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Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study

Won-Young Kim [a,b], Eun-Jung Jo [a], Jung Seop Eom [a], Jeongha Mok [a], Mi-Hyun Kim [a], Ki Uk Kim [a], Hye-Kyung Park [a], Min Ki Lee [a], Kwangha Lee [a,b,*]

[a] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea
[b] Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea

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ABSTRACT

Purpose: To evaluate the efficacy of combined vitamin C, hydrocortisone, and thiamine in patients with severe pneumonia.

Materials and methods: All consecutive patients with severe pneumonia who were treated with the vitamin C protocol (6 g of vitamin C per day) in June 2017–January 2018 (n = 53) were compared to all consecutive patients with severe pneumonia who were treated in June 2016–January 2017 (n = 46). Propensity score analysis was used to adjust for potential baseline differences between the groups.

Results: In the propensity-matched cohort (n = 36/group), the treated patients had significantly less hospital mortality than the control group (17% vs. 39%; $P = 0.04$). The vitamin C protocol associated independently with decreased mortality in propensity score-adjusted analysis (adjusted odds ratio = 0.15, 95% confidence interval = 0.04–0.56, $P = 0.005$). Relative to the control group, the treatment group had a significantly higher median improvement in the radiologic score at day 7 compared with baseline (4 vs. 2; $P = 0.045$). The vitamin C protocol did not increase the rates of acute kidney injury or superinfection.

Conclusions: Combined vitamin C, hydrocortisone, and thiamine therapy may benefit patients with severe pneumonia.

1. Introduction

Despite advances in antibiotic treatment, severe pneumonia remains a major cause of mortality: the mortality rate of patients with pneumonia who are admitted to the intensive care unit (ICU) is as high as 29–47% [1, 2]. An excessive host inflammatory response that impairs gas exchange and contributes to sepsis and organ dysfunction associates with higher mortality rates [3].

Vitamin C is a water-soluble vitamin that acts as a cofactor for several enzymes. In particular, it facilitates the production of catecholamines, vasopressin, and cortisol [4]. It is also an antioxidant: it directly scavenges reactive oxygen species, recycles other antioxidants, maintains endothelial barrier function and vasodilation, and downregulates the expression of proinflammatory modulators that are regulated by nuclear factor kappa-B [5, 6]. It also improves chemotaxis, supports lymphocyte function, and assists in phagocytosis and intracellular killing of bacteria [7]. Several randomized clinical studies have shown that when patients with sepsis or burns are treated with vitamin C, their Sequential Organ Failure Assessment (SOFA) scores, inflammatory marker levels, vasopressor requirements, resuscitation volume, and number of days on mechanical ventilation drop [8-10]. In addition, several meta-analyses of randomized controlled studies have shown that vitamin C may protect against contrast-induced acute kidney injury (AKI), shorten the duration of hospital and ICU stay of cardiac surgery patients, and even reduce blood pressure [11-13].

Other treatments may also improve the outcomes of patients with severe pneumonia. Experimental studies show that corticosteroids inhibit the action of many cytokines that are involved in the inflammatory response [14]. Moreover, a randomized controlled study showed that when septic patients with elevated lactate levels are treated with intravenous thiamine, their lactate levels and mortality rates are lower than

* Corresponding author at: Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea.
E-mail addresses: steve8126@hanmail.net (W.-Y. Kim), 81goodjung@hanmail.net (E.-J. Jo), ejspulm@gmail.com (J.S. Eom), mokgamokga@gmail.com (J. Mok), lovefull777@naver.com (M.-H. Kim), uk303@hanmail.net (K.U. Kim), irisal@daum.net (H.-K. Park), leemk@pusan.ac.kr (M.K. Lee), jubilate@pusan.ac.kr (K. Lee).

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those in placebo-treated patients [15]. In addition, a post hoc analysis of these data showed that the thiamine treatment lowered the creatinine levels of the patients and reduced their progression to renal failure [16].

These findings led to a recent retrospective before-after clinical study that showed that the treatment of patients with sepsis with an intravenously administered combination of vitamin C, hydrocortisone, and thiamine prevented organ dysfunction and reduced the mortality rate [17]. However, to date, this is the only study that has assessed the ability of combined vitamin C, hydrocortisone, and thiamine to reduce the mortality rates of patients with critical illness who require admission to the ICU. Several studies revealed that critically ill patients have low vitamin C levels despite receiving standard ICU nutrition [18, 19]. Given that pneumonia associates with low vitamin C levels [20] and that studies on the usefulness of this combination therapy for patients with severe pneumonia are limited, further research examining its efficacy is warranted.

In this retrospective before-after cohort study, we assessed the efficacy of combined treatment with vitamin C, hydrocortisone, and thiamine (denoted here as the vitamin C protocol) in patients with severe pneumonia who required admission to an ICU. Our institution started using the vitamin C protocol routinely in June 2017. As a result, we were able to compare 'before' and 'after' cohorts, which consisted of all consecutive patients with severe pneumonia who were admitted to the same ICU in the second halves of 2016 and 2017, respectively. To adjust for potential differences between the two groups, a risk stratification model was employed.

2. Material and methods

2.1. Study design and patient selection

This retrospective cohort study consisted of all consecutive critically ill adult patients with severe pneumonia who were admitted to the medical ICU (12 beds) of a 1100-bed university-affiliated tertiary care hospital in Busan, Korea in June 2016–January 2017 and June 2017–January 2018. The patients who were admitted between June 2017 and January 2018 were all treated with the vitamin C protocol and thus formed the treatment group. The patients who were admitted to the same ICU between June 2016 and January 2017 were not treated with the vitamin C protocol and thus formed the control group. Patients were excluded if they were not admitted to ICU and/or required conventional oxygen therapy only, had an acute diagnosis that was not severe pneumonia, the admission to the ICU occurred >48 h after hospitalization, the vitamin C protocol infusion occurred >48 h after hospitalization, and/or a do not resuscitate order issued. The primary study outcome was hospital mortality during the index hospitalization. Secondary outcomes were the number of vasopressor-free days at day 28, number of ventilator-free days at day 28, ICU length of stay, changes in the lactate levels and SOFA score at day 4 relative to those on the day of ICU admission, and the change in the radiologic score at day 7 relative to the score on the day of ICU admission. Potential vitamin C protocol-related adverse events were also analyzed. As sensitivity analysis, the patients who were admitted between February 2017 and May 2017 and were not treated with the vitamin C protocol were analyzed to examine differences in the primary outcome (hospital mortality) between the two control groups. The study protocol was approved by the Institutional Review Board of Pusan National University Hospital (C-1805-014-067). Written informed consent was waived due to the observational nature of the study.

2.2. Treatment protocol

In June 2017, experimental and emerging clinical data led our institution to adopt the vitamin C protocol as a routine adjunct therapy for severe pneumonia. The protocol consists of intravenous vitamin C (1.5 g every 6 h for 4 days), hydrocortisone (50 mg every 6 h for 7 days followed by a taper over 3 days), and intravenous thiamine (200 mg every 12 h for 4 days) [17]. We decided to administer 6 g of vitamin C per day (divided into four equal doses) because intravenous vitamin C at a dose of 6 g/day normalizes leukocyte vitamin C levels in respiratory infections [21]. The vitamin C protocol was not used when the patient had nosocomial pneumonia or a do not resuscitate order. During the control period, the patients with severe pneumonia did not receive either vitamin C or thiamine. However, they did sometimes receive corticosteroids at the discretion of the attending physician.

All patients were managed according to the therapeutic recommendations in the Surviving Sepsis Campaign Guidelines and the lung-protective ventilation strategy [22, 23]. All patients were treated with antibiotics according to international guidelines [24]. Apart from the administration of the vitamin C protocol during the treatment period, the ICU treatment protocols in the before and after study periods were identical. There were also no known significant changes to our study population (i.e., type of admission, criteria for admission, or comorbidities before admission).

2.3. Data collection and definitions

The baseline demographic and clinical characteristics that were collected were age, sex, body mass index, comorbidities, presence of concurrent bacteremia and/or acute respiratory distress syndrome, and the status of the patient within 24 h after ICU admission, namely, whether the patient was being treated with mechanical ventilation, neuromuscular blockers, vasopressors, and/or renal replacement therapy. In addition, the severity of illness at the time of ICU admission was recorded: it was assessed by using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [25] and the SOFA score [26]. Moreover, the daily vital signs, urine output, laboratory data, SOFA score, ventilator settings, vasopressor dosage, and radiologic findings on the first 4 days were extracted. The modified American Thoracic Society criteria (presence of two out of the three minor criteria (PaO_2/FiO_2 of <250, multilobar involvement, and systolic blood pressure of <90 mmHg) or one of two major criteria (requirement for mechanical ventilation and septic shock)) were used to define severe pneumonia [27]. An immunocompromised status was diagnosed if there was an underlying disease or condition that affected the immune system (i.e., human immunodeficiency virus infection, malignancy, or severe neutropenia) or if immunosuppressive therapy was being administered at the time of ICU admission. Acute respiratory distress syndrome was diagnosed on the basis of a consensus definition [28]. The radiologic scores were obtained as described previously [29]. The daily dosage of vasopressors was expressed as the norepinephrine equivalent dose [30]. AKI was defined on the basis of KDIGO (Kidney Disease: Improving Global Outcomes) criteria [31]. Superinfection was diagnosed when patients tested positive for a nosocomial infection from any source.

2.4. Statistical analysis

Continuous variables are presented as median and interquartile range or as mean ± standard deviation. Categorical variables are presented as percentages. The two groups were compared in terms of continuous variables by using Mann-Whitney *U* or Student's *t*-tests, and in terms of categorical variables by using Chi-squared or Fisher's exact tests. The Kruskal-Wallis test was used to compare continuous variables among the three groups.

To adjust for potential baseline differences between the treatment and control groups, propensity score analysis was performed [32]. Thus, propensity scores that indicated the conditional probability of the patients to receive the vitamin C protocol given the individual covariates were generated. The factors that were used for propensity score generation included immunocompromised status; SOFA score at ICU admission; use of neuromuscular blockers, vasopressors, and/or renal replacement therapy within the first 24 h; and the platelet

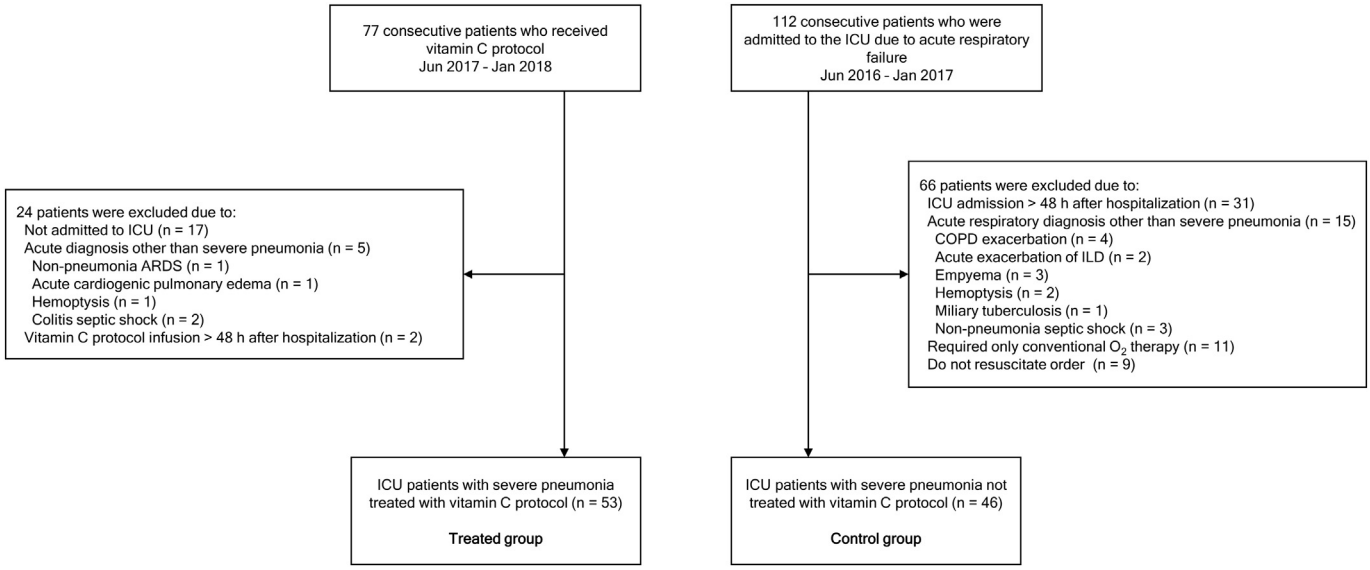

Fig. 1. Disposition of patients in the study. ICU = intensive care unit, ARDS = acute respiratory distress syndrome, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease.

count, the C-reactive protein (CRP) level, and lactate level on day 1 (Supplementary Table 1). Model discrimination was assessed with *c*-statistics ($c = 0.70$), and model calibration was assessed by using the Hosmer-Lemeshow test (Chi-square = 6.49; $P = 0.59$). Multivariate regression analysis using stepwise backward selection was performed with the individual propensity scores to analyze the effect of the vitamin C protocol on hospital mortality. The individual propensity score was incorporated into the model as a covariate to calculate propensity-adjusted odds ratio (OR). The 95% confidence intervals (CI) were also calculated. The treatment and control groups were compared in terms of survival curves by using Cox proportional hazards regression analysis.

We also performed propensity score matching. To develop propensity score-matched pairs without replacement (a 1:1 match), the Greedy 5/1 digit match algorithm was used as described previously [33]. After all of the propensity score matches were performed, we compared the two groups in terms of baseline covariates by using paired *t*-tests or the Wilcoxon signed rank test for continuous variables, and the Chi-squared or Fisher's exact test for categorical variables.

In addition, to analyze the outcomes of the patients with more severe pneumonia, we conducted subgroup analysis. Thus, the patients in the treated and control groups who had a PaO_2/FiO_2 of <120 or APACHE II scores of ≥28 at the time of ICU admission were selected and their hospital mortality was assessed. The cut-off PaO_2/FiO_2 and APACHE II score values were the median values of all included study patients.

All tests of significance were two-tailed. *P* values of <0.05 were considered statistically significant. All analyses were performed by using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA).

3. Results

During the treatment period, 77 consecutive patients received the vitamin C protocol. Of these, 24 were excluded because they were not admitted to the ICU, were not diagnosed with severe pneumonia, or received the vitamin C protocol infusion >48 h after hospitalization (Fig. 1). The remaining 53 patients were included in the treatment group. During the control period, 112 consecutive patients with acute respiratory failure were admitted to the ICU. Of these, 66 were excluded because the ICU admission was >48 h after hospitalization, the diagnosis was not severe pneumonia, only conventional oxygen therapy was needed, or a do not resuscitate order issued (Fig. 1). The remaining 46 patients were included in the control group.

Table 1
Baseline characteristics of the total treatment and control groups.

Variable	Treatment group (n = 53)	Control group (n = 46)
Age, years	73 (62–79)	74 (68–79)
Male sex	41 (77)	29 (63)
Body mass index, kg/m^2	21.4 (18.5–23.8)	20.4 (18.5–23.1)
Comorbidity		
Diabetes	15 (28)	15 (33)
Chronic heart failure	4 (8)	3 (7)
Chronic neurologic disease	17 (32)	15 (33)
Chronic lung disease	21 (40)	15 (33)
Liver cirrhosis	2 (4)	1 (2)
Chronic kidney disease	8 (15)	8 (17)
Malignancy	5 (9)	5 (11)
Immunocompromised	8 (15)	5 (11)
Concurrent bacteremia	4 (8)	3 (7)
ARDS at ICU admission	12 (23)	10 (22)
APACHE II score at ICU admission	28 (21−32)	27 (22−32)
SOFA score at ICU admission	11 (8–14)	11 (7–12)
Use of mechanical ventilation in 1st day	43 (81)	36 (78)
Use of neuromuscular blockers in 1st day	31 (59)	24 (52)
Vasopressor use in 1st day	33 (62)	22 (48)
Use of renal replacement therapy in 1st day[a]	19 (36)	5 (11)
Vital signs & laboratory data on day 1		
Body temperature, °C	37.3 (36.8–38.0)	37.5 (36.8–38.0)
Mean arterial pressure, mmHg	61 (50–71)	61 (47–73)
Respiratory rate, breaths/min	30 (26–32)	30 (26–34)
PaO_2/FiO_2	125 (93–163)	112 (66–160)
$PaCO_2$, mmHg	38 (30–50)	38 (31–47)
Bicarbonate, mEq/L	22.4 (18.2–24.5)	21.0 (18.6–24.7)
Creatinine, mg/dL	1.1 (0.7–1.9)	0.8 (0.6–1.6)
White cell count, 1000/mm^3	12.4 (7.7–18.9)	12.4 (10.5–17.5)
Platelet count, 1000/mm^3	230 (161–311)	239 (177–323)
Total bilirubin, mg/dL	0.7 (0.5–1.2)	0.5 (0.4–0.7)
C-reactive protein, mg/L	189 (100–286)	159 (82–255)
Lactate, mmol/L	2.3 (1.5–4.3)	2.2 (1.2–3.5)
Radiologic score on day 1	7 (5–9)	8 (6–9)

The data are presented as median (interquartile range) or number (percentage) of patients.
ARDS = acute respiratory distress syndrome, ICU = intensive care unit, APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, PaO_2 = arterial partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, $PaCO_2$ = arterial partial pressure of carbon dioxide.
[a] $P = 0.004$ compared by Chi-squared test.

Table 2
Primary and secondary clinical outcomes of the total treatment and control groups.

Variable	Treatment group (n = 53)	Control group (n = 46)	*P*
No. vasopressor-free days at day 28[a]	18.8 ± 11.2	19.6 ± 11.4	0.76
No. ventilator-free days at day 28[a]	10.7 ± 10.8	9.7 ± 10.9	0.66
Length of ICU stay, d	9 (4–14)	12 (6–17)	0.19
Hospital mortality	11 (21)	17 (37)	0.07

The data are presented as median (interquartile range) or number (percentage) of patients unless otherwise indicated. *P* values indicate the results of comparing the treatment and control groups by Mann-Whitney *U*, Student's *t*-, Chi-squared, or Fisher's exact tests.
ICU = intensive care unit.
[a] These data are expressed as mean ± standard deviation.

3.1. Baseline characteristics of the treated and control groups

The baseline characteristics of the two groups are shown in Table 1. The groups were similar in terms of baseline characteristics except that the treated patients tended to be more likely to require vasopressor therapy (62% vs. 48%; $P = 0.15$). They were also significantly more likely to require renal replacement therapy (36% vs. 11%; $P = 0.004$).

3.2. Primary clinical outcome in the treated and control groups

In terms of hospital mortality (the primary outcome), 11 of the 53 patients (21%) in the treatment group and 17 of the 46 patients (37%) in the control group died in hospital ($P = 0.07$) (Table 2). Fourteen of the 32 control patients (44%) in February 2017–May 2017 died in hospital, and the finding was comparable to that from the primary control group (37%; $P = 0.55$). Multivariate unadjusted analysis also showed that the treatment tended to associate with better survival ($P = 0.08$) (Table 3). Subgroup analyses showed that this difference became statistically significant when only the patients with more severe pneumonia (i.e., those with PaO_2/FiO_2 of <120 or APACHE II scores of ≥28) at ICU admission were assessed: in both analyses, the mortality rate in the treatment group was significantly lower than that in the control group (Fig. 2).

3.3. Primary clinical outcome after propensity score adjustment and matching

Based on the covariates listed in Table 1, a multivariate logistic regression model was used to calculate the propensity scores of the patients, which predict the conditional probability that the individual patients will receive the vitamin C protocol given the covariates. Multivariate analysis that adjusted for the variables that associated with hospital mortality plus the propensity score indicated that the vitamin C protocol associated with significantly lower mortality (adjusted OR, 0.15; 95% CI, 0.04–0.56; $P = 0.005$) (Table 3). Fig. 3 shows the survival curves of the patients who did and did not receive the vitamin C protocol ($P = 0.003$).

Propensity score matching yielded 36 pairs of treated and control patients who had similar demographic characteristics, severity indices (APACHE II and SOFA scores), vital signs, and laboratory data at or shortly after ICU admission (Table 4). Indeed, univariate analyses showed that the two groups did not differ in terms of any baseline variables (Table 4). Six of the 36 treated patients (17%) and 14 of the 36 control patients (39%) died in hospital ($P = 0.04$) (Table 5). Multivariate adjusted analysis of the propensity-matched cohort showed that the vitamin C protocol associated with significantly lower mortality (matched OR, 0.31; 95% CI, 0.10–0.95; $P = 0.04$) (Table 3).

3.4. Secondary clinical outcomes in the treated and control groups

The total treatment and control groups did not differ significantly in terms of number of vasopressor-free and ventilator-free days at day 28. While the treatment group did tend to have fewer ICU days than the control group, this difference did not achieve statistical significance ($P = 0.19$) (Table 2). Comparisons of the propensity score-matched treatment and control groups showed that again, the two groups did not differ significantly in terms of vasopressor-free days and ventilator-free days. Again, the treated patients tended to have fewer ICU days, but this difference did not achieve statistical significance ($P = 0.18$) (Table 5).

Fig. 4A shows how the radiologic scores of the propensity-matched treatment and control groups changed during the first 7 days in the ICU. At day 7, the median change in the radiologic score relative to day 1 scores was 4 (range = 1–6) in the treatment group compared with 2 (range = −1–4) in the control group ($P = 0.045$) (Fig. 4B and Supplementary Table 2).

We also examined the effect of treatment on the change in lactate levels and SOFA scores after 4 days in the ICU: the propensity-matched treatment and control groups did not differ in terms of these variables (Supplementary Table 2).

3.5. Associations between hospital mortality and secondary outcomes

Multivariate analysis that adjusted for the presence of superinfection, ICU length of stay, change in the lactate level at day 4 relative to the level on the day of ICU admission, and change in the radiologic score at day 7 relative to the score on the day of ICU admission showed that the improvement in the 7 day radiologic score associated independently with lower hospital mortality (adjusted OR, 0.77; 95% CI, 0.62–0.97; $P = 0.03$) (Supplementary Table 3). ICU length of stay also associated independently with hospital mortality (adjusted OR, 1.08; 95% CI, 1.01–1.15; $P = 0.03$) (Supplementary Table 3).

Table 3
Association between the vitamin C protocol and hospital mortality.

Dependent variable	Crude		Propensity-adjusted cohort		Propensity-matched cohort	
	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
Hospital mortality	0.45 (0.18–1.09)	0.08	0.15 (0.04–0.56)	0.005	0.31 (0.10–0.95)	0.04

Multivariate analyses were adjusted for the presence of an immunocompromised status, APACHE II score at ICU admission, use of mechanical ventilation, neuromuscular blockers, and/or renal replacement therapy within the first 24 h, and lactate levels and radiologic score on day 1. In the propensity adjustment multivariate analysis, the individual propensity scores were incorporated into the model as a covariate.
OR = odds ratio, CI = confidence interval.
[a] Of the 99 patients in the original cohort, 36 pairs were matched.

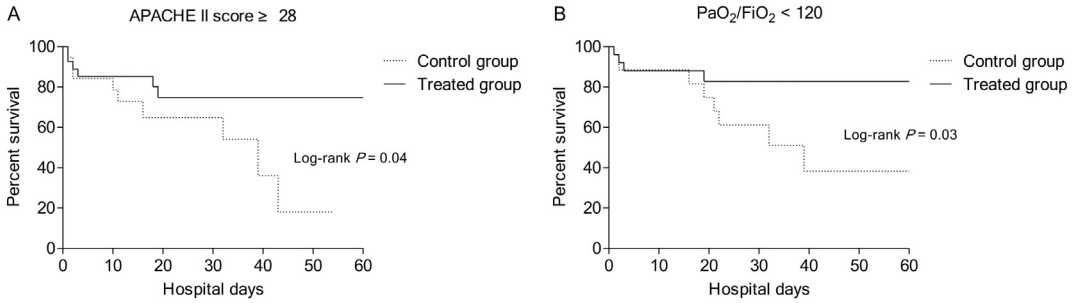

Fig. 2. Kaplan-Meier survival curves of treated and control patients with more severe pneumonia. More severe pneumonia was defined as (A) an APACHE II score ≥ 28 or (B) a PaO_2/FiO_2 of <120. APACHE = Acute Physiology and Chronic Health Evaluation, PaO_2 = arterial partial pressure of oxygen, FiO_2 = fraction of inspired oxygen.

3.6. Adverse events

None of the patients met the criteria for AKI or required renal replacement therapy during the study period. Thirty patients (65%) in the control group were treated with corticosteroids: the median dose of steroid (hydrocortisone-equivalent) was 100 (range = 100–150) mg/day, and the median treatment duration was 11 (range = 7–18) days. When we compared the control patients who did and did not receive corticosteroids at the time of pneumonia diagnosis with the treatment group, we found that the three groups did not differ in terms of superinfection rates (40% vs. 44% vs. 25%, $P = 0.20$), change in SOFA score at day 4, change in radiologic score at day 7, or any of the other secondary outcome variables. In addition, the three groups did not differ in terms of overall hospital mortality ($P = 0.20$) or superinfection-related hospital mortality ($P = 0.26$) (Supplementary Table 4).

Unadjusted multivariate analysis showed that superinfection did not associate significantly with hospital mortality (Supplementary Table 3).

4. Discussion

The main findings of the present study are as follows. First, when the vitamin C protocol was added to the standard treatment for critically ill patients with severe pneumonia, hospital mortality tended to drop. In propensity score analysis, the vitamin C protocol associated with significantly lower mortality. Second, the vitamin C protocol significantly improved the chest radiologic score on day 7, and this improvement associated independently with less hospital mortality. Third, the vitamin C protocol did not associate with increased rates of AKI or superinfection. To the best of our knowledge, this study confirms and expands the findings of previous studies that suggest that adjunct intravenous vitamin C, corticosteroid, and thiamine therapy improve the survival and outcomes of patients with critical illness [8-10, 15-17, 34]. Furthermore, we evaluated the combination of three inexpensive, safe, and readily available agents.

Vitamin C may have a beneficial effect on severe pneumonia via various mechanisms. First, experimental studies on sepsis-induced lung injury show that vitamin C treatment diminishes the proinflammatory and procoagulant changes that induce lung injury [35]. It can also attenuate the sequestration of neutrophils, increase alveolar fluid clearance, and preserve lung barrier function [36]. Moreover, since vitamin C reduces hydrogen peroxide, superoxide anion, and nitric oxide levels [37, 38], it may also counter the oxidative stress caused by the bactericidal effects of antibiotic administration, which can increase inflammation (this is known as the Jarisch-Herxheimer-like reaction) [39]. Thus, vitamin C treatment not only helps to kill the bacteria early after infection, it may also downregulate the inflammation of the host cells at later stages of infection. This notion is supported by our finding that the vitamin C protocol significantly improved the radiologic finding of patients with severe pneumonia. The beneficial role of vitamin C therapy is also supported by several studies on the impact of vitamin C in pneumonia patients [20]. It should be noted, however, that most of these studies did not include patients with severe pneumonia.

Experimental studies show that acute administration of corticosteroids reduces inflammatory cytokine levels and decreases the bacterial burden in severe pneumonia [14, 40]. Corticosteroids may also block a Jarisch-Herxheimer-like reaction [41]. In addition, recent meta-analyses show that corticosteroids significantly reduce the mortality of patients with severe pneumonia [42-44]. There is also some evidence that vitamin C and corticosteroids act synergistically. Vitamin C may restore glucocorticoid receptor function [45], and corticosteroids increase cellular vitamin C uptake by increasing the expression of sodium-vitamin C transporter-2 [46]. Moreover, a study on an experimental model showed that vitamin C and hydrocortisone preserved endothelial integrity better when they were administered together compared to when they were provided on their own [47]. These findings may help to explain why the vitamin C protocol markedly improved the course of severe pneumonia in our study.

Thiamine is the precursor of thiamine pyrophosphate, the essential coenzyme of several decarboxylases required for glucose metabolism, the Krebs cycle, and the pentose-phosphate shuttle [48]. Thiamine deficiency is common in septic patients and is associated with an increased risk of death [15]. Meanwhile, although vitamin C has the potential to

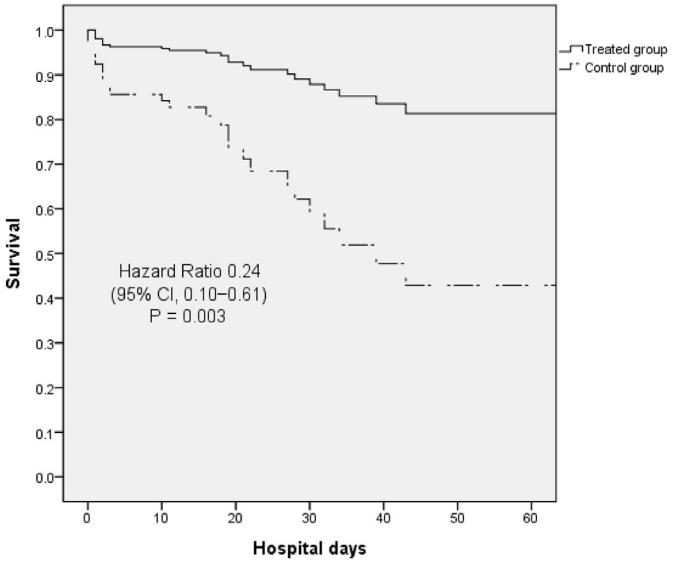

Fig. 3. Cox regression survival curves of the treated and control groups. The data were adjusted for immunocompromised status; the APACHE II and SOFA scores at ICU admission; the use of mechanical ventilation, neuromuscular blockers, vasopressors, and/or renal replacement therapy within the first 24 h; the C-reactive protein and lactate levels on day 1; and the propensity score that indicates the likelihood that each patient will be treated with the vitamin C protocol. APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, ICU = intensive care unit, CI = confidence interval.

Table 4
Baseline characteristics of the propensity score-matched cohort.

Variable	Treatment group (n = 36)	Control group (n = 36)
Age, years	74 (67–81)	74 (63–79)
Male sex	29 (81)	24 (67)
Body mass index, kg/m^2	21.4 (18.9–24.3)	20.4 (18.7–23.1)
Comorbidity		
Diabetes	9 (25)	12 (33)
Chronic heart failure	3 (8)	3 (8)
Chronic neurologic disease	11 (31)	8 (22)
Chronic lung disease	15 (42)	10 (28)
Liver cirrhosis	1 (3)	1 (3)
Chronic kidney disease	5 (14)	7 (19)
Malignancy	4 (11)	4 (11)
Immunocompromised	6 (17)	5 (14)
Concurrent bacteremia	3 (8)	3 (8)
ARDS at ICU admission	7 (19)	7 (19)
APACHE II score at ICU admission	27 (16–31)	29 (23–34)
SOFA score at ICU admission	11 (8–12)	11 (7–13)
Use of mechanical ventilation in 1st day	29 (81)	28 (78)
Use of neuromuscular blockers in 1st day	19 (53)	20 (56)
Vasopressor use in 1st day	20 (56)	21 (58)
Use of renal replacement therapy in 1st day	5 (14)	5 (14)
Vital signs & laboratory data on day 1		
Body temperature, °C	37.5 (36.9–38.0)	37.5 (36.8–38.0)
Mean arterial pressure, mmHg	61 (52–72)	59 (45–72)
Respiratory rate, breaths/min	30 (26–37)	31 (26–36)
PaO_2/FiO_2	133 (101–159)	114 (67–170)
$PaCO_2$, mmHg	39 (31–53)	40 (32–48)
Bicarbonate, mEq/L	22.9 (20.3–24.9)	22.4 (18.3–27.0)
Creatinine, mg/dL	1.0 (0.7–1.5)	0.8 (0.6–1.6)
White cell count, 1000/mm^3	11.7 (7.7–18.5)	12.3 (9.5–17.2)
Platelet count, 1000/mm^3	241 (157–308)	238 (189–322)
Total bilirubin, mg/dL	0.7 (0.5–0.9)	0.5 (0.4–0.7)
C-reactive protein, mg/L	185 (103–288)	168 (97–262)
Lactate, mmol/L	2.1 (1.5–3.5)	2.3 (1.2–3.5)
Radiologic score on day 1	8 (5–9)	8 (6–9)

The data are presented as median (interquartile range) or number (percentage) of patients. There were no significant differences in baseline characteristics between the groups.
ARDS = acute respiratory distress syndrome, ICU = intensive care unit, APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, PaO_2 = arterial partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, $PaCO_2$ = arterial partial pressure of carbon dioxide.

protect against contrast-induced AKI in patients with pre-existing renal impairment [11], it is also possible that the administration of high doses of vitamin C causes calcium oxalate nephropathy, thus worsening renal function [49, 50]. Thiamine may prevent this reaction by decreasing the conversion of glyoxylate to oxalate [16]. This possibility is supported by the fact that none of our patients who received the vitamin C protocol developed renal dysfunction.

The main strength of our study was the inclusion of patients with severe pneumonia who had a marked systemic inflammatory response, as shown by the high baseline CRP levels in both study groups (159–189 mg/L). CRP is an acute-phase protein that is synthesized by the liver during acute inflammation. High levels are linked to higher incidences of organ failure and mortality [51]. In a recent multicenter randomized study, a CRP level of >150 mg/L at admission was chosen to increase the chance of recruiting pneumonia patients with a high inflammatory response [34]. Another strength of our study was that we observed in the propensity-matched cohort that the vitamin C protocol not only reduced hospital mortality, it also improved the radiologic scores of the patients. In addition, this improvement in the radiologic scores was an independent predictor of decreased hospital mortality. These findings are consistent with those of previous studies [52] and support the notion that radiologic change may be an independent surrogate marker of prognosis in patients with severe pneumonia.

When corticosteroids are used for prolonged periods and/or at high dosages, they can hamper various immune host defenses against bacteria [14]. In our study, however, the treated patients did not differ from the control patients in terms of superinfection rates. This is supported by several studies that showed that treating severe pneumonia patients with corticosteroids did not increase the rates of superinfection [34, 53]. These findings may reflect the fact that most clinical studies evaluating corticosteroids in pneumonia, including our own, used short courses of relatively low-dose corticosteroids that are not expected to pose a significant risk of superinfection.

The present study has several limitations. First, its single center nonrandomized design and the use of nonconcurrent control patients increase the risk of selection bias. To control for various baseline differences, we performed propensity score adjustment. However, it remains possible that the control and treatment groups differed in terms of other, as yet unknown, factors. Moreover, propensity score matching may induce a risk of overcorrection by its tendency to adjust many baseline variables in a few rather lopsided matched sets. Second, the sample size was relatively small. The resulting low power of the study may have limited our ability to detect significant effects of the vitamin C protocol on the primary and secondary outcome variables. In this study, the mortality difference became statistically significant only in the propensity-matched cohort or in the subgroup of patients with more severe pneumonia. However, these analyses further reduced the sample size and the power of the study. Third, the nature of our institutional treatment protocol means that we selected the patients who were most likely to benefit from the vitamin C protocol. Thus, the results of this study cannot be extrapolated to patients with low levels of systemic inflammation. Fourth, of the 46 control patients, 30 received corticosteroids. It is possible that this adjunct therapy may have helped the control patients with shock reversal; this may explain, at least in part, why the treatment and control groups exhibited similar declines in vasopressor requirements. It is also possible that the steroid treatment affected other outcomes in the control patients. However, when we divided the control group into those who did and did not receive steroid, we found that the two subgroups did not differ in terms of hospital mortality and superinfection rates. Thus, this limitation does not undermine the original conclusion of the study, namely, that the vitamin C protocol may improve the mortality rates of patients with severe pneumonia. Fifth, the vitamin C levels were not measured in any of the patients. Thus, it remains possible that there were differences between the treated and control groups in terms of vitamin C levels. Such a difference is a possible source of selection bias.

Table 5
Primary and secondary clinical outcomes of the propensity score-matched cohort.

Variable	Treatment group (n = 36)	Control group (n = 36)	*P*
No. vasopressor-free days at day 28[a]	19.8 ± 10.8	20.5 ± 11.1	0.45
No. ventilator-free days at day 28[a]	12.3 ± 11.0	9.9 ± 10.7	0.57
Length of ICU stay, d	9 (5–14)	12 (7–17)	0.18
Hospital mortality	6 (17)	14 (39)	0.04

The data are presented as median (interquartile range) or number (percentage) of patients unless otherwise indicated. *P* values indicate the results of comparing the treatment and control groups by paired *t*-test, the Wilcoxon signed rank test, the Chi-squared test, or Fisher's exact test.
ICU = intensive care unit.
[a] These data are expressed as mean ± standard deviation.

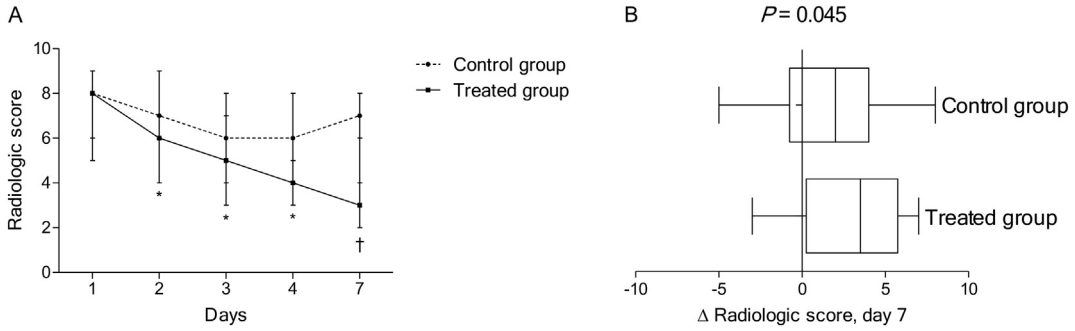

Fig. 4. Comparison of the propensity-matched treated and control groups in terms of change in radiologic scores. (A) Change in radiologic scores over the first 7 days. (B) Median (interquartile range) change in radiologic scores on day 7 relative to the scores on day 1. $^{*}P < 0.05$, $^{\dagger}P < 0.01$ when the treatment and control groups were compared by Mann-Whitney *U* test.

5. Conclusions

In conclusion, our results indicate that the combined use of vitamin C, hydrocortisone, and thiamine improves the chest radiologic findings of patients with severe pneumonia and tends to reduce their mortality. Moreover, the vitamin C protocol did not increase the rate of AKI or superinfection. However, owing to study limitations, large prospective and randomized controlled studies regarding optimal dose, timing, and possible adverse effects are required to justify the routine use of vitamin C protocol for treating severe pneumonia.

Conflicts of interest

None.

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Appendix A. Supplementary data

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