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β-Blockers in sepsis: protocol for a systematic review and meta-analysis of randomised control trials

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ABSTRACT

Introduction: Sepsis is a common and deadly complication of infection. As part of the host response, sympathetic stimulation can result in septic myocardial depression, and metabolic, haematological and immunological dysfunction. Administration of β-blockers may attenuate this pathophysiological response to infection, but the effects on clinical outcomes are unknown. The objective of this systematic review is to determine the efficacy and safety of β-blockers in adults with sepsis using data from randomised control trials.

Methods and analysis: We will identify randomised control trials comparing treatment with β-blockers, versus placebo or standard care in adults with sepsis. Data sources will include MEDLINE, EMBASE, CENTRAL, clinical trial registries and conference proceedings. Two reviewers will independently determine trial eligibility. For each included trial, we will conduct duplicate independent data extraction, risk of bias assessment and evaluation of the quality of the evidence using the GRADE approach.

Ethics and dissemination: Our systematic review will evaluate the effects of β-blockers in adults with sepsis, comprehensively summarising and appraising the available evidence from randomised control trials. The results of this systematic review will help clinicians treating patients with sepsis to understand the potential role of β-blockade, and inform future research on this topic. Our findings will be disseminated through conference presentation and publication in a peer-reviewed journal.

Trial registration number: CRD42016036933.

Strengths and limitations of this study

- This will be the first systematic review of β-blockers in adults with sepsis that conducts independent duplicate risk of bias assessment and assessment of the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach.
- Other strengths include detailed search strategy of published and grey literature, explicit trial inclusion and exclusion criteria and duplicate independent screening, eligibility and data extraction.
- This systematic review will be limited to including data only from randomised control trials, and any conclusions will be limited by the number and quality of trials conducted.

INTRODUCTION

Description of the problem

Sepsis is a common and deadly complication of infection.[1 2] Despite advances in the care of patients with septic shock, mortality remains strikingly high (18–33%) in patients with severe sepsis or septic shock,[2–4] and further treatment options are needed.

In sepsis, the host responds to infection by activating haemodynamic, metabolic and immunological processes to attempt to restore homeostasis. Part of this response includes the activation of the sympathetic nervous system and release of catecholamines. Mediated by stimulation of β-adrenergic receptors in the heart, cardiac contractility, heart rate and cardiac output increase to match the increased metabolic demands required to combat infection.[5]

However, this pathophysiological catecholamine excess can result in septic myocardial dysfunction, characterised by decreased left ventricular ejection fraction. Depression of the cardiovascular system is characterised by left and right ventricular dysfunction, and diastolic dysfunction,[6 7] and may result in autonomic dysregulation, vasodilation, vascular hyporeactivity, myocardial stunning and necrosis. In addition to cardiac effects, adrenergic stimulation can lead to hyperglycaemia, hypercoagulability, inflammatory cytokine release and alteration in metabolism and mitochondrial function.[6 8] By these mechanisms, excessive β-receptor stimulation may contribute to

cardiovascular collapse, organ dysfunction and death in severe sepsis and septic shock.[9 10]

Description of the intervention

Administration of a β-blocker may help to attenuate the persistent, sympathetic stimulation in septic shock and mitigate these effects to improve patient outcomes.[11 12] β-Blockers have been shown to improve mortality in patients with chronic heart failure, possibly by a similar mechanism—by reducing the effects of adrenergic drive on the heart and thereby reducing heart rate and blood pressure, improving ventricular function, preventing left ventricular remodeling or reducing the risk of arrhythmia.[13] From animal studies of sepsis, administration of β-blockers alters the pattern of inflammatory cytokine production; however, studies have shown anti-inflammatory and proinflammatory effects.[14] β-Blockers may improve the metabolic dysfunction in sepsis by decreasing protein catabolism and reduced resting energy expenditure, as shown in a study in paediatric burn patients,[15] and by reducing plasma glucose through inhibition of gluconeogenesis in an animal model of sepsis.[16]

On the other hand, administration of β-blockers in sepsis has the potential to be harmful. Many patients with septic shock receive β-adrenergic receptor agonists in the form of vasopressor and inotrope infusions. Therefore, β-blockade could exacerbate hypotension and bradycardia, leading to hypoperfusion in these critically ill patients. A recent large international randomised control trial (RCT) of oral β-blockade versus placebo in the perioperative setting demonstrated an increased risk of death, especially in the setting of hypotension.[17]

Why it is important to conduct this review?

Two systematic reviews were previously published on the treatment effects of β-blockers in adults with sepsis;[11 12] however, their methodological quality was low (Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score 2 and 3).[18] They identified few RCTs (1 and 2 RCTs, respectively), did not meta-analyse results and did not formally assess risk of bias or quality of the evidence. These reviews concluded that a β-blocker given to patients with sepsis appeared to reduce heart rate, but the effects on haemodynamic measures and clinical outcomes were uncertain.

Our systematic review will use rigorous methodology to identify, summarise and assess the quality of evidence from RCTs to inform clinicians of the treatment effects of β-blockers in adults with sepsis.

Research question

In adult patients with sepsis, what is the impact of a β-blocker, compared to placebo or standard care, on clinical outcomes (mortality and length of stay), physiological outcomes (heart rate, mean arterial pressure, cardiac index and vasopressor dose) and organ dysfunction biomarkers (troponin and lactate)?

METHODS AND ANALYSIS

Criteria for selecting trials for this review

Types of trials

We will include all parallel group RCTs. We will exclude non-randomised studies and quasi-randomised trials. We will not impose restrictions on methodological quality of eligible RCTs or language.

Types of participants

The population of interest is adults (>50% of participants aged 18 years or older) with sepsis, severe sepsis or septic shock (as defined by the investigators in each trial). We will exclude animal studies and trials that are primarily conducted in children, infants or neonates (>50% of participants aged 17 years or younger).

Types of interventions

The interventions of interest are the initiation of a β-blocker by any route, dose or frequency. We will exclude trials that examine a similar but fundamentally different intervention of continuation versus discontinuation of pre-existing β-blocker therapy. Trials must include a comparator or control group not receiving a β-blocker as per a standard care protocol, with or without a matching placebo. We will also exclude trials comparing a β-blocker with another intervention (eg, an antiarrythmic drug).

Types of outcome measures

The key outcomes of interest for this review are as follows:

Primary outcome

- Mortality at 28 days (or the latest follow-up period).

Secondary outcomes

Clinical outcomes

- Length of intensive care unit stay;
- Length of hospital stay.

Physiological outcomes

- Heart rate;
- Mean arterial pressure;
- Cardiac index;
- Vasopressor dose;
- For physiological outcomes, we will collect values at 24 hours, or the closest time point to 24 hours.

Organ dysfunction biomarkers

- Lactate;
- Troponin.
- For organ dysfunction biomarkers, we will collect values at 24 and 72 hours, or the closest data to these time points. For troponin, we will also collect the proportion of patients with elevated troponin according to thresholds of individual assays for abnormal levels.

Search methods for the identification of trials

We will search the following databases for eligible articles: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). Our

MEDLINE search strategy is listed in online supplementary appendix 1. We will perform a similar search using the same keywords in the other databases.

Additional search methods (grey literature)

We will review the reference lists of all identified RCTs, and published systematic reviews and review articles on the topic for potentially relevant trials. We will search the conference proceedings in the last 2 years for the Society of Critical Care Medicine (SCCM), Canadian Critical Care Forum (CCCF), the European Society of Intensive Care Medicine (ESICM), the Australian and New Zealand Annual Scientific Meeting on Intensive Care (ANZICS), the International Society of Intensive Care and Emergency Medicine (ISICEM) and the American Thoracic Society (ATS). We will also search for unpublished, planned, ongoing or recently completed trials using the WHO International Clinical Trials Registry (WHO ICTRP) and the ClinicalTrials.gov registry. We will contact authors to determine whether results are available, and include these trials in the systematic review if appropriate. We will also summarise and list any registered trials that are planned, ongoing or recently completed without available data.

Trial records

After identification of potentially relevant trials, two reviewers (EHD and SJWO) will independently screen all titles and abstracts for relevance using specific eligibility criteria and pretested electronic screening forms (DistillerSR, EvidencePartners, Ottawa, Canada). If at least one reviewer deems the citation relevant, it will be advanced for full-text review. Two reviewers (EHD and SJWO) will independently review all full texts of relevant articles for inclusion using specific eligibility criteria and pretested electronic screening forms (DistillerSR). We will perform an initial calibration exercise reviewing the first 50 titles and abstracts to ensure >90% raw agreement on relevance prior to proceeding with complete screening. We will also perform initial calibration after reviewing the first 10% of full texts, with discussion and revision of forms if significant discrepancies occur in trial inclusion (raw agreement <90%). Disagreements will be settled by discussion and in cases of persistent disagreement, a third independent reviewer (EB-C) will adjudicate eligibility. We will use the κ statistic to calculate chance-corrected agreement on title and abstract screening and full-text trial inclusion between reviewers.

Data collection

We will perform data extraction independently and in duplicate (EHD and SJWO) using pretested data abstraction forms (DistillerSR). Data abstracted will include title, first author, relevant baseline patient data, intervention and comparator, results of key outcomes and data on methodological quality. Disagreements will be settled by discussion, and a third independent data abstractor (EB-C) if necessary.

Assessment of risk of bias

We will evaluate the methodological rigor of each trial using a modified Cochrane Collaboration tool for assessing risk of bias.[19 20] For each outcome in each included RCT, we will provide a description, comment and judgement of 'definitely yes', 'probably yes', 'probably no' and 'definitely no' in each of the following domains: adequacy of sequence generation, allocation concealment, blinding of patients, blinding of clinicians, blinding of data collectors, blinding of data analysts, blinding of outcome adjudicators, selective outcome reporting and other biases. Two independent reviewers will perform the risk of bias assessment, with disagreements resolved by discussion, and a third reviewer if necessary. We will consider the risk of bias for each element to be 'high' when bias is present and likely to affect outcomes, and 'low' when bias is not present, or present but unlikely to affect outcomes.

Summarising data and treatment effect

We plan to conduct meta-analysis for each outcome when data are available in two or more trials (Review Manager (RevMan) V.5.3, Copenhagen, Denmark: the Nordic Cochrane Centre, the Cochrane Collaboration 2014). We will summarise the results of the meta-analysis using the generic inverse variance method to facilitate pooling of estimates of treatment effect. Meta-analyses will be presented using forest plots. We will use relative risks with 95%CI for dichotomous outcomes, and as mean differences or standardised mean differences with 95% CI for continuous outcomes when appropriate. If quantitative synthesis is not appropriate for a particular outcome, we will provide a qualitative summary for that outcome.

In the case of missing data, we will attempt to contact the primary trial authors for additional data. We will acknowledge authors providing additional information and will describe any missing data in our Discussion section. We will perform our analysis based on all published data or data made available to us.

Assessment of heterogeneity

We will assess for heterogeneity between trials for each outcome using the I^2 statistic for quantifying inconsistency (RevMan). We will consider significant heterogeneity present when I^2 is 50% or greater. We will evaluate possible sources of heterogeneity by performing prespecified exploratory subgroup analysis.

Subgroup analysis and investigation of heterogeneity

A potential source of clinical heterogeneity is the severity of illness (sepsis, severe sepsis vs septic shock). Patients with worse sepsis are at a greater risk for death, have a greater proportion of cardiovascular dysfunction and therefore may be more likely to experience an effect of β-blockade. Clinical heterogeneity may also result from differences in the type of β-blocker (esmolol vs other β-blockers). Esmolol is a cardioselective, ultra

rapid acting β-blocker delivered by an intravenous infusion. Esmolol infusions can be reduced or stopped in the case of bradycardia or hypotension, and the medication cleared much more rapidly (mean half life of 9 min) than the majority of available β-blockers.[21] Therefore, theoretically, esmolol may be the safest β-blocker in a critical care setting. Methodological heterogeneity may exist on the basis of different risk of bias in the trials (high vs low risk of bias), as high risk of bias trials may result in overestimation of treatment effects.

We will explore these potential sources of heterogeneity with subgroup analyses, with our a priori hypotheses specified in online supplementary appendix 2. We will perform these exploratory analyses to explain heterogeneity only when there are two or more trials in each subgroup, and acknowledge this may not be possible depending on the trials included.

Assessment of reporting bias

We will investigate the possibility of publication bias using a funnel plot, provided there are at least 10 included studies (RevMan).[22] To test for funnel plot asymmetry, we will use the Egger test[23] for continuous outcomes and the arcsine test[24] for dichotomous outcomes.

Assessment of confidence in estimates of effect

We will assess the quality of evidence for the intervention, examining each outcome using the GRADE approach and rating system (Grading of Recommendations, Assessment, Development and Evaluation).[25] RCTs will start as high quality evidence but may be rated down by one of the following limitations: risk of bias, imprecision, inconsistency, indirectness and publication bias. Based on this assessment, we will summarise our judgement of the quality of evidence for each outcome as 'high', 'moderate', 'low' or 'very low' (GRADEpro, McMaster University, 2014). Two independent reviewers (EHD and SJWO) will perform the quality of evidence assessment, with disagreements resolved by discussion, and a third reviewer (EB-C) if necessary.

DISCUSSION

Mortality in sepsis remains high, and effective treatments are required to help improve the outcomes in these critically ill patients. β-Blockers are a promising therapy for sepsis; however, the possible clinical benefits and risks are largely unknown. Clinicians caring for patients with sepsis require a comprehensive and objective evaluation of evidence from RCTs to help decide whether to use β-blocker therapy.

Using rigorous systematic review methodology, we will summarise the RCT evidence bearing on the efficacy and safety of β-blockers in adults with sepsis. This will be the first systematic review of β-blockers in adults with sepsis that conducts an independent duplicate risk of bias assessment and assessment of the quality of evidence using the GRADE approach. Other strengths of this review will include a detailed search strategy of published and grey literature, explicit trial inclusion and exclusion criteria, and a priori subgroup hypotheses for exploring potential heterogeneity.

ETHICS AND DISSEMINATION

Ethics approval is not required for this systematic review. This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (supplementary appendix 3).[26]

Our findings will be disseminated through conference presentation and publication in a peer-reviewed journal. We will report this systematic review in accordance with the PRISMA statement.[27]

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Contributors EHD, EB-C and DJC conceived the idea for this systematic review. EHD, SJWO, EB-C, FL, PJD, RW and DJC developed the methodology for the systematic review protocol. The manuscript was drafted by EHD and revised by SJWO, EB-C, FL, PJD, RW and DJC. EHD and SJWO developed the search strategy and will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE assessment and data synthesis. EB-C will act as a third reviewer and arbitrator if necessary. EHD is the guarantor of the review.

Competing interests All authors have signed the ICMJE form for disclosure of potential conflicts of interest. PJD discloses grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octopharma, Roche Diagnostics and Stryker, outside the submitted work.

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