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Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on the mortality in sepsis: A meta-analysis

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Abstract

BACKGROUND

The effect of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) on the mortality of patients with sepsis is not well characterized.

AIM

The aim of this study was to elucidate the association between prior ACEI or ARB exposure and mortality in sepsis.

METHODS

The PubMed, Embase, Web of Science, and Cochrane Library databases were searched for all studies of premorbid ACEI or ARB use and sepsis mortality until November 30 2019. Two reviewers independently assessed, selected, and abstracted data from studies reporting ACEIs or ARBs, sepsis, and mortality. The primary extracted data consisted of premorbid ACEI or ARB exposure, mortality, and general patient data. Two reviewers independently assessed the risk of bias and quality of evidence.

RESULTS

A total of six studies comprising 281,238 patients with sepsis, including 49,799 cases with premorbid ACEI or ARB exposure were eligible for analysis. Premorbid ACEIs or

ARBs exposure decreased the 30-day mortality in patients with sepsis. Moreover, the use of ACEIs or ARBs was associated with approximately a 6% decreased risk of 30-day mortality.

CONCLUSION

The results of this systematic review suggest that ACEI or ARB exposure prior to sepsis may be associated with reduced mortality. Further high-quality cohort studies and molecular mechanism experiments are required to confirm our results.

INTRODUCTION

Sepsis is a syndrome that involves physiological, pathological, and biochemical abnormalities resulting from a host response to an infection, and represents a major public health concern (1). Sepsis is a "worldwide medical problem" that endangers human health and is associated with three main characteristics: 1) high incidence; 2) high mortality; and 3) high treatment cost. More than 19 million people suffer from sepsis every year worldwide, with a fatality rate greater than 25%(2).

As sepsis progresses after an infection, an imbalance of the pro-inflammatory and anti-inflammatory response develops (3). The guidelines associated with development of the sepsis pathophysiology suggest: early fluid resuscitation, antibiotic treatment, control of infection sources, use of vasoactive agents, corticosteroids, blood products, immunoglobulins, blood purification as treatment options (2). Although the guidelines for the diagnosis and treatment of sepsis have been revised several times, the monitoring index does not fully reflect the overall situation and dynamic changes of the patients, treatment is associated with a lag period, and the mortality rate remains high (4). Therefore, it is important to accurately identify potential patients who are at a high risk of sepsis and to take specific intervention measures to reduce the mortality of such patients. Such supplement to the previous treatment programs and may improve the prognosis of sepsis patients.

Several studies have suggested ¹ that the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) ³ may represent a therapeutic option for patients with sepsis (5, 6). Moreover, ACEIs and ARBs have been shown to exert anti-inflammatory effects to attenuate the chronic inflammation (7). However, the benefit of using ACE inhibitors or ARBs remains controversial (5, 8). Moreover, there are no published systematic reviews on the effects of premorbid ACEI or ARB exposure on sepsis mortality. Thus, this study sought to investigate sepsis mortality in patients with prior ACEI and ARB exposure.

MATERIALS AND METHODS

Search strategy

This study followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (9). A literature search of relevant published studies that analyzed the association between the sepsis, mortality, and ACEIs or ABBs was conducted on 27 March 2020. We used the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Embase (<http://www.embase.com/>), Web of Science (<http://wokinfo.com/>), and Cochrane Library (<http://www.thecochranelibrary.com/>) databases to identify articles using the following terms: “hypotensor”; “antihypertensive”; “ACEIs”; “captopril”; “enalapril”; “sirapley”; “benazepril”; “petitopril”; “ramipril”; “ARBs”; “losartan”; “irbesartan”; “valsartan”; “telmisartan”; “sepsis”; “toxic shock”; “sepsis shock”; and “mortality”. In addition, the reference lists in each of the studies were reviewed to identify additional studies. The language of the studies was limited to English, and we did not search for unpublished literature.

Study selection criteria

A study was included in the analysis if: 1) it was a case-control or cohort study was conducted; 2) it was an original human clinical trial (independence among studies) that evaluated the association between premorbid ACEI or ARB exposure and sepsis mortality; and 3) it provided sufficient data (e.g., to calculate the relative risk [RR], odds

ratio [OR], or hazard ratio [HR]); and 4) the ([Newcastle-Ottawa Scale](#), NOS) score value was ≥ 5 . We excluded studies that contained overlapping data.

Data extraction

The data extracted from the selected articles included: the first author's name; year of publication; study population; total number of cases; RRs or ORs with 95% confidence intervals (CIs); [Newcastle-Ottawa Scale](#) (NOS); and adjustments made in the studies (Table 1). Some publications separate reported ORs for ACEI-related sepsis mortality and ARB-related sepsis mortality. In these cases, the ORs were separately extracted.

Statistical analysis

The strength of the association between premorbid ACEI or ARB exposure and susceptibility to sepsis mortality was reported using ORs and 95%CIs. ACEIs or ARBs were defined as captopril, enalapril, benazepril, fosinopril, ramipril, losartan, valsartan, and candesartan. When the data was adjusted and crude ORs were provided, the most adjusted ORs were extracted. If the article provided an HR, it was converted to an OR using the appropriate formula (10). We used an I^2 test and Q -statistic to detect any possible heterogeneity between the studies, as a quantitative measure of any inconsistencies among the studies (11). In addition, we clarified the percentage of the total variation across the studies that was due to heterogeneity rather than by chance using the I^2 -statistic. Pooled ORs and 95%CIs were calculated using a random-effects model (12).

All statistical analyses for the meta-analysis were performed using STATA version 12.0 (USA, College Station, TX 77845). Statistical significance was established at a threshold of $P \leq 0.05$. All reported P values were obtained from two-sided statistical tests. *Egger's* and *Begger's* regression models were used to evaluate the potential publication bias (11).

RESULTS

The process used to select the studies for analysis is outlined in **Figure 1**. A total of 48 potentially relevant records were reviewed, of which six articles, which included 49,799 cases that met the inclusion criteria were included in the meta-analysis (5, 8, 13-16) (**Table 1**). A total of 42 studies were subsequently excluded because they used a combined intervention, were duplicated reports, or were of relatively low quality. All of the six selected articles were cohort studies.

Three studies were conducted in Asia and three studies were conducted in other regions (Europe and America). Two studies presented the mortality separately for ACEIs and ARBs. The NOS was 7 and 6 in four and two studies, respectively (**Table 2**). The mortality data for both ACEIs and ARBs were individually extracted. The results from the six studies were inconsistent: two pool results reported that pre-morbid ACEI or ARB use was associated with a significant reduction in sepsis mortality, whereas the other four studies reported no association. The analysis of the six studies yielded a combined risk estimate of (OR: 0.94; 95%CI: 0.91 – 0.97; $P = 0.001$) with a heterogeneity value (I^2) of 94.6% for 30-day mortality (**Figure 2**). We conducted a meta-regression test and found that the geographical area was associated with 25.49% reduction in heterogeneity across the six studies (**Figures 3 and 4**). We further evaluated the role of (ACEIs, ARBs, and ACEIs/ARBs) in a meta-regression test, which was associated with a 35.13% reduction in heterogeneity across the six studies.

Due to differences in the geographic area (Asian or non-Asian countries), NOS (7 or 6), and prior exposure (ACEIs, ARBs, and ACEIs/ARBs) between the studies, we conducted further subgroup analyses to determine the effect of these factors in our analyses (**Table 2**). We obtained a statistically protective effect in Asian population (OR: 0.94; 95%CI: 0.91 – 0.98), ACEIs (OR: 0.94, 95%CI: 0.89 – 0.99), ARBs (OR: 0.84, 95%CI: 0.79 – 0.88), NOS of 6 (OR: 0.88; 95%CI: 0.85 – 0.91), in a non-Asian population (OR: 0.91; 95%CI: 0.74 – 1.09), NOS of 7 (OR: 1.31; 95%CI: 1.24 – 1.39), and ACEIs/ARBs (OR: 1.31; 95%CI: 1.23 – 1.39).

Based on *Egger's* and *Begger's* regression models, there was no evidence of publication bias (**Figures 5 and 6**) regarding prior ACEI or ARB exposure and mortality in sepsis. The *Egger's* funnel plot and *Begger* linear regression test revealed a *P* value > 0.05.

DISCUSSION

This is the first systematic review examining the role of premorbid ACEI or ARB exposure on mortality outcomes in patients with sepsis. Patients receiving ACEIs or ARBs prior to developing sepsis were associated with a 6% reduction in 30-day mortality compared with those who did not receive any ACEIs or ARBs. We further conducted subgroup analyses to determine the effect of the geographic area (Asian or non-Asian countries), NOS (7 or 6), and prior exposure (ACEIs, ARBs, and ACEIs/ARBs) in our analyses (**Table 2**). We obtained a statistically protective effect in the Asian population (OR: 0.94; 95%CI: 0.91 – 0.98), ACEIs (OR: 0.94; 95%CI: 0.89 – 0.99), ARBs (OR: 0.84; 95%CI: 0.79 – 0.88), and a NOS of 6 (OR: 0.88; 95%CI: 0.85 – 0.91). The results of a meta-regression test (**Figures 3 and 4**) revealed that the geographical area and treatment were associated with 60.62% reduction in heterogeneity across the studies.

One cause of the differences in the outcomes between population may be lifestyle and environmental factors associated with Asian and non-Asian populations (17-19). Compared with European and American populations, Asian populations have a relatively healthy diet and a lower prevalence of chronic diseases (e.g., diabetes and coronary heart disease) (20-22), which have a substantial impact on the prognosis of sepsis.

ACE inhibitors and ARBs reduce blood pressure by vasodilation, decreasing angiotensin II formation, and kallikrein degradation to reduce sodium and water retention (23). These effects can also decrease the glomerular filtration rate (GFR) since angiotensin II plays a critical role in the maintenance of GFR, especially during hypovolemia or hypotension (24, 25). In the guidelines for sepsis treatment, the maintenance of a certain tissue perfusion pressure is necessary; however, the use of

ACE inhibitors and ARBs appear to be contrary to the recommended treatment guidelines for sepsis. Moreover, ACE inhibitors and ARBs have not been recommended as a therapeutic drug in previous septic diagnosis and treatment guidelines. In addition to the effect of lowering blood pressure, both ACE inhibitors and ARBs also have anti-inflammatory effects, which can reduce plasma cytokine and nitric oxide concentrations (26). In septic animal models, although ACE inhibitors have been demonstrated to reduce organ damage through the NF- κ B signaling pathway (27), conflicting data exist regarding to whether an angiotensin II blockade improves survival in animal models (28, 29). Moreover, a clinical study of patients hospitalized with sepsis reported that the prior use of ARBs was associated with improved survival (8).

Our findings have potential clinical implications. Clinical medical providers should be able to identify who is at a high-risk of sepsis as early as possible and guide the course of treatment following the initial screening. Combined with our meta-analysis, the use of ACEIs or ARBs can improve the prognosis of sepsis patients, and the comparison of the effect of ACEIs and ARBs on the prognosis of sepsis is presently not supported by any data. Therefore, if patients treated with ACEIs cannot tolerate their adverse reactions, they can continue to use ARBs. It is recommended that ACEIs or ARBs be abandoned only if the adverse effects are severely intolerable (30).

This study analyzed data from six observational studies and included a larger population and range of trials compared to that previous studies, with the largest number of cases analyzed to date. We conformed to the specifications throughout the entire meta-analysis process and we also simultaneously conducted a publication bias detection. The obtained results are robust and the included analysis was free from obvious publication bias. Moreover, this meta-analysis has a high standard for the quality of the included literature, and thus meets a high quality standard.

There are a few limitations regarding this study that should be noted. First, when selecting appropriate literature, only studies written in English were included; however, a large portion of the articles that were included in our study were performed in Asia, where the official language is not English. Second, it was challenging to predict the

effect of misclassification of cohort studies for the results. In addition, the systematic confounding or the risk of bias cannot easily be ruled out in observation studies. Since there was heterogeneity across the studies, we performed a regression analysis to explain the source of such heterogeneity. The observed differences may be due to the differences in the geographical area of the studies. Specifically, differences in the study geographical area and prior treatment (ACEIs, ARBs, and ACEIs/ARBs) may have contributed to the heterogeneity observed in our results (**Figure 4**). Besides, the practice of ACEI and ARB in the clinic are related to disease conditions like hypertension, which might also influence the prognosis of sepsis. Besides, other factors like age may also bring bias. In this analysis, the comparison between the dose and course of treatment of ACEIs or ARBs and the prognosis of sepsis were not included due to the lack of data provided in the original studies.

CONCLUSION

In summary, the findings of this systematic review suggests that exposure to ACEIs or ARBs prior to an episode of sepsis could have a role in reducing sepsis mortality; however, additional evidence is required to clarify whether premorbid ACEIs or ARBs can reduce sepsis mortality, as well as the associated mechanism. Therefore, further high-quality cohort studies and molecular mechanism experiments are required to confirm our results.

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3	Chih-Cheng Lai, Ya-Hui Wang, Cheng-Yi Wang, Hao-Chien Wang, Chong-Jen Yu, Likwang Chen. "Risk of Sepsis and Mortality Among Patients With Chronic Obstructive Pulmonary Disease Treated With Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers", Critical Care Medicine, 2019 Crossref	14 words — 1%