Effect of alkaline phosphatase on sepsis-associated acute kidney injury patients
A systematic review and meta-analysis
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Abstract
Background: This systematic review and meta-analysis were performed to evaluate kidney function in patients with sepsis-associated acute kidney injury (SA-AKI) on alkaline phosphatase (AP) therapy.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched electronically from inception until May 4, 2019 and randomized controlled studies assessing AP treatment in patients with SA-AKI were included. Pool analyses with fixed effects or random effects models calculated pooled mean, standard deviation, and odds ratio (OR) with 95% confidence interval (CI).

Results: Four randomized controlled trials involving AP therapy for 392 patients with SA-AKI were included. AP had a positive effect on endogenous creatinine clearance (ECC) in patients with SA-AKI at day 14 (random effects: mean difference = 10.56, 95% CI = 2.27–18.84, P = .01) and day 28 (random effects: mean difference = 14.30, 95% CI = 6.27–22.33, P = .0005). All-cause mortality at day 28 (fixed effects: OR = 0.62, 95% CI = 0.40–0.97, P = .04) and day 90 (fixed effects: OR = 0.61, 95% CI = 0.39–0.96, P = .03) improved. Plasma creatinine level (fixed effects: mean difference = –76.83, 95% CI = –146.92 to –6.74, P = .03) and biomarkers level (random effects: mean difference = –6.57, 95% CI = –10.74 to –2.40, P < .00001) also improved in the therapy group compared with placebo.

Conclusion: In patients with SA-AKI, AP showed a relatively late protective effect by improving ECC at days 7, 14, and 28. ECC level improved when patients received AP dose of 0.212 mg/kg. Mortality improved at days 28 and 90, respectively, when patients received AP dose of 1.6 mg/kg. Levels of overall AKI biomarkers were improved in short term.

Abbreviations: AKI = acute kidney injury, AP = alkaline phosphatase, BiAP = bovine intestinal phosphatase, DAMP = danger-associated molecular patterns, ECC = endogenous creatinine clearance, eGFR = estimated glomerular filtration rate, GFR = glomerular filtration rate, GST = glutathione S-transferase, IL-18 = interleukin 18, IQR = interquartile range, KIM-1 = kidney injury molecule 1, LPS = lipopolysaccharide, MD = mean difference, NGAL = neutrophil gelatinase-associated lipocalin, OR = odds ratio, PAMP = pathogen-associated molecular patterns, RCT = randomized controlled trial, ROB = risk of bias, RRT = renal replacement therapy, SA-AKI = sepsis-associated acute kidney injury, SD = standard deviation.

Keywords: alkaline phosphatase, endogenous creatinine clearance, mortality, sepsis-associated acute kidney injury, systematic review

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1. Introduction

Sepsis is a common and life-threatening problem worldwide in patients with suspected infection which requires immediate detection and treatment to reduce the number of deaths. It often leads to failures in multiple organs including kidney. The mortality rate of sepsis-associated acute kidney injury (SA-AKI) reaches at almost 70% and the surviving patients have the risk of developing into chronic kidney failures. Despite the achievements in understanding the mechanisms of acute kidney injury (AKI) and sepsis, there is still no effective treatment for improving kidney function in clinical practice, and thus it is urgent to protect the kidney from possible injuries.

It has been reported that alkaline phosphatase (AP), an endogenous and membrane-bound enzyme, can improve kidney function of patients with SA-AKI in intensive care unit. It exists in multiple cells and organs as 4 different isoenzymes, namely liver-bone-kidney, the germ cell line, intestinal and placental AP. It can detoxify various compounds through dephosphorylation, including endotoxin lipopolysaccharide (LPS) which constitutes the outer wall of gram-negative bacteria and is vital for the process of sepsis. Exogenous AP was originally intended for the treatment of sepsis instead of AKI. It has been reported that AP can attenuate innate immune response through the Toll-like receptor 4 pathway and improve survival in animal models of sepsis. In 2009, a randomized controlled study in severe sepsis and septic patients observed improvement in renal function after infusion of AP. Likewise, a clinical trial suggested that AP was promising in improving renal function for patients with severe sepsis or septic shock with AKI. However, recently, a clinical trial in patients with sepsis-associated AKI demonstrated that human recombinant AP did not improve short-term kidney function significantly. But the authors found that there was significant difference between placebo and AP treatment group in 21 days, and mortality rate was lower in the 1.6 mg/kg AP group compared with placebo. Therefore, it is necessary to conduct a meta-analysis aiming at a definitive conclusion of the efficacy of exogenous AP on patients with SA-AKI.

The aim of this systematic review and meta-analysis was to evaluate the effect of AP on the renal function of patients with SA-AKI according to several parameters, including endogenous creatinine clearance (ECC), mortality rate, urinary excretion markers of AKI, urine volumes, plasma creatinine levels, renal replacement therapy (RRT) duration, and requirement days.

2. Methods

2.1. Data sources and search strategy

PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched electronically from inception until May 4, 2019. The ClinicalTrials.gov platform was consulted regarding any ongoing studies or the availability of completed studies with the posted results. The following terms were used in search alone or in combination: (“Alkaline Phosphatase” OR “Human Recombinant Alkaline Phosphatase” OR “Bovine Intestinal Alkaline Phosphatase” OR “Calf Intestinal Alkaline Phosphatase”) AND (“Acute Kidney Injury” OR “Acute Renal Insufficiency” OR “Acute Renal Failure”) AND (“Sepsis” OR “Severe Sepsis” OR “Septic Shock” OR “Septicemia” OR “Pyemia” OR “Pyohemia”) AND (“Randomized Controlled Trial” OR “Controlled Clinical Trial” OR “Randomized” OR “Placebo”). The search strategies are shown in Additional file 1: Table S1, http://links.lww.com/MD/D631.

There was no language or publication status restriction placed on the searches. The reference lists of all studies were also scanned to identify additional literature on this topic. The selection process of the studies is shown in Additional file 1: Figure S1, http://links.lww.com/MD/D622.

2.2. Selection criteria

Only randomized controlled trials (RCTs) assessing AP treatment in patients with SA-AKI were included in this meta-analysis. Besides mean and standard deviation (SD) or underlying numbers enabling calculation of effect measures had to be provided. Studies lacking necessary data were excluded. Letters, conference abstracts, review articles, case reports, expert opinions, and posters were also excluded. In studies with multiple publications from the same population, only data from the most recent publication were included. All articles were assessed independently by 2 investigators, and any questions were resolved by discussion.

2.3. Data extraction and quality assessment

Data was extracted independently by 2 investigators on an Excel database. The following items recorded for each study were extracted: first author, year of publication, center, disease, sequential organ failure assessment score, number of cases and controls, treatment strategy, treatment duration, follow-up time, baseline kidney injury markers.

For the RCTs, we used the Cochrane collaboration risk of bias (ROB) tool to examine study validity. The overall ROB of a study was considered “low” if more than 4 items in the Cochrane collaboration ROB tool were rated as “low risk.” The overall ROB of a study was considered “moderate” if 2 or 3 items in the Cochrane collaboration ROB tool were rated as “low risk.” The overall ROB of a study was considered “high” if fewer than 2 items in the Cochrane collaboration ROB tool were rated as “low risk” or if more than 1 item was rated as “high risk.”

2.4. Data extraction and analysis

Continuous and dichotomous outcomes were compared for patients receiving AP treatment and placebo by calculating mean differences (MDs) and odds ratios (ORs). Data primarily reported as medians with interquartile ranges (IQRs) were re-expressed into mean and SDs assuming a normal distribution. When a study with multiple intervention groups in meta-analysis was included, we split the shared group into several groups with smaller sample size and made independent comparisons according to the Cochrane handbook.

We used a fixed-effects (Mantel–Haenszel method) or random-effects model (DerSimonian–Laird method) when taking into account the heterogeneity showing across studies to calculate pooled mean, SD, and OR. Cochran Q test and $I^2$ were used to evaluate the heterogeneity of pooled outcomes. Cochran $Q <0.10$ or $I^2 >50\%$ represented significant heterogeneity among included studies. To explore the underlying source of heterogeneity, subgroup analysis was conducted according to different doses, all-cause mortality, ECC, or estimated glomerular filtration rate (eGFR) measured at different time point, kidney tubular injury markers, urine output, plasma creatinine, RRT duration, and RRT requirement days.

Sensitivity analysis was conducted to confirm the robustness of the outcome of this meta-analysis by removing one study at a time using the “metaninf” STATA command. Egger linear regression
test and the rank correlation test (Begg test) were used to evaluate publication bias.

RevMan (Cochrane Collaboration), version 5.3, was used to combine data analyses. Bias and sensitivity analyses were performed using STATA 12.0 (StataCorp, College Station, TX). All statistical tests used in this study were 2-sided and \( P < .05 \) was considered statistically significant.

### 3. Results

#### 3.1. Search results

The search strategy found 99 citations: PubMed (\( n = 10 \)), Embase (\( n = 58 \)), Cochrane (\( n = 31 \)). Sixty-nine duplicate articles were excluded after examining titles and abstracts. Subsequently, 30 potentially relevant articles were retrieved for detailed evaluation. After reading full text, 26 articles were excluded because of inaccessibility of study data (\( n = 3 \)), the lack of necessary data (\( n = 2 \)), and duplicate dataset (\( n = 21 \)). Eventually, 4 studies were included in this meta-analysis.

#### 3.2. Characteristics of included studies

The main characteristics of the 4 studies included are displayed in Additional file 1: Table S2, http://links.lww.com/MD/D632. The 4 studies were all RCTs with 392 participants involved. All studies were multicentered. The age of patients included ranged from 18 to 85, and all had SA-AKI (Additional file 1: Table S3, http://links.lww.com/MD/D633).

Based on the Cochrane collaboration ROB tool, 3 RCTs were rated as “low risk” and 1 study was rated as “unclear risk” (Additional file 1: Fig. S2, http://links.lww.com/MD/D623). The quality assessment of the included studies is presented in Additional file 1: Table S4, http://links.lww.com/MD/D634.

#### 3.3. ECC or eGFR measurement after AP therapy

Data were divided into 5 groups (3 from Pickkers 2018[7]) to evaluate the association of ECC or eGFR improvement with exposure to AP (Figs. 1 and 2). The result showed that there was no statistically significant association between AP therapy and ECC alteration at day 1 (random effects: \( MD = -6.59, 95\% CI = -13.42 \text{ to } 0.24, P = .06 \)). The results of day 7 ECC analysis suggested no association between AP and ECC enhancement (random effects: \( MD = 5.32, 95\% CI = -1.52 \text{ to } 12.16, P = .13 \)). However, data of day 14 and day 28 indicated that AP may have a positive effect on ECC in patients with SA-AKI (random effects: \( MD = 10.56, 95\% CI = 2.27 \text{ to } 18.84, P = .01 \); random effects: \( MD = 14.30, 95\% CI = 6.27 \text{ to } 22.33, P = .0005 \), respectively) (Additional file 1: Table S5, http://links.lww.com/MD/D635). Meta-analysis of the 3 groups of data from Pickkers 2018[7] showed no evidence of association between AP exposure and eGFR amelioration at day 60 or day 90 (\( MD = 0.29, 95\% CI = -6.77 \text{ to } 7.35, P = .94 \); \( MD = 0.82, 95\% CI = -5.72 \text{ to } 7.36, P = .81 \), respectively).

Figure 1. Forest plots and meta-analysis of endogenous creatinine clearance (mL/min) among patients with sepsis-associated acute kidney injury measured at days 1, 7, 14, and 28, respectively.
Heterogeneity was detected at days 7, 14, and 28 ($I^2 = 88\%, P = .13$; $I^2 = 91\%, P = .01$; $I^2 = 89\%, P = .0005$, respectively). We conducted Egger linear regression test and rank correlation test (Begg test) to assess publication bias. Funnel plot shapes did not show an obvious asymmetry among studies in the subgroups (Additional file 1: Table S6, http://links.lww.com/MD/D636 and Fig. S3, http://links.lww.com/MD/D624). To evaluate the stability of the overall result, we performed a sensitivity analysis to investigate the influence of individual studies on the pooled MD by removing one study at a time. The analysis showed that the pooled MD and its 95% CIs were not obviously affected, thus confirming the stability of the result Additional file 1: Figure S4, http://links.lww.com/MD/D625.

### 3.4. All-cause mortality at day 28 and day 90

Three studies evaluated the association between exposure to AP therapy and time of ECC and eGFR measurement. The MDs of all-cause mortality at day 28 (fixed effects: OR = 0.62, 95% CI = 0.40–0.97, $P = .04$) and day 90 (fixed effects: OR = 0.61, 95% CI = 0.39–0.96, $P = .03$) were significantly lower in AP therapy group compared with placebo (Figs. 3 and 4). No heterogeneity

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**Figure 2.** Forest plots and meta-analysis of estimated glomerular filtration rate (mL/min) among patients with sepsis-associated acute kidney injury measured at days 60 and 90, respectively. AL = alkaline phosphatase.

**Figure 3.** Forest plots and meta-analysis of all-cause mortality at day 28 among patients with sepsis-associated acute kidney injury with alkaline phosphatase.
3.5. Relationship of AP therapy and plasma creatinine in patients with SA-AKI

Two studies evaluated plasma creatinine of patients with SA-AKI on AP therapy. The MD was significantly lower in AP therapy group compared with placebo (fixed effects: MD = −0.87, 95% CI = −1.46 to −0.28, P = .008) (Additional file 1: Fig. S5, http://links.lww.com/MD/D626). No heterogeneity was detected among studies (I² = 0%, P = .45).

3.6. Relationship of AP therapy and urine output in patients with SA-AKI

Two studies evaluated the association between exposure to AP therapy and urine output. The MD of urine output was not significantly lower in AP therapy group compared with placebo (fixed effects: MD = −0.53, 95% CI = −1.53 to 0.46, P = .383) (Additional file 1: Fig. S6, http://links.lww.com/MD/D627). No heterogeneity was detected among studies (I² = 0%, P = .79).

3.7. Relationship of AP therapy and day 1 urinary biomarkers of renal injury in patients with SA-AKI

Three studies evaluated the association between exposure to AP therapy and day 1 urinary biomarkers of renal injury. The MD of overall biomarkers level was higher in AP therapy group compared with placebo (random effects: MD = −0.65, 95% CI = −1.04 to −0.26, P = .02) (Fig. 5). Heterogeneity was detected among studies (I² = 95%, P < .00001), and we believed that it mainly came from the differences of the 7 biomarkers.

3.8. The optimal dose of AP for SA-AKI

Four studies evaluated the association between AP doses and ECC alteration in patients with SA-AKI. The MD of 0.212 mg/kg AP dose was significantly higher in AP therapy group compared with placebo, while no significant difference was detected in 0.4 mg/kg AP, 0.8 mg/kg AP, and 1.6 mg/kg AP group (0.212 mg/kg AP: random effects: OR = 2.75, 95% CI = 0.55–13.84, P = .22; 0.4 mg/kg AP: random effects: OR = 2.75, 95% CI = 0.55–13.84, P = .22; 0.8 mg/kg AP: random effects: OR = 2.75, 95% CI = 0.55–13.84, P = .22; 1.6 mg/kg AP: random effects: OR = 2.75, 95% CI = 0.55–13.84, P = .22) (Additional file 1: Fig. S7, http://links.lww.com/MD/D628). Heterogeneity was detected among subgroup studies (I² = 83.3%, P = .07).

3.9. Relationship of AP therapy and RRT duration days or RRT-requirement days in patients with SA-AKI

Two studies evaluated the association between AP therapy and RRT duration days or RRT-requirement days. The MD of RRT duration days was significantly higher in AP therapy group compared with placebo in Pickkers 2012[6] (random effects: MD = −0.87, 95% CI = −1.46 to −0.28, P = .008) (Additional file 1: Fig. S8, http://links.lww.com/MD/D629). No heterogeneity was detected among subgroup studies (I² = 24%, P = .27).

4. Discussion

This systematic review and meta-analysis revealed that ECC elevated among patients with SA-AKI when treated with 0.212 mg/kg AP. All-cause mortality was lowered at day 28 and day 90, respectively, only when patients with SA-AKI were administered with 1.6 mg/kg of AP. No significance in mortality was observed.
in the 0.212, 0.4, and 0.8 mg/kg AP group, which indicates that only a relatively higher dose of AP can have an effect on improving mortality. AP had no significant effect on short-term ECC but had a significant effect in improving ECC at days 7, 14, and 28. Levels of AKI biomarkers were improved in short term. AP had no significant effect in improving urine volumes. Plasma creatinine levels were lower in short-term after the infusion of AP. RRT duration and requirement period was shortened when 0.212 mg/kg of AP was administered. We believe the heterogeneity in this study came from the doses of AP or the type of AP or the combination of both.

Both infectious and noninfectious causes can lead to sepsis. Noninfectious causes include pancreatitis, tissue ischemia, trauma and surgical tissue injury, burns, thromboembolism, vasculitis, drug reactions, and autoimmune and neoplastic processes. The sites of infection for infected patients are most commonly the lungs (64%), abdomen (20%), bloodstream (15%), and renal or genitourinary tract (14%). About 47% of infected patients with positive microbiology are Gram positive (Staphylococcus aureus alone accounted for 20%), 62% Gram negative (20% Pseudomonas spp and 16% Escherichia coli), and 19% fungal. AKI is common in severe sepsis and substantially increases mortality rates.

The SA-AKI is thought to result from inflammation and hypoxia combined, leading to reduced kidney perfusion, ischemia, and subsequent tubulus necrosis. It is believed that the damage caused by inflammation, ischemic damage caused by altered microcirculation and impaired renal bioenergetics collaboratively contribute to the pathogenesis of SA-AKI. The inflammation process is started by recognition of “pathogen-associated molecular patterns” (PAMPs) such as LPS followed by the increased production of inflammatory mediators. The damage caused by this inflammatory process leads to impaired renal microcirculation and cell damage or cell death due to hypoxia. Subsequently, “danger-associated molecular patterns” (DAMPs) are released resulting in a sustained inflammatory effect. In addition, DAMPs and PAMPs also interact with receptors in the proximal tubule of the kidney resulting in a local inflammatory response leading to leukocyte infiltration and tubular lesions. Renal cell apoptosis ultimately leads to AKI. As AP dephosphorylates and detoxifies LPS, it was initially designed as an anti-inflammatory sepsis drug. This anti-inflammatory effect could reduce the risk of AKI by the detoxification of LPS in the kidney. Application of AP could reduce circulating LPS and lower cytokine levels, thus preventing the development of renal hypoxia which leads to AKI.

In this meta-analysis, kidney protection from AP can be observed at days 7, 14, and 28, but no significant difference was detected in ECC at days 1, 60, and 90, which means that AP presents a late protective effect in ECC and the short-term effect is
not significant. Since ECC is a late functional marker and is considered to be inaccurate in evaluating kidney function in unsteady conditions, it might not be appropriate to evaluate the underlying organ damage that only becomes evident later by taking acute measures. It was suggested that the lower mortality in the 1.6 mg/kg AP treatment group compared with placebo may influence the evaluation of short-term ECC. The estimation of a relatively lower ECC in the most severely ill, but surviving, patients in the treatment group may have attenuated the increase in overall ECC levels. In this meta-analysis, ECC measured at day 1 with 0.212 mg/kg, 0.4, 0.8, and 1.6 mg/kg of AP did not elevate significantly. If the data of 1.6 mg/kg AP is excluded, the insignificant result remains. We assumed that the insignificant elevated short-term ECC is not the result of lower mortality detected only in the 1.6 mg/kg AP group. In this analysis, short-term serum creatinine decreased but short-term ECC and urine volumes showed no significant changes. In the early phase of AKI, glomerular filtration rate (GFR) decreases rapidly and remains at an extremely low level before recovery. According to the well-known relation between GFR and serum creatinine, when GFR fluctuates between 80 and 120 mL/min, serum creatinine level changes between 0 and 2 mg/dL. However, when GFR fluctuates between 0 and 80 mL/min, serum creatinine level changes between 2 and 10 mg/dL (Additional file 1: Fig. S9, http://links.lww.com/MD/D630). ECC is often 10% lower than GFR because of tubular reabsorption, which suggests that as ECC gradually improves in the early phase of AKI after certain treatment, serum creatinine will show a more significant change compared with that in ECC. It is assumed that short-term ECC changes in AKI is too insignificant to be detected, and serum creatinine may have more accuracy in evaluating short-term kidney function in patients with AKI on therapies.

Sepsis-mediated hypoperfusion and associated ischemia leading to tubular necrosis is considered to be the primary pathophysiology for SA-AKI. Tubular cellular injury, inflammation, and apoptosis result in the propagation of AKI during sepsis. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary kidney injury molecule 1 (KIM-1) are common biochemical biomarkers of renal tubular injury. NGAL is a protein belonging to the lipocalin family. It is secreted from renal epithelial cells after AKI as early as 3 hours. NGAL in kidneys is produced in the ascending loop of Henle and the intercalated cells of the collecting duct and is filtered by the glomerulus and reabsorbed by the proximal tubule. AKI may result in less tubular reabsorption of NGAL and increase its urinary excretion. Likewise, KIM-1 presents low expression in healthy organs and upregulation in mainly proximal tubule cells of injured kidneys. The shedding of the extracellular domain of KIM-1 from the cell surface by a metalloproteinase-dependent process together with the increased secretion in injured kidneys collaboratively lead to the upregulated urine excretion. Glutathione S-transferases (GSTs), a family of cytoplasmic and membrane-associated enzymes, become detectable in the urine when renal tubular epithelial cells are injured. GSTs have been reported to have the power to predict or diagnose AKI. The amounts of GSTA1 and GSTP1 in urine differentiate between proximal and distal tubular cell injury. GSTP1 and GSTA1 levels have improved among patients with SA-AKI in this meta-analysis, suggesting them as promising biomarkers for patients with sepsis-associated AKI on AP. Because increases in urinary excretion of NGAL, GSTA1, GSTP1, and KIM-1 indicate tubular injury, these markers were evaluated in this meta-analysis to provide evidence for tubular necrosis. Other renal injury biomarkers evaluated in this study include urinary interleukin 18 (IL-18). IL-18 is a cytokine from the IL-1 superfamily. An increase secretion of IL-18 was detected in tubular epithelial cells of damaged kidneys compared with the intercalated cells of the collecting ducts in normal kidneys. IL-18 is considered as a biomarker of AKI due to its pathophysiologic characteristics, which makes urinary IL-18 an imperative adjunctive biomarker. And it was suggested that IL-18 deficiency can protect mice from AKI. According to a clinical trial conducted by Pickkers et al., urinary excretion of KIM-1 and IL-18 declined significantly in patients on AP compared with those on placebo. No difference was detected regarding the levels of NGAL and GST enzymes among groups. The insignificant outcome may be the result of large variance among patients and inadequate power.

There are several strengths of this study. Firstly, this is the first comprehensive meta-analysis on AP use in patients with SA-AKI which evaluates kidney function after AKI from several different aspects and provides plausible explanation for the results. Serum creatinine and urine output are considered to be biochemical markers of glomerular filtration and global assessment of nephron function, respectively. Urinary NGAL, urinary KIM-1, serum creatinine, and urine output are common biomarkers used for detection of AKI. Serum creatine, RRT duration, and urine output are involved in the diagnostic criteria of AKI (RIFLE, AKIN, and KDIGO). The above-mentioned indexes are all included in this meta-analysis for evidence of AKI. Secondly, the search for included literature, study selection, and data extraction were performed independently by 2 investigators. However, limitation exists in this meta-analysis. First, a larger number of studies and patients are required toward a more definite result. The relatively small number of included studies in this analysis may have weakened the statistical power of the overall result. Early trials have been excluded to lower the heterogeneity of this analysis. Second, heterogeneity exists among groups. Origins of AP differ among included studies. Moreover, the doses of AP, timing of administration, and duration of therapy may inevitably contribute to the heterogeneity. Third, in Method section, it has already been mentioned that data primarily reported as medians with IQRs were re-expressed into means and SDs assuming a normal distribution. In addition, if a study with multiple intervention groups was included, we split the shared group into more groups with smaller sample size and included more reasonably independent comparisons according to the Cochrane handbook. These methodologic considerations may bias the overall result due to inaccessibility to the crude information of included studies.

5. Conclusion

In conclusion, this meta-analysis provides a comprehensive view on the kidney function of patients with SA-AKI treated with AP. In patients with SA-AKI, AP shows a relatively late protective effect by improving ECC at days 7, 14, and 28. ECC level improved when patients were administered with 0.212 mg/kg of AP. Mortality improved at days 28 and 90, respectively, when patients were administered with 1.6 mg/kg of AP. AKI biomarkers levels were improved in short term. Short-term plasma creatinine levels improved. RRT duration and requirement period were shortened when patients were administered with 0.212 mg/kg of AP.
Author contributions
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References
[1] Fernando SM, Rochwerg B, Seely AJE. Clinical implications of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). CMAJ 2018;190:E1058–9.
[2] Peters E, van Elsas A, Heemskerk S, et al. Alkaline phosphatase as a treatment of sepsis-associated acute kidney injury. J Pharmacol Exp Ther 2013;344:2–7.
[3] Heemskerk S, Masereeuw R, Moesker O, et al. Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients. Crit Care Med 2009;37:417–23.
[4] Poelstra K, Bakker WW, Klok PA, et al. Dephosphorylation of endotoxin by alkaline phosphatase in vivo. Am J Pathol 1997;151:1163–9.
[5] Beumer C, Wulferink M, Raaben W, et al. Calf intestinal alkaline phosphatase, a novel therapeutic drug for lipopolysaccharide (LPS)-mediated diseases, attenuates LPS toxicity in mice and piglets. J Pharmacol Exp Ther 2003;307:737–44.
[6] Pickkers P, Heemskerk S, Schouten J, et al. Alkaline phosphatase for treatment of sepsis-induced acute kidney injury; a prospective randomized double-blind placebo-controlled trial. Crit Care 2012;16:R14.
[7] Pickkers P, Mehta RL, Murray FT, et al. Effect of human recombinant alkaline phosphatase on 7-day creatinine clearance in patients with sepsis-associated acute kidney injury: a randomized clinical trial. JAMA 2018;320:1998–2009.
[8] Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 2011;Available at www.hankbook.cochrane.org.
[9] Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785–805.
[10] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
[11] Melsen WG, Bootsma MC, Rovers MM, et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123–9.
[12] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[13] Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ 2016;353:i1585–90.
[14] Humeke-Opfers F, Hemelaar P, Pickkers P. Innovative drugs to target renal inflammation in sepsis: alkaline phosphatase. Front Pharmacol 2019;10:919.
[15] Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. Intensive Care Med 2017;43:816–28.
[16] Peters E, Heemskerk S, Masereeuw R, et al. Alkaline phosphatase: a possible treatment for sepsis-associated acute kidney injury in critically ill patients. Am J Kidney Dis 2014;63:1038–48.
[17] Sutton TA, Fisher CJ, Molontin BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. Kidney Int 2002;62:1539–49.
[18] Shemesh O, Golbetz H, Kris JP, et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 1985;28:830–8.
[19] Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ 2019;364:k4891.
[20] Schrenzeimer EV, Barasch J, Budde K, et al. Biomarkers in acute kidney injury – pathophysiological basis and clinical performance. Acta Physiol (Oxf) 2017;219:554–72.
[21] Schmidt-Ott KM, Mori K, Li JY, et al. Dual action of neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2007;18:407–13.
[22] Hvidberg V, Jacobsen C, Strong RK, et al. The endocytic receptor megalin binds the iron transporting neutrophil-gelatinase-associated lipocalin with high affinity and mediates its cellular uptake. FEBS Lett 2005;579:773–7.
[23] Ichimura T, Bonventre JV, Bailly V, et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem 1998;273:4133–42.
[24] Han WK, Bailly V, Abichandani R, et al. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 2002;62:237–44.
[25] Ichimura T, Hung CC, Yang SA, et al. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol 2004;286:F552–63.
[26] Westhuyzen J, Endre ZH, Reece G, et al. Measurement of tubular enzymeuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003;18:543–51.
[27] Gauer S, Schlier O, Obermuller N, et al. IL-18 is expressed in the intercalated cell of human kidney. Kidney Int 2007;72:1081–7.
[28] Franko EL, Vanderbrink BA, Hile KL, et al. Renal IL-18 production is macrophage independent during obstructive injury. PLoS One 2012;7:e47417.
[29] Wu H, Craft ML, Wang P, et al. IL-18 contributes to renal damage after ischemia-reperfusion. J Am Soc Nephrol 2008;19:2331–41.