias risk trials that observed beneficial effects, whereas trials with high risks of bias did not observe significant effects. This is contrary to the usual observation, in which intervention effects are overestimated in high-bias risk trials.[9–11, 15, 39] In the present review, the low-bias risk trials were very small and with very few deaths. Therefore, our findings could be because of random

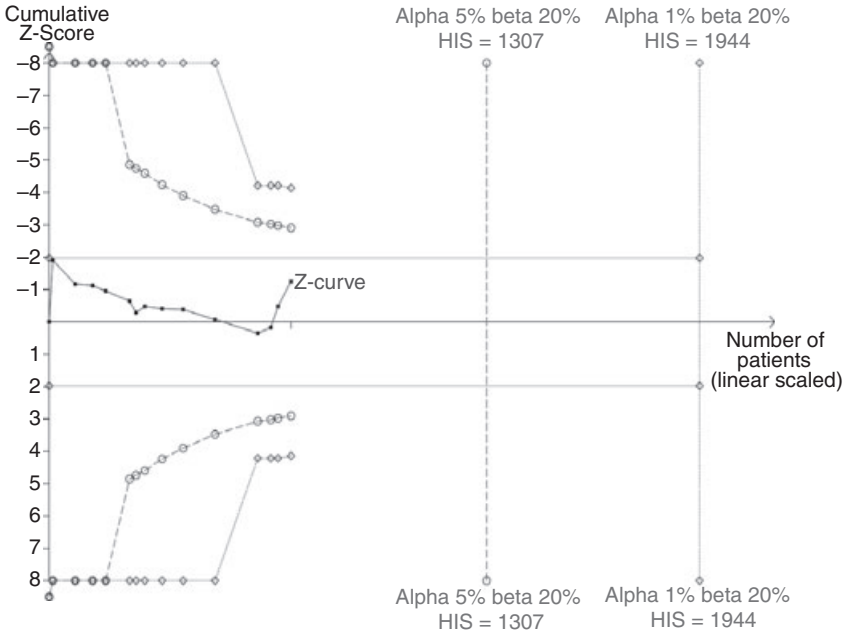

Figure 3. Trial sequential analyses of 15 trials on glucocorticosteroids vs. placebo or no intervention for patients with alcoholic hepatitis. The heterogeneity-adjusted information size (HIS) based on a relative risk of 0.80, mortality in the control group of 50%, alpha = 5%, and beta = 20% is 1307 patients (vertical dotted line). The dotted lines are trial sequential monitoring boundaries calculated accordingly. The heterogeneity-corrected information size (HIS) using alpha = 1% and beta = 20% is 1944 patients (vertical etched line). The etched lines are trial sequential monitoring boundaries calculated accordingly. The horizontal lines are *z* scores of −1.96 and 1.96, equal to two-sided $P = 0.05$. *X*-axis: the information size, i.e., the number of patients randomized (and the *z*-score of the accumulating data) and *Y*-axis is *z* score.

Table 4. Logistic-regression analysis adjusting the treatment effect (glucocorticosteroids vs. placebo, no intervention, or nutrition for patients with alcoholic hepatitis) for the influence of imbalances in prognostic descriptive variables

Variables	Coefficients	Standard errors	*t*-values	*P*-values
Age	0.157528	0.033677	4.678	0.000079
Serum bilirubin	0.056781	0.025656	2.213	0.035868
Therapy (experim/control)	−0.098128	0.207481	0.473	0.640198
Constant	−8.604332	1.656400	−5.195	0.00002
		s.d. of residuals = 0.5652400		
		$R^2 = 0.52$	Adjusted $R^2 = 0.47$	$P = 0.00022$

errors.[12–15] Accordingly, trial sequential analyses demonstrated no significant effect of glucocorticosteroids. Furthermore, our subgroup analyses suggested that a possible beneficial effect of glucocorticosteroids was observed in patients with either Maddrey's score of at least 32 or hepatic encephalopathy. However, most of the remaining trials had a similar or higher control group mortality, but no significant effect of glucocorticosteroids. This observation questions why glucocorticosteroids might have beneficial effects in certain subgroups but not in others. Results based on subgroups should always require confirmation in new trials.[15]

Accordingly, there seems to be insufficient evidence to support glucocorticosteroids for patients with alcoholic hepatitis. First, there was no significant effect of glucocorticosteroids considering all the 15 trials. In all our analyses, there was a significant and substantial heterogeneity ($P < 0.1$ and $I^2 \geq 50\%$). This

heterogeneity raises the possibility that meta-analyses may provide biased information. All the trials were small. Small trials, irrespective of their methodological quality, tend to overestimate intervention effects.[13–15] We properly require approximately 1000 patients randomized to glucocorticosteroids vs. placebo before we can demonstrate or reject a clinically relevant 20% mortality reduction. Neither our present nor previous analyses,[2] taking prognostic factors at randomization into consideration, show a significant effect of glucocorticosteroids on mortality. We confirm our previous analyses showing funnel plot asymmetry with small trials finding the largest benefit.[2] We observed that glucocorticosteroids gave rise to several adverse events, which, in many cases, may be considered severe.

Our systematic review has several limitations. As for all systematic reviews, the quality and quantity of available evidence limit the findings. The methodological quality of most of the trials was assessed using the published reports, which may not accurately reflect the conduct of the trials. Few authors responded to our requests for further information. Many trials were not powered to detect the influence of glucocorticosteroids on mortality. In fact, only three trials provided a sample size estimation. The examined patient populations varied. The type, dose and duration of glucocorticosteroids as well as the length of follow-up varied. We observed the most beneficial effects of glucocorticosteroids on mortality in the trials with the least risk of bias. This may seem to contrast with previous findings,[9–11, 39–41] but it is in accord with previous studies of meta-analyses.[15, 39–41] Our decision to conduct trial sequential analysis was taken after the protocol for this review had been published.[16] These analyses may, therefore, be considered post-hoc analyses. However, trial sequential analysis methods have mainly been developed after publication of our protocol.[12, 42–45] The trial sequential analyses demonstrate that we have never had convincing evidence in favour of glucocorticosteroids for alcoholic hepatitis – and we are still far from having it.

Our review includes 15 randomized trials, i.e. two more trials than previous meta-analyses.[3] We did not include trials that used nutrition as control intervention, but included such trials in sensitivity analyses.[36, 37] This did not have a noticeable effect on our results. There is still uncertainty about the effects of enteral or parenteral nutrition on mortality in patients with alcoholic hepatitis.[46, 47]

Data on other outcomes are also too sparse to support or refute glucocorticosteroids for alcoholic hepatitis.[48] However, absence of evidence is not evidence of absence.[39] Large, high quality randomized trials comparing glucocorticosteroids vs. placebo are still needed.

CONTRIBUTORS

HHS drafted the protocol. EC and CG revised the protocol. CG and AR co-ordinated the identification of trials. AR, HHS, and EC conducted the trial selection and the data extraction. AR, HHS, and CG conducted the standard statistical analyses. EC conducted the statistical analyses taking prognostic factors at randomization into consideration. KT, JW, and CG conducted the trial sequential analyses. AR and CG drafted and revised the review. HHS, EC, KT, and JW revised the review.

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SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article:

Appendix S1. List of excluded publications and reasons for exclusion

Figure S1. Trial sequential analyses of 15 trials on glucocorticosteroids vs. placebo or no intervention for

patients with alcoholic hepatitis. The heterogeneity-corrected information size (HIS) based on a relative risk of 0.33 in low-bias risk trials, mortality in the control group of 53.6%, alpha = 5%, and beta = 20% is 95 patients (vertical dotted line). The dotted lines are trial sequential monitoring boundaries calculated accordingly. The heterogeneity-corrected information size (HIS) using alpha = 1% and beta = 20% is 142 patients (vertical etched line). The etched lines are trial sequential monitoring boundaries calculated accordingly. The green lines are *z* score of −1.96 and 1.96, equal to two-sided $P = 0.05$. *X*-axis: the information size, i.e., the number of patients randomized (blue line) and *Y*-axis is *z* score

Figure S2. Trial sequential analyses of six trials on glucocorticosteroids vs. placebo or no intervention for patients with alcoholic hepatitis including patients with Maddrey's score of at least 32 or hepatic encephalopathy. The heterogeneity-corrected information size (HIS) based on a relative risk of 0.80, mortality in the control group of 50%, alpha = 5%, and beta = 20% is 1714 patients (vertical dotted line). The dotted lines are trial sequential monitoring boundaries calculated accordingly (merges with the dotted lines below). The heterogeneity-corrected information size (HIS) using alpha = 1% and beta = 20% is 2549 patients (vertical etched line). The etched lines are trial sequential monitoring boundaries calculated accordingly. The green lines are *z* score of −1.96 and 1.96, equal to two-sided $P = 0.05$. *X*-axis: the information size, i.e. the number of patients randomized (blue line) and *Y*-axis is *z* score

Figure S3. Funnel plot of mortality in 15 trials on glucocorticosteroids vs. placebo or no intervention for patients with alcoholic hepatitis. The *X*-axis depicts the relative risks (RR) observed in the individual trials and the *Y*-axis depicts the standard error (S.E.) to the log RR. Due to lack of events in one trial only 14 trials provided data

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