Glucocorticosteroids for people with alcoholic hepatitis

Protocol information

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What's new

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History

Date	Event	Description

Abstract

Background

Objectives

Search methods

Selection criteria

Plain language summary

Background

Description of the condition

The term 'alcoholic hepatitis' was used for the first time in a paper by Beckett and colleagues in 1961 (Beckett 1961), but clinical jaundice after excessive ethanol consumption was reported in the literature long before that (Gerber 1973). Most probably, these reports represented patients with alcoholic hepatitis (Mendenhall 1984a; Jensen 1994a).

Alcoholic hepatitis is a serious form of alcoholic liver disease (injury of the liver due to excessive alcohol consumption) (WHO 2010). Alcoholic hepatitis is synonymous with alcoholic steatohepatitis (Stickel 2013).

The first stage of liver damage in alcoholic hepatitis is usually reversible if people abstain from drinking, but the risk of progression to fibrosis and cirrhosis increases with resumed drinking (Ellis 2012). The accumulation of fat in the hepatocytes causes disruption of the mitochondrial beta-oxidation of fatty acids, accumulation of lipotoxic metabolites, and release of reactive oxygen species (Lieber 1999; Wu 1999; Petrasek 2013). Lipotoxic metabolites and reactive oxygen species lead to cell death and liver inflammation (Wu 1999; Petrasek 2013). Alcoholic hepatitis can be asymptomatic or symptomatic, and the risk of whether or not cirrhosis will develop in a person varies (WHO 2013). Alcoholic hepatitis is a histological form of alcoholic liver disease, characterised by steatosis (the earliest stage of alcoholic liver damage) and necroinflammation (European Association for the Study of Liver 2012). Only 10% to 35% of heavy drinkers (defined as consumption of more than 60 g to 80 g in men and more than 20 g in women alcohol per day), with evidence of fatty liver, are expected to develop hepatitis. With time, alcoholic hepatitis causes liver fibrosis, liver cirrhosis, and primary liver cancer (hepatocellular carcinoma) (WHO 2013).

Severe alcoholic hepatitis may be characterised by clinically clear signs of jaundice, coagulopathy, liver decompensation with ascites, portal hypertension, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, systemic inflammatory response syndrome, or sepsis (Becker 1996; European Association for the Study of Liver 2012). Typically, alcoholic hepatitis presents in people between 40 and 50 years. Among the risk factors of developing severe alcoholic hepatitis are female sex, Hispanic ethnicity, various types of alcohol, binge drinking, poor nutrition, obesity, etc (WHO 2010). Several composite prognostic scores exist to distinguish people with poor prognosis from those who can become abstinent, instituting supportive care, until recovery is achieved. Some of these scores, designed to predict mortality, are Maddrey's discriminant function (Maddrey 1978), the model of end-stage liver disease (MELD) score (Dunn 2005), the Glasgow alcoholic hepatitis score (Forrest 2005), and the age, bilirubin, international normalised ratio, creatinine (ABIC) score (Dominguez 2008).

The Maddrey discriminant function is the most often used score in severe alcoholic hepatitis to identify people in potential need of glucocorticosteroids. The one-month survival of people with alcoholic hepatitis and with Maddrey's score higher than 32 varied between 50% and 65% (Carithers 1989; Phillips 2006). The Lille Model is the only validated model so far to assess glucocorticosteroid response and is highly predictive of death at six months (P value < 0.000001) in people with severe alcoholic hepatitis (Louvet 2007) (www.lillemodel.com). A Lille Model score greater than 0.45, calculated after seven days of treatment with prednisolone, means failure to respond to treatment and predicts a six-month mortality of about 75% (Lefkowitch 2005).

Description of the intervention

Glucocorticosteroids are used as anti-inflammatory drugs. They are also known as glucocorticoids, corticosteroids, or steroids. Glucocorticosteroid agents mimic the endogenous-produced glucocorticoid (cortisol) (Rhen 2005). Glucocorticosteroids, primarily regulated by corticotropin, are considered to have anti-inflammatory effects as well as metabolic and immunogenic effects in our body, by blocking the infiltration of the white blood cells in the liver tissue. (Rhen 2005). It is agreed that the anti-inflammatory effect of glucocorticosteroids are mediated primarily through repression of gene transcription (Schäcke 2002).

How the intervention might work

Glucocorticosteroids administered to people with alcoholic hepatitis repair the liver injury by decreasing the liver polymorphonuclear neutrophils (PMN) (effector cells) infiltrates and the level of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-alpha), intercellular adhesion molecule 1, and interleukin (IL)-6 and IL-8 in the liver tissue (Taïeb 2000; Spahr 2001). The benefits of corticosteroids ensue from short-term vascular changes (Schäcke 2002). However, adverse events have still been poorly reported.

Why it is important to do this review

Over the years, the benefits and harms of corticosteroids for people with alcoholic hepatitis have been studied extensively in a number of randomised clinical trials in order to determine the best route of administration, dose, and duration. However, results have been contradictory. So far, we have found six published meta-analyses with randomised clinical trials (Reynolds 1989; Imperiale 1990; Daures 1991; Christensen 1995; Rambaldi 2008; Mathurin 2011). The various conclusions regarding patient-oriented outcomes were explained by the review authors with differences in glucocorticosteroid regimens, trial quality, participants' characteristics, and clinical spectrum of the disease. Reynolds 1989 concluded that corticosteroid treatment could help only the most severely ill people with severe alcoholic hepatitis characterised by high levels of serum bilirubin, prolonged prothrombin times, and development of hepatic encephalopathy. Imperiale 1990 concluded that glucocorticosteroids reduced short-term mortality in people with severe alcoholic hepatitis provided that they also had hepatic encephalopathy but did not have severe gastrointestinal bleeding. Daures 1991 concluded that further randomised clinical trials were needed to confirm the benefits and harms of glucocorticosteroids, especially in people with severe alcoholic hepatitis. Christensen 1995 could not find sufficient proof supporting the routine use of glucocorticosteroids in people with alcoholic hepatitis, including those with hepatic encephalopathy. Rambaldi 2008 concluded that glucocorticosteroids did not improve overall survival in people with alcoholic hepatitis. Based on the trial sequential analysis of the subgroup of people with Maddrey's score of at least 32 or spontaneous hepatic encephalopathy, the required information size of 2420 people for the outcome mortality was far from reached with only 249 participants randomised in the six randomised trials (Rambaldi 2008). Using the Lille model, Mathurin 2011 concluded that glucocorticosteroids significantly improved 28-day survival in people with severe alcoholic hepatitis. The Mathurin 2011 meta-analysis was based on individual data from five randomised clinical trials. This is why, we decided to conduct this Cochrane systematic review in order to assess the efficacy of glucocorticosteroids in people with severe alcoholic hepatitis with or without complications thereof.

Objectives

To assess the benefits and harms of glucocorticosteroids in people with alcoholic hepatitis.

Methods

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials in which glucocorticosteroids have been assessed in people with alcoholic hepatitis, irrespective of year of publication or language. We will include randomised clinical trials also if reported in an abstract form.

We will include quasi-randomised studies and observational studies identified during our searches for the assessment of harms.

Types of participants

We will include adult participants with alcoholic hepatitis, according to the diagnostic work-up used in the individual randomised clinical trial.

We will consider alcoholic hepatitis as mild if randomised participants had jaundice for less than three months, Maddrey's score was less than or equal to 32, bilirubin level less than 50 μmol/L, and the person is an active drinker.

We will consider alcoholic hepatitis as severe at any stage of the alcoholic liver disease with the presence of spontaneous hepatic encephalopathy, or Maddrey's score higher than 32 [Maddrey's score = 4,6 x prothrombin time (sec) + serum bilirubin (mg per dl)] (Maddrey 1978). We will pay attention to trials published before or after 1989, as the Maddrey's score was modified in 1989 in order to stratify severe alcoholic hepatitis and define the group of people to be treated.

Included trial participants diagnosed with severe alcoholic hepatitis may also manifest with hepatic encephalopathy, gastro-intestinal bleeding, cirrhosis (e.g., classified with Child-Pugh score - Child-Pugh type C (Pugh 1973)), ascites, hepatorenal syndrome, hyponatraemia, and spontaneous bacterial peritonitis.

Types of interventions

Glucocorticosteroids administered in any route, dose, and duration versus placebo or no intervention.

We will allow co-interventions in the intervention groups of a trial, provided they do not differ.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Health-related quality of life (any valid continuous outcome scale as defined by the trial authors).
- Serious adverse events during treatment. We will use the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997), that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We will consider all other adverse events as non-serious (see below).

Secondary outcomes

- Alcohol liver-related mortality.
- Proportion of trial participants with any complication (i.e., ascites, hepato-renal syndrome, spontaneous bacterial peritonitis, gastrointestinal bleeding, hepatic encephalopathy, nonobstructive jaundice, systemic inflammatory response syndrome, sepsis, or hepatocellular carcinoma, or a combination of any of these).
- Proportion of people with non-serious adverse events.

Exploratory outcomes

- Proportion of trial participants with an increase of liver enzymes.
- Proportion of trial participants with a decrease of prothrombin index.

- Proportion of trial participants with a decrease of serum albumin.

We plan to collect data at 'up to three months follow-up' for all the outcomes above, as it has been shown that survival of people with alcoholic hepatitis will mainly rely on their abstinence beyond that time point (see Background). In addition, glucocorticosteroids are known to have short-term effects. By making up to three months our primary time point, we will likely not be mixing outcomes like deaths because of alcoholic hepatitis, because of cirrhosis, and because of recidivism of alcoholism. In addition, we will also assess the effects of glucocorticosteroids on maximal follow-up, but outcomes here may likely be confounded.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2015), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index Expanded (Royle 2003). We will apply no language or document type restrictions. Appendix 1 shows the preliminary search strategies with the expected time spans of the searches.

We plan to search The LILACS database (Castro 1997) as well.

Searching other resources

We will identify additional references by handsearching the reference lists of articles from the computerised databases and relevant review articles.

We will search on-line trial registries such as ClinicalTrial.gov, EMA (European Medicines Agency www.ema.europa.eu), WHO International Clinical Trial Registry Platform, www.who.int/ictrp), the FDA (Food and Drug Administration, www.fda.gov), and pharmaceutical company sources for ongoing or unpublished trials.

Data collection and analysis

We will follow the available guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the Cochrane Hepato-Biliary Group Module (Gluud 2015). We will perform the analyses using Review Manager 5.3 (RevMan 2014) and Trial Sequential Analysis (CTU 2011; Thorlund 2011). We will assess the evidence according to Jakobsen and colleagues (Jakobsen 2014).

Selection of studies

We will retrieve publications we consider to be potentially eligible for inclusion, after reading their abstracts, and review articles that may provide useful references for studies. Three review authors (CP, DV, MT) will independently review publications for eligibility. They will assess each publication to determine if trial participants and the interventions administered meet the inclusion criteria. We will only include abstracts if sufficient data are provided for analysis. We will resolve disagreements by discussion or using any of the remaining authors for arbitration.

Data extraction and management

Three review authors (CP, DV, MT) will independently complete a data extraction form for all included studies. They will extract general information on the trial such as publication title, place and year of publication, and trial design, inclusion and exclusion criteria, preliminary sample size calculation reached or not, number of participants randomised in each trial and following treatment allocation, diagnostic work-up, age (mean (or median), sex or sex ratio, race, co-infection, type and dose, and route of administration of glucocorticosteroids, dose and route of administration of glucocorticosteroids and their possible link with adverse events, concurrent medications used, length of trial and length of follow-up. They will insure that they have retrieved all possible data required for measuring the outcomes of this protocol. The three review authors (CP, DV, MT) will resolve disagreements by discussion or using any of the remaining authors for arbitration.

The three authors will also extract data on malnutrition, if malnutrition is clearly defined by the trial authors. We will use the extracted information for discussion only.

Assessment of risk of bias in included studies

Three review authors (CP, DV, and MT) will independently assess the risk of bias of each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary Group Module (Gluud 2015), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012a; Savović 2012b). We will use the following definitions in the assessment of risk of bias.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random. Such studies will be included only for assessments of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the

investigators (e.g., if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. Such studies will be included only for assessments of harms.

Blinding of participants and personnel

- Low risk of bias: it was mentioned that both participants and personnel providing the interventions were blinded, and the method of blinding was described, so that knowledge of allocation was prevented during the trial.
- Unclear risk of bias: it was not mentioned if the trial was blinded, or the trial was described as blinded, but the method or extent of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Blinded outcome assessment

- Low risk of bias: it was mentioned that both participants and personnel providing the interventions were blinded, and the method of blinding was described, so that knowledge of allocation was prevented during the trial.
- Unclear risk of bias: it was not mentioned if the trial was blinded, or the trial was described as blinded, but the method or extent of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk: the trial reported the following pre-defined outcomes: all-cause mortality, serious adverse events, and alcohol liver-related mortality. If the original trial protocol was available, the outcomes should be those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g., www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes will not be considered to be reliable.
- Unclear risk: not all pre-defined were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk: one or more pre-defined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or analyses of results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other bias domains (e.g. academic bias or authors have conducted trials on the same topic) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.

We will classify each trial as having a low, uncertain, or high risk of bias based on the definitions described above. We will include a bias risk assessment combining all domains and categorise trials as low risk of bias if none of the domains are classed as high or unclear risk of bias. Moreover, we will consider trials with one or more domains with unclear or high risk of bias as trials with high risks of bias.

We will assess the domains 'Blinding of outcome assessment', 'Incomplete outcome data', and 'Selective outcome reporting' for each outcome result. Thus, we will be able to assessed the bias risk for each outcome result in addition for each trial (overall risk of bias of each trial). We will base our primary conclusions on the outcome results of our primary outcomes with low risk of bias.

Measures of treatment effect

Dichotomous outcomes

We will use risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes.

Continuous outcomes

We will use mean difference (MD) with 95% CI for continuous outcomes. We will use the standardised mean difference (SMD) with 95% CI for continuous outcomes only if the included studies use different scales for quality of life.

Unit of analysis issues

The single participant, randomised in the trial.

Dealing with missing data

If dichotomous or continuous data are missing in a published report, we will, whenever possible, contact the original investigators to request the missing data.

If trialists used intention-to-treat analysis to deal with missing data, we will use these data in our primary analysis. If required data for intention-to-treat analysis are missing, we may not be able to perform such an analysis.

Dealing with missing data using sensitivity analysis

We will include missing data by considering participants as treatment failures or treatment successes by imputing them according to the following two scenarios:

- extreme case analysis favouring the experimental intervention ('best-worse' case scenario): none of the participants who dropped-out from the experimental trial group experienced the outcome, but all of the participants who dropped-out from the control trial group experienced the outcome; including all randomised participants in the denominator.
- extreme case analysis favouring the control ('worst-best' case scenario): all participants who dropped-out from the experimental trial group, but none from the control trial group experienced the outcome; including all randomised participants in the denominator.

For continuous outcomes, as in our case quality of life, we will perform a 'best-worst' case scenario analysis assuming that all participants lost to follow-up in the experimental group had an improved outcome (the group mean plus 1 standard deviation (SD)); and all those with missing outcomes in the control group have had a worsened outcome (the group mean minus 1 SD) (Jakobsen 2014). We will also perform 'worst-best' case scenario analysis assuming that all participants lost to follow-up in the experimental group had a worsened outcome (the group mean minus 1 SD); and all those with missing outcomes in the control group have had an improved outcome (the group mean plus 1 SD) (Jakobsen 2014).

We will perform the two sensitivity scenario analyses only for our primary outcomes. We will present the results of both scenarios in our review.

Assessment of heterogeneity

We will address the presence of heterogeneity in both clinical and statistical ways.

We will assess heterogeneity by visual inspection of the forest plots.

To formerly assess heterogeneity between the trials, we will specifically examine the degree of heterogeneity observed in the results using the I^2 statistic (Higgins 2002). As thresholds for the interpretation of I^2 can be misleading, we will use the following rough guide for interpretation of heterogeneity provided in the Handbook (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g., P value from the chi-squared test, or a CI for I^2).

For the heterogeneity adjustment of the required information size in the Trial Sequential Analysis, we will use diversity (D^2) because the I^2 statistics used for this purpose consistently underestimate the required information size (Wetterslev 2009).

Depending on the number of eligible trials, we will add co-variates that may explain heterogeneity to a meta-regression model to adjust for heterogeneity.

Assessment of reporting biases

If we include 10 or more trials, we will draw funnel plots to assess reporting biases from the individual trials by plotting risk ratio (RR) on logarithmic scale against its standard error (Egger 1997; Higgins 2011)).

For dichotomous outcomes, we will test asymmetry using the Harbord test in case tau^2 is less than 0.1 (Harbord 2006) and we will use Rücker 2008 in case tau^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test (Egger 1997) and the adjusted rank correlation (Begg 1994).

Data synthesis

Meta-analysis

We will perform the meta-analyses using Review Manager 5.3 (RevMan 2014) and according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will present the results of dichotomous outcomes of individual trials as relative risks (RR) with 95% CI and the results of the continuous outcomes as mean difference (MD) with 95% CI.

Assessment of significance

We will perform the meta-analyses using Review Manager 5.3 (RevMan 2014). We will present the results of dichotomous outcomes of individual trials as RR with 95% CI and the results of the continuous outcomes as mean difference (MD) with 95% CI. We will apply both the fixed-effect model (DeMets 1987) and the random-effects model (DerSimonian 1986) meta-analyses. If there are statistically significant discrepancies in the results (e.g., one giving a significant intervention effect and the other no significant intervention effect), we will report the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate is the estimate closest to zero effect. If the two point estimates are equal, we will use the estimate with the widest CI as our main result of the two analyses. We will consider a P value of 0.025 or less, two-tailed, as statistically significant if the required information size is reached due to the three primary outcomes (Jakobsen 2014). We will use the eight-step procedure to assess if the thresholds for significance are crossed (Jakobsen 2014). We will present heterogeneity using the I^2 statistic (Higgins 2002). We will present the results of the individual trials and meta-analyses in the form of forest plots.

Where data are only available from one trial, we will use Fisher's exact test for dichotomous data (Fisher 1922) and Student's t-test for continuous data (Student 1908) to present the results in a narrative way.

Trial Sequential Analysis

We will apply Trial Sequential Analysis for both dichotomous and continuous outcomes (Thorlund 2011; TSA 2011), as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To control random errors, we will calculate the diversity-adjusted required information size (DARIS) (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2010).

In our meta-analysis, we will base the DARIS for dichotomous outcomes on the event proportion in the control group; assumption of a plausible relative risk reduction of 20% of the risk observed in the included trials with low risk of bias; a risk of type I error of 2.5% due to three primary outcomes (Jakobsen 2014), a risk of type II error of 20%, and the diversity of the included trials in the meta-analysis. For quality of life, we will estimate DARIS using a minimal relevant difference of 10% of the mean response observed in the control group; the standard deviation; alpha of 2.5% due to the primary outcomes (Jakobsen 2014); beta of 20%; and the diversity as estimated from the trials in the meta-analysis (Wetterslev 2009). We will also calculate and report the Trial Sequential Analysis adjusted 95% CI (Thorlund 2011).

The underlying assumption of trial sequential analysis is that testing for statistical significance may be performed each time a new trial is added to the meta-analysis. We will add the trials according to the year of publication, and, if more than one trial has been published in a year, we will add trials alphabetically according to the last name of the first author. On the basis of the DARIS, we will construct the trial sequential monitoring boundaries for benefit, harm, and futility (Wetterslev 2008; Thorlund 2011). These boundaries will determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the DARIS; if the trial sequential monitoring boundary for benefit or harm is crossed before the DARIS is reached, firm evidence may be established and further trials may be superfluous. However, if the boundaries are not crossed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. However, if the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility, no more trials may be needed.

A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa/ (Thorlund 2011).

Subgroup analysis and investigation of heterogeneity

Whenever possible, we will perform the following subgroup analyses:

- Trials with low risk of bias compared to trials with high risk of bias.
- Trials with participants with mild alcoholic hepatitis compared to trials with severe alcoholic hepatitis, following the Maddrey's score equal or lower than 32 or higher than 32, or another score used.
- Trials with dose of the glucocorticosteroid equal or less than 40 milligram compared to trials with dose of the glucocorticosteroid more than 40 milligram.
- Trials with people with severe hepatic hepatitis without cirrhosis compared to trials with people with severe alcoholic hepatitis with cirrhosis. If cirrhosis is classified by Child-Pugh score, then we may be able to perform additional subgroup analyses in order to adjust for the clinical spectrum of the disease.
- Trials with people with severe alcoholic hepatitis without hepato-renal syndrome compared to trials with people with severe alcoholic hepatitis with hepato-renal syndrome.
- Trials with people with severe alcoholic hepatitis without ascites compared to trials with people with severe alcoholic hepatitis with ascites.

Additional subgroup analyses maybe considered at the review stage. Due to the large number of subgroup analyses, we will interpret them conservatively.

Sensitivity analysis

To assess the robustness of the eligibility criteria, in addition to the sensitivity analyses specified under Dealing with missing data, we will undertake sensitivity analyses that may explain our findings as well as any observed heterogeneity.

Summary of findings' tables

We will create 'Summary of findings' tables on all review outcomes using GRADEpro (ims.cochrane.org/revman/other-resources/gradepro). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias, indirectness of the evidence, heterogeneity of the data, imprecision of effect estimates (wide CIs and as evaluated with our TSAs) (Jakobsen 2014), and risk of publication bias (Balshem 2011; Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013).

- We will define the levels of evidence as 'high', 'moderate', 'low', or 'very low'. These grades are defined as follows:High certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.
- Moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.
- Low certainty: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different is high.
- Very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

Results

Description of studies

Risk of bias in included studies

Effects of interventions

Discussion

Authors' conclusions

Implications for practice

Implications for research

Acknowledgements

Peer reviewers: Richard Hu, USA; Sreeram Parupudi, USA.
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Contributions of authors

Chavdar Pavlov (CP) and Giovanni Casazza (GC): drafted the protocol.
Dimitrinka Nikolova (DN): revised the protocol.
Edvard Volcek (EV), Emmanuel Tsochatzis (ET), and Christian Gluud (CG) commented on the protocol.
All authors addressed comments by peer reviewers and editors, reviewed the final version of the protocol, and approved its validity for publication.

Daria Varganova (DV) from Russia will join the authors' team at the review stage.

Declarations of interest

The authors of this protocol declare no financial, academic, or personal conflicts of interest.

Differences between protocol and review

Published notes

Cochrane Reviews can be expected to have a high percentage of overlap in the methods section because of standardised methods. In addition, overlap may be observed across two of our protocols as they share at least four common authors.

Characteristics of studies

Characteristics of included studies

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

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Other published versions of this review

Classification pending references

Data and analyses

Figures

Sources of support

Internal sources

- The Cochrane Hepato-Biliary Group Editorial Team Office, Denmark

External sources

- No sources of support provided

Feedback

Appendices

1 Search strategies

Database	Search performed	Search strategy
Cochrane Hepato-Biliary Controlled Trials Register	At the review stage.	(glucocortico* or steroid* or dexamethasone or prednis* or hydrocortisone or corticosteroid* or cortiso* or budesonide* or beclomethasone*) AND (alcohol* and (liver or hepati*))
Cochrane Central Register of Controlled Trials (CENTRAL)	At the review stage.	#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees #2 (glucocortico* or steroid* or dexamethasone or prednis* or hydrocortisone or corticosteroid* or cortiso* or budesonide* or beclomethasone*) #3 #1 or #2 #4 MeSH descriptor: [Hepatitis, Alcoholic] explode all trees #5 (alcohol* and (liver or hepati*)) #6 #4 or #5 #7 #3 and #6
MEDLINE (Ovid SP)	At the review stage.	1. exp Adrenal Cortex Hormones/ 2. (glucocortico* or steroid* or dexamethasone or prednis* or hydrocortisone or corticosteroid* or cortiso* or budesonide* or beclomethasone*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. exp Hepatitis, Alcoholic/ 5. (alcohol* and (liver or hepati*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 7 and 8
EMBASE (Ovid SP)	At the review stage.	1. exp corticosteroid/ 2. (glucocortico* or steroid* or dexamethasone or prednis* or hydrocortisone or corticosteroid* or cortiso* or budesonide* or beclomethasone*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp alcohol liver disease/ 5. (alcohol* and (liver or hepati*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 and 8
Science Citation Index Expanded	At the review stage.	#5 217 #4 AND #3 #4 1,347,943 TS=(random* or blind* or placebo* or meta-analys*) #3 1,060 #2 AND #1 #2 36,574 TS=(alcohol* and (liver or hepati*)) #1 425,242 TS=(glucocortico* or steroid* or dexamethasone or prednis* or hydrocortisone or corticosteroid* or cortiso* or budesonide* or beclomethasone*)

Graphs