Adjunctive sepsis therapy with aminophylline (STAP): a randomized controlled trial

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Abstract

Background: Sepsis is a serious disease caused by infection. Aminophylline has anti-asthma and anti-inflammatory effects. We aimed to explore the safety and effect of aminophylline in sepsis.

Methods: We conducted a clinical randomized controlled trial involving 100 patients diagnosed with sepsis within 48 h after intensive care unit (ICU) admission in two sites. All patients were randomized in a 1:1 ratio to receive standard therapy with or without aminophylline. The primary clinical outcome was all-cause mortality at 28 days.

Results: From September 27, 2018 to February 12, 2020, we screened 277 septic patients and eventually enrolled 100 patients, with 50 assigned to the aminophylline group and 50 to the usual-care group. At 28 days, 7 of 50 patients (14.0%) in the aminophylline group had died, compared with 16 of 50 (32.0%) in the usual-care group ($P = 0.032$). Cox regression showed that the aminophylline group had a lower hazard of death (hazard ratio = 0.312, 95% confidence interval: 0.129–0.753). Compared with the usual-care group, patients in the aminophylline group had a longer survival time ($P = 0.039$ by the log-rank test). The effects of aminophylline on vasopressor dose, oxygenation index, and sequential organ failure assessment score were time-dependent with treatment. There were no significant differences in total hospitalization days, ICU hospitalization days, and rates of serious adverse events (all $P > 0.05$). No adverse events were observed in the trial.

Conclusions: Aminophylline as an adjunct therapy could significantly reduce the risk of death and prolong the survival time of patients with sepsis.

Trial registration: ChiCTR.org.cn, ChiCTR1800019173.

Keywords: Aminophylline; Mortality; Randomized controlled trial; Sepsis

Introduction

Sepsis has been listed as a health priority by the World Health Organization[1] due to its resultant mortality rate of 25% to 30% and its associated extent of medical resources' use.[2-4] The primary treatment strategies, including early recognition, source control, antibiotics, fluid resuscitation, immunomodulatory agents, and other supportive treatments, have been widely explored.[5-9] But sepsis-related mortality is still very high, and sepsis remains a major cause of health loss worldwide.[10] During sepsis development, microcirculatory perfusion disorders and inflammatory immune responses ultimately lead to multiple organ dysfunction.[11-13] Therefore, improving the uncontrolled inflammatory response and cellular permeability may be one of the most important methods for successful treatment of sepsis.

Theophylline is a bronchodilator and exercises an anti-inflammatory role by regulating the production of pro-inflammatory cytokines in chronic obstructive pulmonary disease.[14,15] Concurrently, theophylline can increase the anti-inflammatory effect of glucocorticoids.[16,17] During an acute asthma attack, aminophylline acts as an anti-inflammatory by inhibiting the influx of neutrophils and eosinophils into the airway.[18,19] As a non-selective

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adenosine receptor antagonist, aminophylline can antagonize adenosine receptors and inhibit the release and production of inflammatory factors by inhibiting phosphodiesterase activity. Aminophylline has been reported for the treatment of idiopathic capillary leakage syndrome.[20,21] In addition, aminophylline can stimulate respiration, enhance respiratory muscle contractions, improve pulmonary ventilation, and even improve tolerance to hypoxia without increasing oxygenation.[22,23] It can also block the purinergic signaling cascade of adenosine to inhibit the tubuloglomerular feedback loop, preventing a decrease in glomerular filtration rate and urine output, and thus provide a possible benefit in renal protection.[24,25] A previous study by Dai *et al*[26] has found that aminophylline can increase urine volume, improve oxygenation, and enhance cardiac function in sepsis patients. A recent study has shown that aminophylline can reduce endothelial cell permeability by downregulating the related protein level in a lipopolysaccharide (LPS)-induced inflammatory model,[27] and it may potentially have an effect on sepsis. However, there is a lack of clinical evidence for this phenomenon. We therefore, conducted this pilot study to explore the safety and efficacy of aminophylline in sepsis.

Methods

Ethical approval

This study has been approved by the Scientific Research and Clinical Trial Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Drug-2018-94). Each patient or their caregiver(s) signed a written informed consent after they were provided a comprehensive explanation of the study.

Study design and oversight

From September 27, 2018 to February 12, 2020, we conducted a randomized controlled trial in two sites (General Intensive Care Unit [ICU], the First Affiliated Hospital of Zhengzhou University, and the Critical Care Department, First Affiliated Hospital of Kunming Medical University) to explore the effect of aminophylline in sepsis. Patients were assigned in a 1:1 ratio to receive standard treatment with or without aminophylline.

Selection and description of participants

All the patients in the ICU with sepsis were screened. Inclusion criteria were as follows: (1) According to Sepsis-3 diagnostic criteria of the American Society of Critical Care Medicine/European Society of Critical Care Medicine: A. Suspected or confirmed infection: Diagnosed by a clinician; B. Evidence of acute organ dysfunction: Patients without previous chronic organ dysfunction (assuming the baseline sequential organ failure assessment [SOFA] score is zero): SOFA ≥2; Patients with previous chronic organ dysfunction (SOFA score should be based on the baseline situation): SOFA increase ≥2. (2) Patients were eligible if diagnosed with sepsis in 48 h.[7] Exclusion criteria were as follows: (1) Patients aged <18 years or >70 years; (2) Pregnancy or lactation; (3) New York Heart Association Grade four congestive heart failure, acute myocardial infarction, malignant arrhythmias, non-infectious cardiogenic shock, or uncontrolled acute blood loss; (4) Recipients of solid organ or bone marrow transplantation; (5) Patients received cardiopulmonary resuscitation within 72 h before enrollment; (6) Neutrophil count $<0.5 \times 10^9$/L (except secondary sepsis); (7) Human immunodeficiency virus serological positive; (8) The estimated survival time less than 2 months, owing to reasons such as malignant tumor, etc.; (9) Failure to obtain informed consent or authorization; (10) Participation in other exploratory clinical trials within 6 months before screening; (11) Epilepsy and convulsions; (12) Chronic kidney disease at stage five; (13) A history of active peptic ulcer during the preceding 3 months; (14) Patients with allergy to this product.

Patients who met all the inclusion criteria and did not meet any exclusion criteria were eligible for the study.

Patient randomization

We used random numbers in a 1:1 ratio for central randomization: The 100 enrolled patients were considered as samples, which were listed serially using numbers from 1 to 100 in Excel; then certain functions were used to generate 100 random numbers, each of these representing a number belonging to the initial serial numbers; thereafter, the random numbers obtained were sorted in ascending order. The first 50 samples constituted the aminophylline group, and the remaining 50 samples constituted the control group. Then, sequence number columns were arranged in ascending order to complete random grouping. The sequence was maintained in sealed, opaque envelopes to ensure allocation concealment. When entering the group, investigators at each participating site contacted the allocation center for a sequence number, and the envelopes corresponding to the serial number were extracted in turn according to the time sequence of patient screening. Randomization had to be completed within 2 h after enrollment. The medical staff at both hospitals were aware of the treatment assignments. However, the investigators who evaluated the outcomes and the technicians who conducted the laboratory tests were blinded to treatment allocation. Patients were stratified according to shock status at screening. There were 55 patients in the septic shock subgroup, 28 in the aminophylline group, and 27 in the control group.

Study interventions

After randomization, the usual-care group continued to receive standard therapy as determined by the treating clinicians, who were encouraged to follow the Surviving Sepsis Campaign guidelines[9] in the two sites. The aminophylline group was given aminophylline intravenously based on the standard treatment: Aminophylline was injected intravenously at 3 mg/kg for 30 min, before being pumped intravenously at 0.4 mg · kg^{-1}· h^{-1} for 5 days. The aminophylline was provided by the hospital pharmacy and not by the drug manufacturer. At least one trained staff member was available throughout the intervention period.

The day of screening was recorded as day 0, and patients in the aminophylline group began to receive aminophylline according to the study protocol on day 0.

Outcome measures

The primary outcome was all-cause mortality at 28 days. The secondary outcomes included all-cause mortality at 60 days; the scores on the SOFA on each day from days 0 to 5; the scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) on days 0 and 5; mechanical ventilation; lengths of stay in the hospital and ICU; duration of survival; output urine on each day from days 0 to 5; 24-h fluid intake on each day from days 0 to 5; oxygenation index and heart rate on each day from days 0 to 5; the blood concentration of aminophylline on days 1, 3, and 5; and assay indexes of routine blood, coagulation function, biochemistry, arterial blood gas analysis, C-reactive protein, procalcitonin, and routine urine on each day from days 0 to 5.

Adverse events were monitored until 48 h after the end of treatment. Several major adverse events (tachycardia, arrhythmia, and convulsions) associated with aminophylline were pre-specified in case report forms and screened daily by investigators.

Statistical analysis

The primary comparisons of the two groups were tested at a two-sided type I error rate of 5%, without adjustment for multiplicity. Continuous variables were reported as means and standard deviations or medians and interquartile ranges. Categorical variables were reported as proportions. We employed the last-observation-carried-forward method to fill in the missing values. We used the Fisher test or the chi-squared test to compare group differences among the categorical variables. Multivariate analysis of variance (ANOVA) was used. The data conforming to the spherical test were analyzed using a monadic ANOVA; otherwise, multivariate ANOVA was used. We used covariance analysis to detect changes in the continuous endpoints of the APACHE II scores between the two groups. Non-repetitive data were tested using the *t* test or Mann–Whitney *U* rank-sum test. The survival data were analyzed using Kaplan–Meier survival curves, and the difference between the two groups was detected using the log-rank test. We screened the indicators with forward-LR (factors were selected if $P < 0.20$ in the univariate analysis, or $P > 0.20$, but it has important clinical value and may predict the prognosis according to clinical) and predicted the risk of death using Cox proportional hazard regression analysis. SPSS version 21 (IBM Corp., Armonk, NY, United States) was used for all the analyses.

Results

Patients

From September 27, 2018 to February 12, 2020, we screened 277 patients with sepsis at the two study sites, resulting in the enrollment of 100 patients (80 patients in Zhengzhou and 20 patients in Kunming), including 50 patients in the aminophylline group and 50 patients in the usual-care group. In the usual-care group, four patients with septic shock were missing repeated measurements (two died and two had discharge requests) and were not involved in repeated data ANOVA. We assessed the four patients' survival status at 28 days and 60 days [Figure 1].

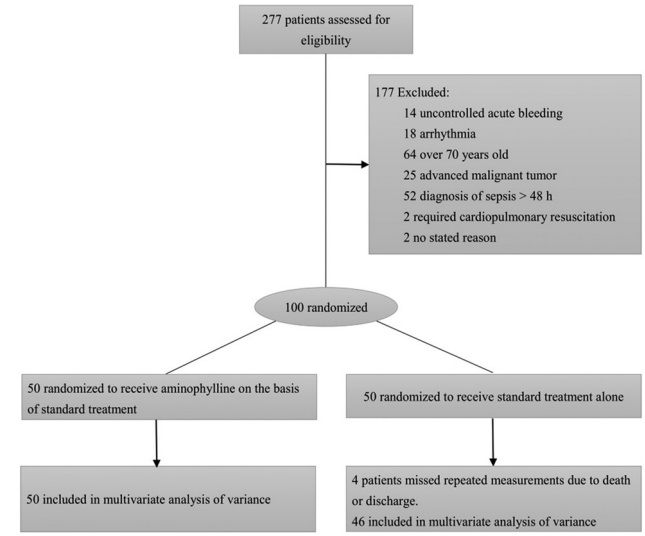

Figure 1: Flow chart of participants' enrollment, grouping and analysis.

The two groups were well-matched at baseline [Table 1]. The most common site of infection in the aminophylline and usual-care groups was the lung (58% and 52%, respectively), and there was no statistical difference between the two groups. The criterion for septic shock was met in 28 patients (28/50, 56.0%) in the aminophylline group and 27 patients (27/50, 54.0%) in the usual-care group, showing no statistical difference.

ANOVA for repeated data

At the baseline of repeated measurements, patients in the aminophylline group had higher platelet counts and fibrinogen [Table 2]. The data for repeated measurements were analyzed by multivariate ANOVA because they did not conform to the spherical test. The results showed that platelet, fibrinogen, creatinine, total protein, albumin, PH, C-reactive protein, procalcitonin, SOFA scores, 24-h fluid intake, oxygenation index, and heart rate improved gradually with the extension of treatment time ($P < 0.05$). The groups did not show any statistical significance for each repeated measurement index. In the aminophylline group, the effect of aminophylline gradually appeared in SOFA score and the oxygenation index with the prolongation of treatment time ($P < 0.05$) [Supplementary Table S1, http://links.lww.com/CM9/B413].

The results of shock subgroup analysis showed that the dosage of noradrenaline, fibrinogen, creatinine, total protein, albumin, PH, C-reactive protein, procalcitonin, SOFA scores, 24-h fluid intake, and 24-h urine output improved gradually with the extension of treatment time ($P < 0.05$) [Supplementary Table S2, http://links.

Table 1: Characteristics of the participants at baseline[*].

Characteristics	Aminophylline group ($n = 50$)	Usual-care group ($n = 50$)	*P* value
Age, median (IQR) (years)	51.5 (40.0–64.3)	51.5 (42.3–60.5)	0.637
Male sex, *n* (%)	36 (72.0)	35 (70.0)	0.826
Underlying disease, *n* (%)[†]			
Hypertension	15 (30.0)	11 (22.0)	0.362
Coronary heart disease	3 (6.0)	3 (6.0)	1.000
Liver disease	4 (8.0)	2 (4.0)	0.678
COPD	3 (6.0)	1 (2.0)	0.617
Nervous system disease	5 (10.0)	4 (8.0)	1.000
Diabetes mellitus	12 (24.0)	7 (14.0)	0.202
Trauma	3 (6.0)	2 (4.0)	1.000
Tumor	1 (2.0)	4 (8.0)	0.362
Other diseases	9 (18.0)	8 (16.0)	0.790
Site of infection, *n* (%)			
Lungs	29 (58.0)	26 (52.0)	0.546
Abdomen	16 (32.0)	16 (32.0)	1.000
Urogenital tract	5 (10.0)	4 (8.0)	1.000
Blood	10 (20.0)	12 (24.0)	0.629
Other sites	13 (26.0)	12 (24.0)	0.817
Mechanical ventilation, *n* (%)	22 (44.0)	22 (44.0)	1.000
Shock, *n* (%)	28 (56.0)	27 (54.0)	0.841

CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range. [*] There were no statistically significant differences between the two groups. [†] Underlying diseases were self-reported and assessed by the physician.

Table 2: Comparison of laboratory and clinical indexes between the two groups.

Clinical indexes	Aminophylline group ($n = 50$)	Usual-care group ($n = 50$)	*P* value
Dose of vasopressors, median (IQR) ($\mu g \cdot kg^{-1} \cdot min^{-1*}$)	0.05 (0.00–0.32)	0.00 (0.00–0.28)	0.652
White blood cell count, median (IQR) ($\times 10^3/\mu L$)	12.08 (8.79–16.77)	12.82 (7.55–18.87)	0.730
Red blood cell count, median (IQR) ($\times 10^6/\mu L$)	3.55 (2.85–4.13)	3.30 (2.74–3.79)	0.301
Hemoglobin, mean (SD) (g/L)	103.08 (32.16)	102.14 (26.04)	0.873
Platelet count, median (IQR) ($\times 10^3/\mu L$)	158.50 (86.25–242.75)	112.50 (28.50–213.50)	0.046
Prothrombin time, median (IQR) (s)	13.40 (11.48–15.15)	14.25 (11.78–15.73)	0.274
Activated partial thromboplastin time, median (IQR) (s)	31.20 (28.10–40.30)	33.40 (28.28–41.70)	0.539
Fibrinogen, median (IQR) (g/L)	4.59 (3.26–6.92)	3.65 (2.67–4.99)	0.037
D-dimer, median, (IQR) (mg/L)	1.94 (0.85–3.28)	2.36 (1.05–3.95)	0.282
Blood urea nitrogen, median (IQR) (mmol/L)	8.64 (5.11–15.67)	10.00 (5.07–18.89)	0.725
Serum creatinine, median (IQR) (μmol/L)	79.00 (58.98–154.03)	79.75 (53.75–149.00)	0.992
Glomerular filtration rate, median (IQR) (mL/min)	76.75 (43.46–105.79)	81.88 (42.51–108.36)	0.942
Alanine aminotransferase, median (IQR) (U/L)	25.50 (11.75–76.75)	35.85 (21.75–63.50)	0.197
Aspartate aminotransferase, median (IQR) (U/L)	32.50 (22.75–76.75)	40.50 (19.53–97.25)	0.588
Total protein, median, (IQR) (g/L)	56.80 (50.65–62.20)	56.40 (46.33–62.75)	0.754
Albumin protein, median (IQR) (g/L)	25.55 (22.95–31.58)	25.75 (21.50–30.90)	0.756
Total bilirubin, median (IQR) (μmol/L)	16.25 (8.18–29.15)	14.45 (10.65–35.90)	0.408
Direct bilirubin, median (IQR) (μmol/L)	8.20 (4.65–16.28)	8.95 (5.28–27.78)	0.224
Indirect bilirubin, median (IQR) (μmol/L)	4.80 (3.03–10.18)	6.25 (3.20–10.58)	0.414
pH value, median (IQR)	7.42 (7.36–7.46)	7.41 (7.36–7.46)	0.664
Blood lactate, median (IQR) (mmol/L)	1.50 (1.10–2.23)	1.60 (1.10–2.83)	0.617
C-reactive protein, median (IQR) (mg/L)	156.91 (104.07–236.40)	136.25 (73.50–217.19)	0.343
Procalcitonin, median, (IQR) (ng/mL)	7.77 (1.04–18.65)	3.03 (0.88–13.70)	0.212
Urine specific gravity, median (IQR)	1.02 (1.02–1.02)	1.02 (1.01–1.02)	0.157
APACHE II score, median (IQR)	17.00 (11.75–21.00)	14.00 (11.00–20.00)	0.165
SOFA score, median (IQR)	8.00 (6.00–11.00)	8.00 (5.00–11.25)	0.906
24-h liquid intake, median (IQR) (mL)	4238.00 (3178.00–5371.50)	4052.00 (3259.00–5308.00)	0.777
24-h urine output, median (IQR) (mL)	2380.00 (1714.29–4066.07)	2950.00 (1440.00–4065.00)	0.989
Oxygenation index[†], median (IQR)	211.00 (170.75–274.98)	249.50 (172.25–305.25)	0.190
Heart rate, mean (SD) (min)	100.66 (25.41)	97.90 (24.12)	0.579

IQR: Interquartile range; SD: Standard deviation. [*] The only vasopressor used in shock patients at the two centers was noradrenaline. [†] Oxygenation index = PaO_2/FiO_2, the normal value is 400–500 mmHg, and when it is <300 mmHg, this can be taken as an indication of pulmonary respiratory dysfunction.

lww.com/CM9/B413]. The fibrinogen in aminophylline group was higher than that in the control group, but the baseline of fibrinogen in the aminophylline group was higher.

Mortality

A total of 23 patients died on the 28th day, including 20 (20/55) in the shock subgroup. The mortality of the aminophylline group was lower than that of the usual-care group (28-day mortality rate, 14.0% *vs*. 32.0%; 60-day mortality rate, 16.0% *vs*. 36.0%). In the shock subgroup, the 28-day and 60-day mortalities of the aminophylline group were significantly lower than those of the control group (28-day mortality rate, 25.0% *vs*. 48.2%; 60-day mortality rate, 28.6% *vs*. 51.9%), but there was no statistical difference between the two shock subgroups [Figure 2].

Survival analysis

The survival benefits seen in the aminophylline group were better than those in the usual-care group. There was a significant difference in the duration of survival between the two groups ($P = 0.039$ by the log-rank test) [Figure 3].

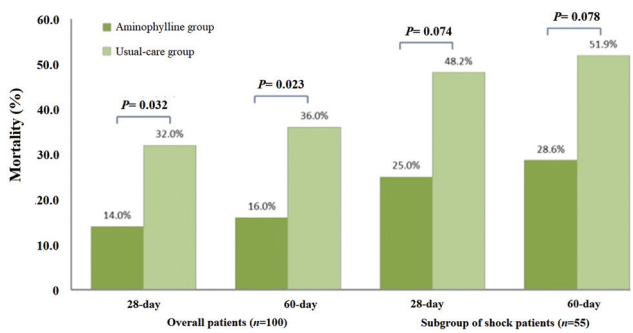

Figure 2: Comparison of mortality rates between the two groups.

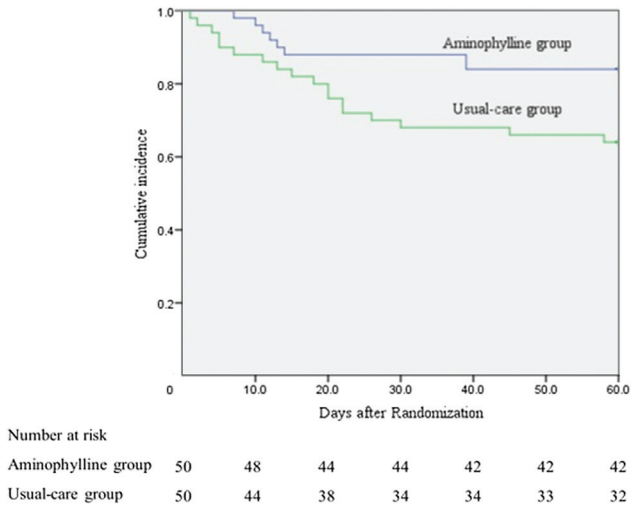

Figure 3: Kaplan–Meier Analysis by Randomization Group. Overall cumulative incidence was significantly different between the groups ($P = 0.039$ by the log-rank test).

The COX proportional-hazards model adjusted imbalance baseline (platelet count and fibrinogen) showed that the following — namely, group (hazard ratio [HR] = 0.312, 95% confidence interval [CI]: 0.129–0.753, $P = 0.010$), shock (HR = 4.695, 95% CI: 1.402–15.722, $P = 0.012$), bloodstream infection (HR = 3.290, 95% CI: 1.332–8.126, $P = 0.010$), SOFA score (HR = 1.180, 95% CI: 1.023–1.360, $P = 0.023$), D-dimer (per 1 mg/L, HR = 1.109, 95% CI: 1.034–1.190, $P = 0.004$), and platelet count (per $10 \times 10^3/\mu L$, HR = 1.083, 95% CI:1.033–1.136, $P = 0.001$) — were all independent risk factors for death events.

Further bivariate correlation analysis showed that the platelet count on day 0 was positively correlated with survival time (correlation coefficient = 0.025, $P = 0.807$) and mortality risk (correlation coefficient = 0.059, $P = 0.475$), but the association was not statistically significant. The change in platelet count on day 5 was positively correlated with survival time (correlation coefficient = 0.284, $P = 0.005$) and negatively correlated with risk of death (correlation coefficient = −0.279, $P = 0.001$); the association was statistically significant.

Other secondary outcomes

The lengths of stay in the hospital and ICU were similar in the two groups, and the difference was not statistically significant. In the aminophylline group, the median lengths of stay in the hospital and ICU were 18.50 days (11.75, 31.25) and 10.00 days (7.00, 16.00), respectively. In the usual-care group, the median lengths of stay in the hospital and ICU were 18.50 days (11.75, 31.25) and 10.00 days (7.00, 16.00), respectively. In the shock subgroup, the median lengths of stay in the hospital and ICU were 16.50 days (9.50, 28.75) and 9.00 days (7.00, 13.75), respectively, in the aminophylline group, and 17.00 days (9.00, 23.00) and 9.00 days (7.00, 16.00), respectively, in the usual-care group, showing no statistical significance in the two groups.

According to the adjusted baseline APACHE II scores on day 0, the APACHE II scores on day 5 in the aminophylline and usual-care groups were 10.79 (95% CI: 9.20–12.38) and 12.84 (95% CI: 11.18–14.49), respectively. There was no statistically significant difference between the two groups ($P = 0.083$, $F = 3.072$, difference = −2.042, 95% CI: −4.356 to 0.272). In the shock subgroup, there was also no statistically significant difference in the adjusted APACHE II scores on day 5 between the aminophylline and usual-care groups (11.21, 95% CI: 8.96–13.45 *vs*. 13.58, 95% CI: 11.10–16.06, $P = 0.166$, $F = 1.974$, difference = −2.371, 95% CI: −5.763 to 1.022).

Adverse effects

One patient of the aminophylline group developed atrial fibrillation with rapid ventricular rate, which was considered to be associated with hypokalemia. No remarkable/major adverse events related to aminophylline use were reported during the study period.

Adverse reactions to aminophylline are closely related to the drug concentration. If the concentration of aminophylline exceeds 15 μg/mL, the risk of mild adverse reactions is increased; when it exceeds 20 μg/mL, tachycardia and other arrhythmias may occur; and over 40 μg/mL, fever, dehydration, convulsions, and even cardiac arrest may occur. We monitored the concentrations of aminophylline on days 1, 3, and 5, and these were 6.66 ± 3.30, 8.09 ± 4.23, and 7.74 ± 3.67 μg/mL, respectively. The difference in aminophylline concentration at three-time points was statistically significant ($P = 0.024$): At day 3, this was 1.425 μg/mL (95% CI: 0.191–2.659, $P = 0.019$) higher than on day 1. At day 5, the difference was 1.077 μg/mL (95% CI: −0.405 to 2.558) higher than on day 1 and not statistically significant ($P = 0.233$). The difference on day 5 was decreased by 0.348 μg/mL (95% CI: −1.575 to 0.880) compared with day 3, with no statistically significant difference ($P = 1.000$).

With the extension of aminophylline application time, the numbers of patients with an aminophylline concentration exceeding 15 μg/mL increased: One patient on day 1 (23.08 μg/mL), three patients on day 3 (19.60, 18.34, and 15.20 μg/mL), and four patients on day 5 (17.40, 15.60, 15.20, and 15.06 μg/mL).

Discussion

The results of this study suggested a mortality benefit in patients with sepsis. The 28 and 60-day mortalities of the aminophylline group were significantly reduced, and the survival time was prolonged. Simultaneously, with the prolongation of treatment time, it was observed that intravenous aminophylline administration promoted an improvement in the SOFA score and oxygenation index of patients with sepsis. Increased vascular permeability is one of the major hallmarks of sepsis and is also associated with edema formation in other organs.[28,29] An *in-vitro* study found that aminophylline reduced the permeability of endothelial cells in a LPS-induced inflammation model.[27] We suspect that aminophylline may improve organ dysfunction in patients with sepsis by stabilizing capillary permeability, so as to improve the overall prognosis. However, this is a small open-label trial with significant limitations, and the results merit investigation in large multicenter studies with greater statistical power.

Pulmonary infection occurred in 55% of the sepsis patients included in this study (58% and 52% in the aminophylline and control groups, respectively). Aminophylline showed no statistically significant difference in the oxygenation index but did demonstrate some interaction with the time factor. With the extension of application, the improvement in the oxygenation index of the aminophylline group was gradually obvious. Studies have shown that aminophylline can stimulate respiration, enhance respiratory muscle contractility, increase pulmonary ventilation, and improve the tolerance to hypoxia without increasing oxygenation.[22,23] The effect of aminophylline on the oxygenation index of patients with sepsis is reasonable. It may take longer to see the effect, which is a limitation of our study.

There were 55 patients in the septic shock subgroup, 28 in the aminophylline group, and 27 in the control group. This study did not show a significant advantage in test indicators, but the 28-day mortality rate in the aminophylline group was lower than that in the control group (25.0% *vs.* 48.2%). It has been reported that aminophylline can be effectively used in the treatment of hypotension and bradycardia in paraplegic patients.[30] However, the results of this study did not demonstrate a specific benefit of aminophylline in septic shock.

Our study showed that the effect of aminophylline on the SOFA score was correlated with application time and the same is true of the effect of aminophylline on the oxygenation index. The SOFA score was used to evaluate the function of multiple organs in sepsis patients. Oxygenation index is one of the six indicators of SOFA score, suggesting that aminophylline improves SOFA score through oxygen index.

The diuretic effect of aminophylline has been recognized in some studies.[31-33] Studies have shown that a low dose of aminophylline, acting as a non-selective adenosine receptor, can increase renal perfusion and improve urine volume by dilating glomerular renal arterioles.[24] Aminophylline has been shown to reduce the incidence of acute kidney injury after cardiac surgery in children, but this finding remains controversial.[32,34,35] The diuretic effect of aminophylline was more significant in the early stages.[32] The aminophylline group had higher urine volume at the beginning in our study, but there was no significant difference from the control group. As the treatment progressed, the urine volume of the two groups was similar. We did not detect difference in urine volume between the two groups, which may be due to insufficient sample size.

Cox regression analysis adjusting for baseline imbalance (platelet count and fibrinogen on day 0) showed that aminophylline was a protective factor, and that decrease in thrombocytopenia, shock, bloodstream infection, and SOFA score, as well as increase in D-dimer, were independent risk factors. Platelet activation is an important pathophysiological mechanism in the development of sepsis. The platelet number, morphology, and function may be used as biomarkers for risk stratification of patients with sepsis. A lower admission platelet count is associated with a higher incidence of septic shock and an increased mortality rate.[36,37]

No aminophylline-related adverse reactions were observed during the study period. Although aminophylline is widely used in clinical practice, it has a narrow safety margin at regular doses, which is the reason for its limited clinical application. Usually, the effective plasma concentration of aminophylline is about 10 μg/mL. There is an increased risk of adverse reactions when aminophylline concentrations exceed 15 μg/mL (Supplementary, http://links.lww.com/CM9/B263).

The results of this study showed that the blood concentration of aminophylline was at a low level but still showed a therapeutic effect. The results also showed

that with the extension of the application time of aminophylline, the numbers of patients with an aminophylline concentration >15 μg/mL tended to increase, specifically for one patient, three patients, and four patients on days 1, 3, and 5, respectively. Therefore, the monitoring of blood drug concentrations should be enhanced with the application of aminophylline to avoid adverse reactions.

There were several limitations in this study. First, there exists no prior study to assist in calculating a reasonable sample size, and the sample size in this study was small. Second, this study was an open-label trial in which the risk of imbalance in combined interventions cannot be completely ruled out. However, the outcome assessment and experimental monitor were blind. Given the objective clinical results of this study, the results might not have been significantly affected by the open label design. Third, the respiratory system, kidney system, and inflammatory indicators were not completely adequate to reflect the role of aminophylline in these systems. A larger randomized controlled study is needed to further confirm the potential survival benefits seen in our preliminary study and also to investigate its mechanism of action in humans.

Conclusions

Aminophylline can reduce the risk of death in patients with sepsis, showing certain advantages in the respiratory system and circulatory system. The therapeutic effect of aminophylline in sepsis needs to be further verified in large-sample clinical studies.

Conflicts of interest

None.

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