INPLASY

Role of the renin angiotensin aldosterone system in the pathogenesis of sepsis-induced acute kidney injury: a systematic review

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 June 2023 and was last updated on 30 June 2023.

INTRODUCTION

Review question / Objective In adult patients with sepsis-induced acute kidney injury, are renin angiotensin aldosterone inhibitors compared to placebos, effective in reducing morbidity and mortality rates of sepsis?.

Rationale In this paper, we examined the role of the renin angiotensin aldosterone system (RAAS) in the pathogenesis of sepsis-induced acute kidney injury (S-AKI) and the potential emerging therapeutic role of RAAS inhibitors in mitigating the consequences of S-AKI. This is significant because sepsis is a life threatening condition and a major health concern worldwide, with kidney injury being a major ramification and source of mortality. However, treatment for S-AKI is nonspecific and reactive. Based on a thorough database search in PubMed and Google Scholar, we recognized that several original studies have assessed the efficacy of RAAS antagonists on the development and severity of S-AKI in the past five years. Healthcare providers, researchers, and policymakers are presented with large amounts of information; therefore, it is important to compile these findings and assess whether patterns of results have occurred. This systematic review establishes whether the scientific findings on the use of RAAS inhibitors in cases of sepsis and S-AKI are consistent and can be applied to future studies, helping direct clinicians to possible therapies and researchers to study procedures.

Condition being studied Sepsis is a major issue that has affected the history of healthcare, and to this day, remains a major cause of morbidity and mortality in the modern world. This life-threatening condition is characterized by a systemic inflammatory response, under-stood as a dysregulated immunological balance of anti- and pro-inflammatory factors. Major concerns of sepsis arise from system-wide organ damage and possible progression to septic shock, a state of

profound circulatory and metabolic failure with increased risk of mortality.

METHODS

Search strategy Studies were searched for using electronic databases (Medline via PubMed, Google Scholar) from inception to May 2023. This systematic review article of current and international literature was conducted using the major online database, PubMed. Studies published in the last ten years were included, including those published from November 2014 and up to May 2023 were included. Studies and review articles were selected using the relevant keywords "sepsis", "sepsis-induced acute kidney injury", "renin angiotensin aldosterone system", "angiotensin II"; "endothelial cell damage", "oxidative stress"; and "microthrombi formation". Additionally, reference lists from articles were used to further search for related references.

Participant or population Adult patients (aged 18 or greater), diagnosed with sepsis or septic shock, all genders included, no restrictions on country/ location.

Intervention Have used prior to disease onset or have been treated with after the onset of disease, renin angiotensin aldosterone inhibitors.

Comparator Have not used prior to disease or have not been treated with after the onset of disease, renin angiotensin aldosterone inhibitors.

Study designs to be included The protocol for this study is performed based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility criteria Inclusion criteria included randomized control trials (RCTs) and cohort studies and systematic reviews that are full-text articles, in the English language (or translated into the English language), and have relevance to the previously stated relevant keywords. Human studies involved participants aged 18 years or older, from both genders, and from five continents. Studies addressing the use of renin angiotensin aldosterone inhibitors (RAASi) in both premorbid and therapeutic purposes in septic patients were included. Additionally, papers with a focus on sepsis-induced acute kidney injury were included.Studies conducted on both human and animal subjects were included since each offers an essential component to our scientific understanding. Studies utilizing animal models impose specific clinical events and examine laboratory, histological, and gross specimens. Human studies demonstrate trends in rates of disease development, out-comes, and medication use. Exclusion criteria included studies that were not relevant to the research question, those that did not meet the inclusion criteria, and those with inadequate or incomplete data. Studies that were not full-text or were in a language other than English were not in-cluded. Additionally, studies that were not focused on the RAAS or the use of RAASi were excluded to promote the assessment for direct associations.

Information sources Electronic databases: PubMed and Google Scholar Reference lists found within articles of these search databases will be used to further search for related materials.

Main outcome(s) The RAAS system is critical in regulating blood pressure and blood osmolality. An-giotensin II and aldosterone mediate these effects via vessel vasoconstriction and sodium retention. Activation of the RAAS is triggered by the autonomic nervous system in periods of stress, low blood pressure, or low blood osmolality. During sepsis, the prior use of RAAS inhibitors may present as a concern due to possible exacerbations of hypotension and interfering with the normal physiologic mechanism to modulate blood pressure. The use of RAAS inhibitors as a risk factor for developing sepsis or S-AKI has been analyzed in several studies. Individual patient characteristics are more predominant in determining the risk for developing S-AKI rather than the independent use of RAAS antagonists. On the other hand, key components in the RAAS, especially angiotensin II, contribute to the pro-inflammatory damage and coagulopathy observed in the pathogenesis of S-AKI. Recommendations towards physician include adjusting RAAS inhibitors according with estimated Glomerular Filtration Rate (eGFR) and to withhold these medications during times of acute illness.
The use of RAAS antagonists as a therapeutic option in sepsis has recently been considered with emerging studies that help form a greater understanding on the role of RAAS inhibitors in sepsis. Several studies observed decreased rates of S-AKI, renal tissue damage, and levels of pro-inflammatory cytokines and oxidative stress with the use of RAAS antagonists as treatment during sepsis, as well as evidence of playing a protective role in other organs including the lung, heart, and spleen. Although one study found that using angiotensin II as treatment for septic mice had beneficial results on kidney function and administration of losartan reversed this protection, the limited size of the study sample should be

considered. To address the possible ramification of hypotension due to RAAS inhibitor therapy while attaining.

Data management The organization and management of the data includes summarizing data findings into a table with appropriate columns of last name of first author, year, study setup, number of patients or participants, data method collection, and critical numbers used.

Quality assessment / Risk of bias analysis Search and selection strategy was performed by two independent authors, S.T. and G.Z., and a third reviewer, H.M., evaluated the studies in cases of disagreement. Quality assessment of the cohort studies for human populations used in this systematic review was conducted using the Joanna Briggs Institute (JBI) tool. This critical appraisal checklist considers study design and protocol, internal validity and risk of bias, and data interpretation and reporting to form a score out of 11 quality criteria. Quality assessment data individually analyzed by each of the authors, S.T. and G.Z., were compared and are summarized in Table S1. SYRCLE's Risk of Bias (RoB) tool for animal intervention studies consists of ten characteristics to assess for risk of bias including selection bias, performance bias, and detection bias. SYRCLE's RoB tool was used to assess the methodological quality of animal studies of this study, and two authors (S.T. and G.Z.) independently appraised these studies.

Strategy of data synthesis A narrative method will be used to discuss the data findings due to the heterogeneity of the datasets. Each study will be introduced with an overview of the methodology and an explanation of the results.

Subgroup analysis Since this review will be focused on a narrative method of explaining data results, a subgroup analysis will not be conducted.

Sensitivity analysis Since this review will be focused on a narrative method of explaining data results, a sensitivity analysis will not be conducted.

Language restriction Yes, only articles in the English language or translated into the English language will be used.

Country(ies) involved United States.

Keywords sepsis; acute kidney injury; inflammation; oxidative stress; endothelial damage; microthrombi; RAAS; ACEi; ARB.

Dissemination plans Dissemination plans include publication with a medical journal.

Contributions of each author

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