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Vitamin C and thiamine for the treatment of refractory septic shock in surgical critically ill patients: a retrospective before-and-after study

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ABSTRACT

Introduction. This study aimed to evaluate whether early vitamin C and thiamine administration was associated with a lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock.

Patients and methods. We performed a retrospective before-and-after study on patients with refractory septic shock. According to local protocol, hydrocortisone is initiated in case of refractory septic shock. In January 2017, the protocol was changed and vitamin C and thiamine were included. Patients who were admitted in 2015-2016 and 2017-2018 were included in the control and treatment groups, respectively. The primary end point was 28-day and in-hospital mortality. Secondary end points were ICU mortality, ICU and hospital length of stay, duration of vasopressors and mechanical ventilation, use of renal replacement therapy (RRT), and the modification in serum procalcitonin and SOFA score during the first 72 h.

Results. A total of 120 patients were included (58 in the treatment group and 62 in the control group). Log-rank test in Kaplan-Meier curves showed lower 28-day and in-hospital mortality over time in the treatment group (p=0.021 and p=0.035, respectively) but it not reached statistical significance in ICU mortality over time (p=0.100). The need of RRT was less frequent in treatment group (17.2% vs. 37.1%, p=0.024). There were no differences in other secondary outcomes.

Conclusions. Intravenous vitamin C and thiamine administration in surgical patients with refractory septic shock may be associated with a lower 28-day and in-hospital mortality. Further prospective studies are needed in refractory septic shock.

Keywords: septic shock; vitamin C; thiamine; mortality; vasopressor

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Vitamina C y tiamina para el tratamiento del shock séptico refractario en pacientes críticos quirúrgicos: un estudio retrospectivo antes-después

RESUMEN

Introducción. El objetivo de este estudio fue evaluar si la administración precoz de vitamina C y tiamina estaba asociada a una reducción en la mortalidad a los 28 días y hospitalaria en pacientes críticos quirúrgicos con shock séptico refractario.

Pacientes y métodos. Realizamos un estudio retrospectivo antes-después en pacientes con shock séptico refractario. Según el protocolo local, se inicia tratamiento con hidrocortisona en situación de shock séptico refractario. En enero de 2017 se cambió el protocolo y se incluyó vitamina C y tiamina. Los pacientes que fueron ingresados en 2015-2016 y 2017-2018 se incluyeron en el grupo control y tratamiento, respectivamente. Los objetivos primarios fueron la mortalidad a los 28 días y hospitalaria. Los objetivos secundarios fueron la mortalidad en UCI, la duración de estancia en UCI y hospitalaria, la duración del tratamiento vasopresor y de la ventilación mecánica, el uso de técnicas de reemplazo renal (TRR), y la modificación en la procalcitonina sérica y la puntuación SOFA durante las primeras 72h.

Resultados. Se incluyeron un total de 120 pacientes (58 en el grupo tratamiento y 62 en el grupo control). El test Log-rank en las curvas de Kaplan-Meier mostró mortalidad a los 28 días y hospitalaria más baja a lo largo del tiempo en el grupo tratamiento (p=0,021 and p=0,035, respectivamente) pero no alcanzó significación estadística en la mortalidad en UCI a lo largo del tiempo (p=0,100). La necesidad de TRR fue menos frecuente en el grupo tratamiento (17,2% vs. 37,1%, p=0,024). No hubo diferencias en otros resultados secundarios.

Conclusiones. La administración de vitamina C y tiamina intravenosa en pacientes quirúrgicos con shock séptico refractario podría estar asociada a una menor mortalidad a los 28 días y hospitalaria. Se necesitan más estudios prospectivos en pacientes con shock séptico refractario.

Palabras clave: shock séptico; vitamina C; tiamina; mortalidad; vasopresor

INTRODUCTION

Sepsis is defined as a potentially fatal organ dysfunction produced by a dysregulated host response to infection [1]. The incidence of sepsis has raised, presumably due to the growing aging of the population, provided that several studies have evidenced a relationship between age and incidence of sepsis and a higher number of people with disease comorbidities [2]. Several studies have showed a lower mortality associated to sepsis over the years [3-5]. However, the total number of patients that die as a result of sepsis is growing, resulting in more than 5 million deaths world widely every year. These numbers make sepsis a major public health concern [6]. New therapeutic interventions for sepsis have been investigated over the last decades with uncertain benefits [7]. Therefore, there is an imperative need for new interventions to restrict sepsis-induced tissue damage and organ dysfunction.

Vitamin C regulates inflammation through antioxidant activity and is a primary co-factor for the synthesis of endogenous adrenaline, cortisol, and vasopressin [8]. During sepsis, vitamin C may prevent neutrophil-induced lipid oxidation and protect against endothelial barrier loss [9]. In a recent study, vitamin C administration ameliorated peripheral tissue perfusion and microvascular reactivity [10]. Thiamine is a crucial co-factor in glucose metabolism, adenosine triphosphate generation, and nicotinamide adenine dinucleotide phosphate production, as well as glutathione cycling, an important antioxidant pathway [11]. Moreover, thiamine may reduce the risk of renal oxalate crystallization [12]. Even though a recent retrospective study revealed that the combination of vitamin C, hydrocortisone, and thiamine improved survival in patients with sepsis [13], several randomized trials of vitamin C alone or in combination with hydrocortisone and thiamine have been performed without showing association with a significantly improved outcome [14-17]. The use of corticosteroids has been shown to reverse septic shock [18,19], but only in one trial it was possible to control hydrocortisone administration [15]. Vitamin C administration is not well studied in refractory septic shock.

This retrospective before-and-after study aimed to evaluate whether early vitamin C and thiamine administration was associated with lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock.

PATIENTS AND METHODS

Study design and participants. We performed a retrospective before-and-after study on patients with refractory septic shock admitted to the Surgical Critical Care Unit (SCCU) of the University Hospital La Paz (Madrid, Spain) between January 2015 and December 2018. The study was approved by the institutional review board (HULP PI 3738) and by the Spanish Medical Agency. The research was consistent with the principles of the declaration of Helsinki. The study was performed in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement [20]. Septic shock was defined according to sepsis-3 definition as sepsis, requirement of vasopressor therapy to maintain main arterial pressure (MAP) ≥65 mm Hg and serum lactate level >2 mmol/L, despite adequate fluid resuscitation [1]. Septic shock was considered refractory if norepinephrine dose >0.5 μg/Kg/min was required (expressed as norepinephrine tartrate), or equivalent dose of another drug, as previously defined [21]. Patients were included in the study if they had a refractory septic shock with adequate source control during the inclusion period. They were excluded if they were younger than 18 years; they were pregnant or breastfeeding; they had a "do not resuscitate" order in case of cardiac arrest; Simplified Acute Physiology Score (SAPS II) was > 65 at admission, or they had chemotherapy or bone marrow transplant-induced neutropenia. According to SCCU protocols, all patients received standard treatment according to Surviving Sepsis Campaign Guidelines, including broad spectrum-antibiotics initiation that was then de-escalated according to microbiologic data and clinical evolution and vasopressors to maintain a main arterial pressure ≥65 mmHg. Initial resuscitation was performed with 30 ml/kg of IV crystalloid fluid, and we guided additional resuscitation by reassessment of hemodynamic status. According to local protocol, balanced crystalloids were employed. Renal replacement therapies (RRT) were initiated in patients with acute kidney injury (AKI) and an absolute indication (refractory hyperkalemia, refractory acidemia and metabolic acidosis, refractory pulmonary edema due to fluid overload, and complications attributable to uremia). Continuous RRT were employed. Norepinephrine was the vasopressor of the first choice. Vasopressin was not available at our institution [22]. According to local protocol, hydrocortisone 200mg every 24h in continuous infusion is initiated in case of refractory septic shock. In January 2017, the protocol changed and vitamin C 1.5 g every 6h for 4 days or until ICU discharge and thiamine 200 mg every 12 h for 4 days or until ICU discharge were included in case of refractory septic shock. Patients who were admitted to our SCCU between January 2015 and December 2016 and met inclusion criteria were included in the control group, and patients admitted between January 2017 and December 2018 and met inclusion criteria were included in the treatment group. Clinical and demographic data, including age, sex, comorbidities, site of infection, use and duration of vasopressors, duration of mechanical ventilation, occurrence of acute kidney injury (AKI) according to KDIGO guidelines, use of renal replacement therapies (RRT); and laboratory data, including procalcitonin (PCT), serum lactate and serum creatinine at treatment initiation and PCT after 72h were recorded. The Simplified Acute Physiology Score II (SAPS II) at Intensive Care Unit (ICU) admission and the Sequential Organ Failure Assessment (SOFA) at treatment initiation and after 72h were calculated to assess the severity of the illness. Length of ICU and hospital stay (LOS) and ICU, 28-day and in-hospital mortality were recorded too.

Objectives. The primary objective of our study was to assess the association between the use of vitamin C and thiamine with 28-day and in-hospital mortality in refractory septic shock. The secondary objective was to assess the association of

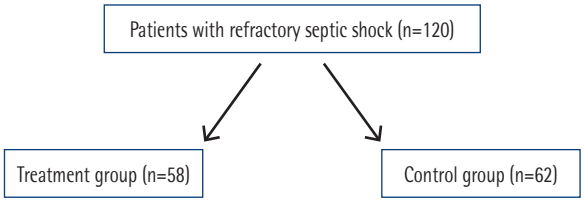

Figure 1 | **Flow chart of included patients.**

the use of vitamin C and thiamine with ICU mortality, ICU and hospital LOS, duration of vasopressors and mechanical ventilation, use of RRT, and the modification in serum PCT and SOFA score during the first 72 h (DPCT 72h and DSOFA 72h respectively).

Statistical analyses. The categorical variables were described by frequency (%), and quantitative variables by mean (SD) or medians and interquartile range, as appropriate. Univariate analysis by Fisher exact or $\chi 2$ test for categorical variables and the Student's T-Test or Mann-Whitney U test for quantitative variables was performed to compare data between the treatment and control groups. Kaplan–Meier survival curves were constructed to compare mortality within 28 days, in hospital and ICU. Cox regression multivariable models (step-wise procedure) were performed using 28-day and in-hospital mortality as dependent variables, and those with clinical-epidemiological relevance and/or showing differences in the univariate analysis as independent variables. The limit of 5 to 10 events (or nonevents, whichever is less) per introduced variable was not exceeded. Data were analyzed with SAS 9.3 statistical software (SAS Institute Inc, Cary, NC). We admitted as statistically significant those comparisons whose p-value was below 0.05.

RESULTS

A total of 120 patients with an average age of 67.6 ±14.2 years were included in the study. A total of 58 patients (48.3%) were included in the treatment group and 62 (51.7%) in the control group (Figure 1). In table 1 we present baseline characteristics of patients according to treatment group. Arterial hypertension (AHTN) was the most frequent comorbidity (n=79, 65.8%). Patients in the treatment group had a history of cardiac failure less frequently (6.9% vs. 22.6%, p=0.021). There were no differences between groups for other variables. Mean SAPS II at ICU admission was 50.7 ±17.6, without differences between groups. In most patients, the source of infection was abdominal, presenting with complicated intra-abdominal infection (CIAI) (80.0%). Patients with CIAI, complicated urinary tract infections (CUTI), skin and soft tissue infections, vascular graft infections, and mediastinitis underwent emergency surgery for source control. Regarding the surgical site in CIAI, the colon was the most frequent (31 patients), followed by biliary tract (22 patients), small bowel (21 patients), gastroduodenal tract (13 patients) and others (6 patients), without differences between groups (p=0.813).

The 28-day and in-hospital mortality rate was 31.7% and 39.2%, respectively. The 28-day mortality was lower in treatment group (22.4 %vs. 40.3%, p=0.049) but there were no differences in hospital mortality (31.0% vs. 46.8%, p=0.094). Regarding secondary end points, ICU mortality was lower in the treatment group (17.2% vs. 37.1%, p=0.024) and the need for RRT was less frequent (17.2% vs. 37.1%, p=0.024). There were no differences between groups in other secondary outcomes (Table 2).

Log-rank test in Kaplan-Meier curves showed lower 28-day and in-hospital mortality over time in the treatment group (p=0.021 and p=0.035, respectively). Log-rank test did not reach statistical significance in ICU mortality over time (p=0.100). The Kaplan-Meier curves for 28-day survival are presented in Figure 2.

In multivariable cox regression analysis, only age and DSOFA 72h were independent predictors of 28-day mortality (OR=1.043, 95% CI 1.012-1.076, p=0.006; and OR=0.861, 95% CI 0.775-0-957, p=0.006, respectively), after adjusting for group, coronary arterial disease (CAD) and body mass index (showing differences in the univariate analysis). Age and DSOFA 72h were also independent predictors of hospital mortality, after adjusting for the same variables (OR=1.044, 95% CI 1.015-1.073, p=0.002; and OR=0.875, 95% CI 0.799-0-959, p=0.004, respectively).

DISCUSSION

The main finding of this analysis suggests that the administration of vitamin C and thiamine may be associated with lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock. Although patients in the treatment group had a history of cardiac failure less frequently, this variable was not associated to mortality, so this finding probably does not affect results.

Marik et al found in another retrospective study a reduction in hospital mortality with hydrocortisone, vitamin C, and thiamine administration in patients with severe sepsis and septic shock, with similar mortality and severity in control group (40.4% and SOFA at admission 8.7±3.7) [13]. Although several randomized trials have not shown significantly improved outcomes with the use of vitamin C [14-17], the only trial that compared vitamin C, thiamine, and hydrocortisone vs. hydrocortisone was the VITAMINS randomized clinical trial [15]. In the CITRIS-ALI randomized clinical trial [14], performed on patients with sepsis and severe acute respiratory failure, authors did not find differences between groups in primary outcomes (modified SOFA score and plasma biomarkers levels), but 28-day mortality as a secondary outcome was lower in the intervention group (29.8% vs. 46.3%, p=0.03). In trials that did not find differences in 28-day or 30-day mortality, it ranged from 20.4% to 29.30% in the control group. These different results

Table 1 Baseline characteristics.

Variable	Total (n=120)	Treatment group (n=58)	Control group (n=62)	p
Age (years), mean ± SD	67.6 ± 14.2	66.1 ± 13.9	69.0 ± 14.3	0.336
Male, n (%)	69 (57.5)	31 (53.4)	38 (61.3)	0.461
Comorbidities, n (%)				
AHTN	79 (65.8)	39 (67.2)	40 (64.5)	0.848
DM	35 (29.2)	18 (31.0)	17 (27.4)	0.692
Cardiac failure	18 (15.0)	4 (6.9)	14 (22.6)	0.021
CAD	19 (15.8)	6 (10.3)	13 (21.0)	0.137
Stroke	6 (5.0)	2 (3.4)	4 (6.5)	0.681
Chronic renal failure	18 (15.0)	6 (10.3)	12 (19.4)	0.206
SAPS II, mean ± SD	50.7 ± 17.6	51.3 ± 14.9	50.10 ± 20.0	0.372
SOFA, mean ± SD	8.1 ± 3.3	7.8 ± 3.5	8.3 ± 3.0	0.410
Site of infection, n (%)				
CIAI	96 (80.0)	44 (75.9)	52 (83.9)	No p value
CUTI	12 (10.0)	6 (10.3)	6 (9.7)	
Skin and soft tissue	6 (5)	5 (8.6)	1 (1.6)	
Vascular graft	1 (0.8)	1 (1.7)	0 (0.0)	
Mediastinitis	1 (0.8)	0 (0.0)	1 (1.6)	
Catheter-related	1 (0.8)	0 (0.0)	1 (1.6)	
CAP	1 (0.8)	1 (1.7)	0 (0.0)	
Unknown	2 (1.6)	1 (1.7)	1 (1.6)	
PCT (ng/mL), mean ± SD	29.53 ± 58.76	26.69 ± 51.32	32.22 ± 65.37	0.945
Lactate (mmol/l), mean ± SD	3.66 ± 2.52	3.64 ± 2.56	3.68 ± 2.50	0.765
Creatinine (mg/dl), mean ± SD	1.77 ± 1.04	1.76 ± 1.03	1.79 ± 1.06	0.811

AHTN: arterial hypertension; DM: diabetes mellitus; CAD: coronary arterial disease; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; CIAI: complicated intra-abdominal infection; CUTI: complicated urinary trasct infection; CAP: Community-Acquired Pneumonia; PCT: procalcitonin.

might be due to the inclusion of more severe patients in the CITRIS-ALI trial and in our study, as we included only patients with refractory septic shock. Furthermore, Shin et al performed a before-and-after multicenter analysis that included 1,144 patients with septic shock that found that treatment with early vitamin C and thiamine was associated with lower in-hospital mortality rates in the subgroup of patients with SOFA scores>10 [23]. All these results are consistent with a nationwide cohort study performed by Jung et al, that reported that vitamin C administration was associated with a lower hospital and 90-day mortality in patients with older age, a larger amount of comorbidities, septic shock, and under mechanical ventilation [24]. However, in a recent randomized, placebo-controlled trial performed in patients with sepsis receiving vasopressor therapy, authors found a higher risk of death or organ dysfunction at 28 days in patients who received vitamin C [25].

No differences were found in the duration of vasopressors between groups, similarly to recent randomized controlled trials [15,17,26]. Rosengrave et al, in a pilot randomized controlled trial, observed no differences in vasopressors duration and dose [26]. In contrast, Mahomoodpoor et al demonstrated a reduction in the duration of mechanical ventilation and vasopressors in critically ill patients with severe pneumonia with the use of vitamin C [27]. They also found a reduction in PCT levels. Only a small proportion of their patients received corticosteroids. However, in our study all patients in both groups received corticosteroids. The possible effect of corticosteroid use on this result is unclear. A metaanalysis performed by Hemilä et al also reported a reduction in the duration of mechanical ventilation with the use of vitamin C [28].

We found a lower frequent need for RRT in the treatment

Table 2 Outcome by study group.

Variable	Total (n=120)	Treatment group (n=58)	Control group (n=62)	p
28-day mortality, n (%)	38 (31.7)	13 (22.4)	25 (40.3)	0.049
Hospital mortality, n (%)	47 (39.2)	18 (31.0)	29 (46.8)	0.094
ICU mortality, n (%)	33 (27.5)	10 (17.2)	23 (37.1)	0.024
ICU LOS (d), mean ± SD	10.7 ± 12.3	10.2 ± 9.2	11.3 ± 14.7	0.617
Hospital LOS(d), mean ± SD	31.1 ± 36.7	37.0 ± 44.4	25.7 ± 27.1	0.060
Duration of MV (h), mean ± SD	115.0 ± 268.9	76.8 ± 151.3	149.4 ± 339.8	0.111
Duration of vasopressors (h), mean ± SD	89.4 ± 113.0	86.1 ± 114.1	92.4 ± 112.9	0.940
RRT, n (%)	53 (44.2)	20 (34.5)	33 (53.2)	0.045
DSOFA 72h	2.7 ± 3.3	2.8 ± 3.1	2.5 ± 3.5	0.656
DPCT 72h (ng/mL), mean ± SD	17.7 ± 39.0	16.6 ± 38.4	18.8 ± 39.9	0.592

ICU: Intensive Care Unit; LOS: length of stay; MV: mechanical ventilation; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment; PCT: procalcitonin.

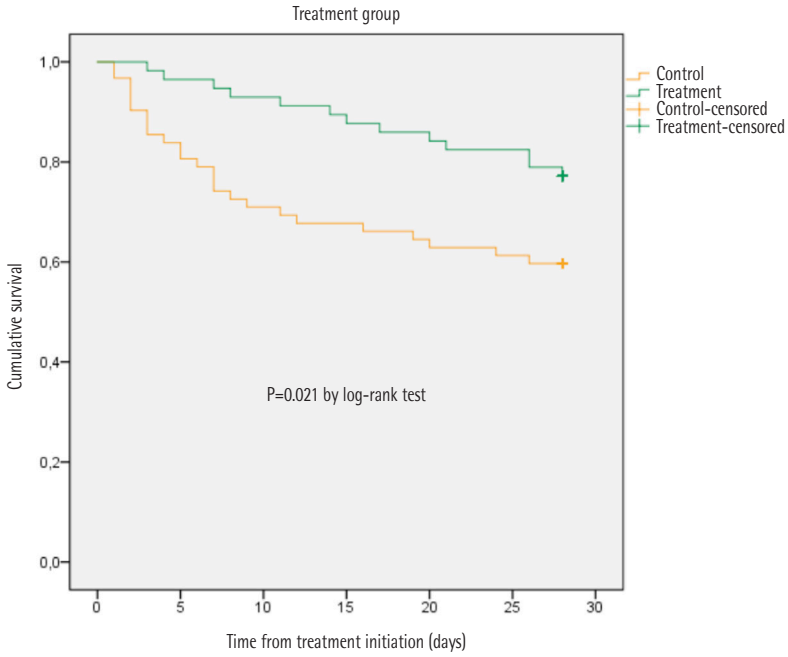

Figure 2 Kaplan-Meier curves for 28-day survival in treatment and control groups.

group as Marik et al [13]. Randomized trials that have studied kidney replacement-therapy-free days have not found any differences between groups, although the incidence of severe AKI with the need for RRT was very low [15,17]. The high frequency of RRT need in our patients (44.2%) due to severe AKI may justify this result. In 2016, during the study period, the AKIKI trial was published. Authors found no significant difference in mortality between an early and a delayed approach for the initiation of RRT [29]. As we have previously declared, according to our local protocol, in our study continuous RRT were initiated in the presence of AKI and an absolute indication, therefore our usual clinical practice did not change between 2015 and 2018.

The effect of vitamin C on underlying sepsis-induced biological anomalies may account for this difference in 28-day mortality despite the fact that we did not find any difference in terms of duration of vasopressors, duration of mechanical ventilation, and organ failure assessed by SOFA score. Furthermore, thiamine is a crucial co-factor in several metabolic pathways, and low levels may be correlated with worse outcomes [30]. Early death in the control group would require further evaluation. Furthermore, lower mortality in treatment group could explain the trend to longer LOS in this group

The absence of steady benefits in preceding trials of vitamin C in sepsis may also be attributable to inadequate dosage. For instance, some patients in the ACTS trial, with negative results, received only 1 dose of the study drug [16], and patients included in the treatment group of the CITRIS-ALI trial, that found lower 28-day mortality in the treatment group, received a higher dose of vitamin C (50 mg/kg every 6 hours) [14].

A recently published systematic review concluded that evidence from randomized controlled trials does not establish a survival benefit for vitamin C in severe infections [31]. Possibly certain phenotypes of patients, not included in randomized trials, as patients with refractory septic shock, may benefit from this treatment. Further studies are needed to elucidate the role of precision medicine in this context.

Strengths and limitations. To our knowledge, this is the first study that analyzes the association between the treatment with vitamin C and thiamine and outcomes in patients with severe refractory septic shock. Another strength is the homogeneity of included patients, given that in 80% of patients the source of infection was abdominal.

On the other hand, this study has several limitations. First, the retrospective nature of the analysis and the before-and-after design may predispose to unmeasured confounders. Besides, the non-randomized design makes it impossible to determine the causality of the association between treatment and outcomes; additionally, there are differences between groups in one comorbidity. Third, the study was performed in one tertiary academic institution with limited sample size, so the ability to generalize these results in other settings is limited. Fourth, we have no data about vasopressors total dose. Fifth, the study may be underpowered due to the limited sample size.

Conclusions. Intravenous vitamin C and thiamine administration in surgical patients with refractory septic shock may be associated with a lower 28-day and in-hospital mortality. Further prospective studies are needed to clarify the impact of vitamin C and thiamine administration in refractory septic shock.

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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