



Vitamin C, Complex B and Hydrocortisone in Septic Patients Treated at ICU of The General Hospital 11 IMSS Piedras Negras Coahuila

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ABSTRACT

Introduction: Sepsis is defined as severe organ dysfunction as with a dysregulated response of the host with a documented or suspected infection. In Mexico sepsis represents 11,183 hospitalizations and is 27.3% of ICU admission. The Surviving Sepsis Campaign is aimed at early identification and timely treatment of these patients.

Objective: Describe the difference between ICU and hospital mortality among septic patients treated with standard treatment vs standard treatment + Vitamin C + Hydrocortisone + Thiamine + Cyanocobalamin + Pyridoxine (Complex B).

Material and Methods: A prospective, longitudinal, experimental cohort study was conducted in August 2019 to October 2020 ICU of the General Hospital of Zone 11 IMSS in Piedras Negras, Coahuila, conducted in 2 phases: Phase 1: control group: standard treatment accordingly GPC, duration of 6 months. Phase 2: experimental: standard treatment + treatment protocol that consist to Vitamin C 1.5 g IV every 6 hours, Hydrocortisone 50 mg IV every 6 hours and in case of v í enteral Complex B (Thiamine 100 mg Pyridoxine 5 mg Cyanocobalamin 50 mcg) 1 tablet every 6 hours for 4 consecutive days or until discharge of the patient; duration of 6 months.

Results: 19 patients were enrolled for this study (12 phase 1 and 7 phase 2). The general characteristics were: Age 52.4 years, Female 31.6%, BMI 33.4, main sources of infection: Pulmonary 47.4%, Abdominal 36.8%, ICU LOS 7.0 Hospital LOS 16.3; ICU and Hospital survival 73.7%, 52.6% respectively, The only statistical difference between the two groups was steroid use and CRP. The factors associated with ICU survival were: LOS, second vasopressor use, NE dose, EPI dose, CRP, and with Hospital survival were: LOS, Hydrocortisone use, SAPS3 score, SAPS3 predicted mortality, qSOFA, SOFA, Respiratory SOFA, Renal SOFA, Hematologic SOFA, second vasopressor use, EPI dose. Vitamin C, Complex B and Hydrocortisone had no statistical significance with survival. There was no difference in organic failure and vasopressor use in both groups.

Conclusion: In septic patients administration of Vitamin C, Complex B and Hydrocortisone + standard treatment vs standard treatment alone was no associated with a statistical difference in Hospital survival, organic failure or vasopressor use.

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Sepsis, Infection, Vitamin C, Complex B.

Introduction

Sepsis is defined as a severe organ dysfunction with a dysregulated response of the host to an infection, documented or suspected [1]. The definition of sepsis changed considerably in 2016 with the publication of the Third Consensus Definitions Sepsis and Shock (Sepsis-3); prediction tools were used to assessed organ dysfunction and mortality unlike previous that were based on the systemic inflammatory response criteria [1].

Definitions derived Sepsis-3 are: 1. Sepsis organic dysfunction, life - threatening caused by a dysregulated response of the host due an infection [1]. 2. Organic Dysfunction: acute change in the Sequential Organ Failure Assessment (SOFA) > 2 points

secondary to an infection [1]. Assuming the basal SOFA is 0 in patients without preexisting organ failure; SOFA > 2 points associated with increased mortality 10% in general hospital population with suspected infection [2]. 3. Septic Shock: Sepsis with circulator, cellular and metabolic severe disorders that increase mortality substantially. Persistent hypotension is defined as vasopressor required to maintain pressure or mean arterial n > 65 mmHg and a lactate > 2 mmol / L (18 mg / dL), despite adequate resuscitation.

Score of quick SOFA (qSOFA): Tool for use at the bedside of the patient to identify patients with suspected infection or increased risk of hospital mortality. It evaluates the respiratory

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rate > 22, altered mental state, systolic blood pressure < 100 mmHg [3]

In Mexico sepsis represents 11,183 hospitalizations per year, which is 27.3% of diagnosis at admission to ICU [4]. Carrillo, R in it's epidemiological study reported that approximately every 2.6 hours a patient dies from sepsis [4].

The goal of treatment is early antibiotic, hemodynamic support and treating or preventing organ failure [24] but there is also urgent need of supplying nutrients and vitamins that may be deficient or improve metabolic processes. Marik et al showed a reduction in organ dysfunction including acute renal failure and reduction in mortality in patients with severe sepsis and shock treated with vitamin C, thiamine and hydrocortisone, without reporting adverse events or side effects to treatment to limit their use [17].

These results encouraged VICTAS trial [18], placebo-controlled study designed to demonstrate the efficacy of Vitamin C, Thiamin, and hydrocortisone in the treatment of these patients is currently under enrollment with sample calculation 2000 patients [18].

The main outcome of this study was to describe the difference between ICU and hospital survival between septic patients treated with Vitamin C, Complex B and hydrocortisone + standard treatment VS standard treatment alone. Secondary outcomes were: describe the difference in progression in organ failure, and difference in vasopressor use between the two groups.

Methods

The study was prospective from September 2019 to September 2020 at the Intensive Care Unit of General Hospital Zone 11 IMSS in Piedras Negras, Coahuila. Enrollment was made in two phases: Phase 1: control group, standard treatment, duration of 6 months. Phase 2: standard treatment + Vitamin C 1.5 g IV every 6 hours, Hydrocortisone 50 mg IV every 6 hours and Complex B (Thiamine 100 mg Pyridoxine 5 mg Cyanocobalamin 50 mcg) 1 tablet every 6 hours for 4 days or until ICU discharge

Inclusion criteria were: Suspected or confirmed infection. Cardiovascular and/or respiratory dysfunction associated with sepsis following criteria: Need for vasopressor: infusion: norepinephrine, epinephrine, dobutamine, dopamine, vasopressin, phenylephrine or any other vasoactive agent at any dose for longer than one hour with aim to maintain a median arterial pressure of 65 mmHg despite intravenous supply of crystalloid of at least 1000 ml. Need for respiratory support: persistent hypoxemia ($(\text{PaO}_2) / (\text{FiO}_2) < 300$ or $(\text{SpO}_2) / (\text{FiO}_2) < 315$) treated with: invasive or no invasive mechanical ventilation, or oxygen supplementation with any device. Confirmed or anticipated admission to ICU.

Exclusion criteria were: Organ dysfunction present for > 24 hours at the time of enrollment. DNR directives, Hospitalization > 30 day, Chronic hypoxemia with oxygen supplementation, Chronic heart failure with ventricular assist devices or infusion of inotropic periodically (levosimendan). Allergy or medical contraindication to treatment. Previous treatment with vitamin C, pyridoxine, and cyanocobalamin that exceeds the doses used in this study.

The demographic characteristics, diagnostics, origin of sepsis, vasopressor use and evolution, complications, and hospital mortality in the ICU was recorded.

Statistical analysis was made with StatCalc software version 1500.1.3 © AcaStat software 2018. and Wizard Pro version 1.9.44. The quantitative variables were described as media and SD (standard deviation), qualitative in frequency and percentage, X² test was performed for a significance $p < 0.05$ and logistic regression analysis was performed to evaluate the association with outcome.

The present research was performed in accordance with good clinical practices, in accordance with General Health Law (Mexico) on Health Research, Declaration of Helsinki and International Council of Harmonization.

The study was approved by the Local Committee for Health Research 506 of the Mexican Institute of Social Security (R-2019-506-009), in addition to having a registry in clinicaltrials.gov with the number NCT04197115.

Informed consent letter was requested from the patients included in the study, the personal identification data of the patients was protected, being in accordance with the law on the protection of personal information.

The study did not have any institutional financing or by companies external to it.

Results

During the Sept 2019 to Sept 2020 56 patients were treated at ICU, 19 of this population met inclusion criteria for this study (12 phase 1 and 7 phase 2). The general characteristics were: Age 52.4 years SD \pm 9.15, Female 31.6%, BMI 33.4 DS \pm 6.01, main sources of infection: Pulmonary 47.4%, Abdominal 36.8% ($p = 0.024$), ICU LOS 7.0 SD \pm 3.6, Hospital LOS 16.3 SD \pm 6.2; ICU and Hospital survival 73.7%, 52.6% respectively ($p = 0.03$)

The only statistical difference between the two groups was steroid use and CRP (Table 1).

The factors associated with ICU survival ($p < 0.05$) were: LOS, SAPS3 predicted mortality, SOFA, Respiratory and Renal SOFA, second vasopressor use, NE dose, EPI dose, CRP, and with Hospital survival ($p < 0.05$) were: Hydrocortisone use, SAPS3 score, SAPS3 predicted mortality, qSOFA, SOFA, Renal SOFA, second vasopressor use, EPI dose. Vitamin C, Complex B and Hydrocortisone all together, had no statistical significance with survival. (Table 2).

In order to assess the impact of Vitamin C + complex B + Hydrocortisone in organ failure evolution, survival analysis by group was made with no difference in SOFA, only hydrocortisone by itself had an interaction with this outcome. (Graphic 1, Graphic 2).

Discussion

In our prospective study of septic patients we evaluated the difference between ICU and hospital survival between septic patients treated with Vitamin C, complex B and hydrocortisone + standard treatment VS standard treatment alone.

During the time frame of the study 56 patients were treated at the ICU, and only 19 met inclusion criteria, the main

Table 1: Main characteristics of septic patients treated with Vit C, Hydrocortisone and Complex B vs Standard Therapy at ICU in HGZ 11 IMSS Piedras Negras Coahuila.

	CONTROL n= 12	Vit C n = 7	p
Age, years media (SD)	50.8 (12.9)	55.4 (16.5)	0.77
BMI, media (SD)	32.1 (7.82)	35.8 (12.3)	0.29
Female n (%)	3 (25%)	3 (42.9%)	0.41
Sepsis source			
Pulmonary n (%)	7 (58.3%)	2 (28.6%)	0.42
Abdominal n (%)	3 (25%)	4 (57.1%)	0.42
ICU LOS, days, media (SD)	8.0 (5.4)	5.4 (4.9)	0.48
Hosp LOS, days, media (SD)	15.3 (8.4)	18.1 (12.4)	0.59
Steroid use n (%)	6 (50%)	7 (100%)	0.024
SAPS3 media (SD)	77 (13.3)	84.6 (9.1)	0.16
SAPS3 mort media (SD)	60.8% (17.5)	78.1% (8.7%)	0.16
qSOFA media (SD)	2.8 (0.3)	2.9 (0.3)	0.71
SOFA media (SD)	12.9 (3.0)	13.3 (4.6)	0.96
SOFA cardio media (SD)	3.3 (0.9)	3.7 (0.7)	0.90
SOFA resp media (SD)	2.7 (0.8)	2.4 (1.6)	0.77
SOFA renal media (SD)	2.5 (1.1)	2.9 (1.3)	0.90
SOFA hep media (SD)	1.2 (0.6)	1.4 (1.3)	0.65
SOFA hemat media (SD)	1.2 (1.0)	1.3 (1.2)	0.77
SOFA neuro media (SD)	2.1 (1.0)	1.6 (0.9)	0.53
VASOPRESSOR USE n (%)			
1	10 (83.3%)	6 (85.7%)	0.89
2	4 (33.3%)	2 (28.6%)	0.82
3	1 (8.3%)	0	0.43
VASSOPRESOR DAYS media (SD)	2.9 (1.3)	2.1 (2.1)	0.19
NE dose (mcg/kg/min) media (SD)	0.3 (0.2)	0.6 (0.7)	0.59
EPI dose (mcg/kg/min) media (SD)	0.05 (0.06)	0.1 (0.2)	0.90
Dobutamine dose (mkg/kg/min) media (SD)	0.6 (1.3)	0	0.77
CRP media (SD)	16.5 (4.7)	27.9 (12.1)	0.05
PCL positive media (SD)	4.7 (2.4)	4 (2.4)	0.71
ICU survival n (%)	9 (75%)	5 (71.4%)	0.86
Hosp survival n (%)	7 (58.3%)	3 (42.9%)	0.51

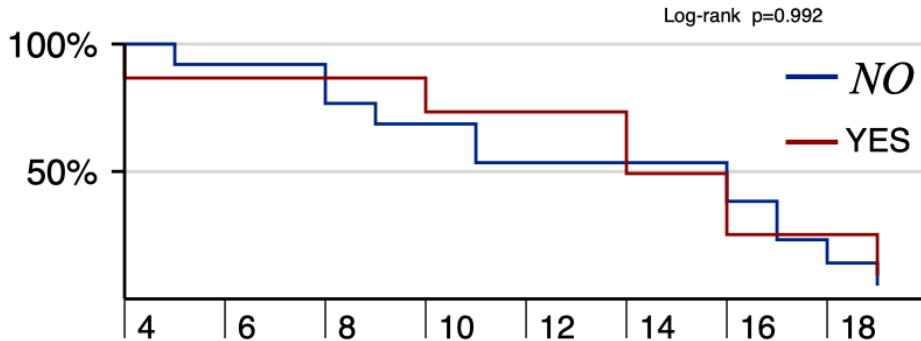
Abbreviations: BMI: Body Mass Index; ICU: Intensive Care Unit; SAPS 3: Simplified Acute Physiology Score 3; qSOFA: quickSOFA; SOFA: Sequential Organ Failure Assessment; SD: Standard Deviation; NE: norepinephrine; EPI: epinephrine; CRP: C-reactive protein; PCL: procalcitonine.

Table 2: Factor associated with ICU and Hospital Survival of septic patients treated with Vit C, Hydrocortisone and Complex B vs Standard Therapy at ICU in HGZ 11 IMSS Piedras Negras Coahuila.

	ICU survival R2/Covariance/p	Hospital survival R2/Covariance/ p
Hosp LOS	0.38 / 3.66 / 0.004	<0.001 / 0.07 / 0.96
Vitamin C	0.002 / -0.009 / 0.87	0.02 / -0.04 / 0.5
Complex B	0.002 / -0.009 / 0.87	0.02 / -0.04 / 0.5
Hydrocortisone	0.16 / -0.08 / 0.85	0.41 / -0.16 / 0.003
SAPS3 score	0.18 / -3.47 / 0.07	0.53 / -6.64 / <0.001
SASPS3 predicted mortality	0.20 / -0.05 / 0.05	0.49 / -0.09 / <0.001
qSOFA	0.09 / 0.05 / 0.19	0.24 / 0.10 / 0.03
SOFA	0.24 / -1.04 / 0.03	0.35 / -1.58 / 0.002
SOFA Respiratory	0.24 / -1.04 / 0.03	0.03 / -0.13 / 0.48
SOFA Renal	0.26 / -0.38 / 0.025	0.38 / -0.52 / 0.005
Second Vasopressor use	0.38 / -0.14 / 0.004	0.24 / -0.12 / 0.03
NE dose	0.55 / -0.19 / <0.001	0.19 / -0.13 / 0.45
EPI dose	0.64 / -0.06 / <0.001	0.29 / -0.05 / 0.01
CRP	0.38 / -3.11 / 0.005	0.07 / -1.47 / 0.29

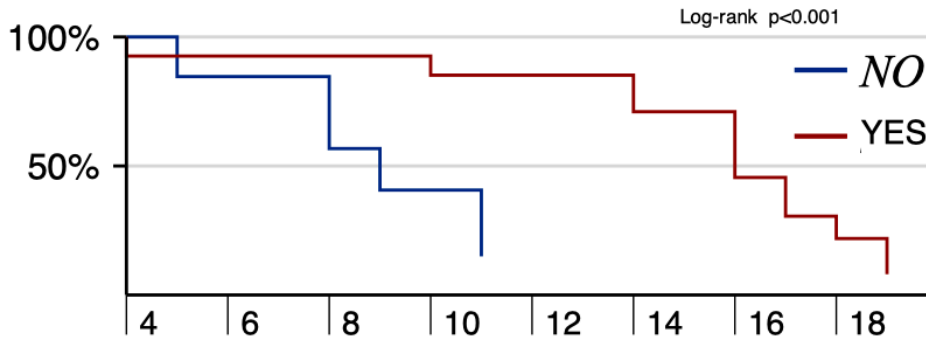
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Graphic 1: SOFA and Survival in septic patients treated with Vit C at ICU in HGZ 11 IMSS Piedras Negras Coahuila



SOFA: Sequential Organic Failure, ICU: Intensive Care Unit, Vit C: Vitamin C, HGZ : in spanish Hospital General Zona, IMSS: in spanish Instituto Mexicano del Seguro Social

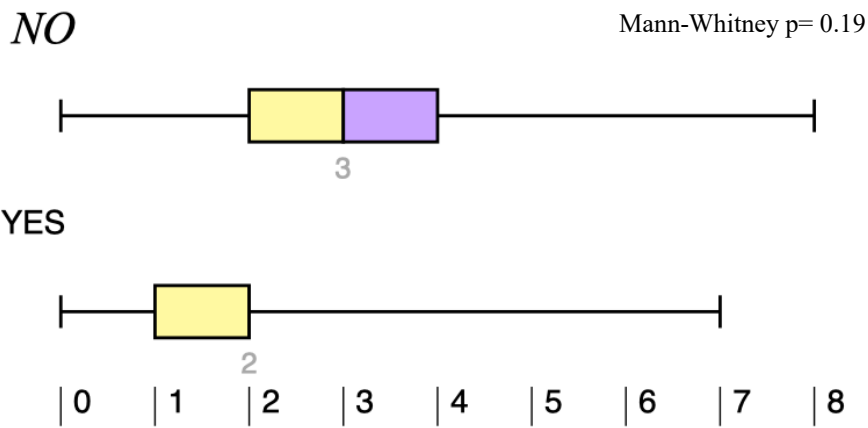
Graphic 2: SOFA and Survival in septic patients treated with Hydrocortisone at ICU in HGZ 11 IMSS Piedras Negras Coahuila



SOFA: Sequential Organic Failure, ICU: Intensive Care Unit, Vit C: Vitamin C, HGZ : in spanish Hospital General Zona, IMSS: in spanish Instituto Mexicano del Seguro Social

The difference between groups fo vasopressor use (days) was not statistically significant. (Graphic 3).

Graphic 3: Vasopressor use (days) in septic patients treated with Vit C at ICU in HGZ 11 IMSS Piedras Negras Coahuila



ICU: Intensive Care Unit, Vit C: Vitamin C, HGZ: in spanish Hospital General Zona, IMSS: in spanish Instituto Mexicano del Seguro Social

characteristics were: Age 52.4 years SD + 9.15, Female 31.6%, this is similar from the reported in literature; Tomoko, F et al [25] reported age 61.2 years SD + 15.9, female 37.5%. We reported a hospital survival in control and interventional groups of 58.3% vs 42.9% p=0.51; Zubair, M et al [26] reported hospital survival in control and interventional groups of 47% vs 43% p=0.4. The SOFA score we reported was higher (13.1 SD + 4.6) as compared with international reports (8.4 SD + 2.7) [25]. The primary infection site reported in interventional grupo was Abdominal 57.1% concordant with literature reported Gastrointestinal in 29.8% [25].

The Hospital and ICU LOS was no statically different between control vs intervention groups (15.3 SD ± 8.4 vs 18.1 SD ± 12.4 p=0.59 and 8.0 SD ± 5.4 vs 5.4 SD ± 4.9 p=0.48), Mitchell, A et al. [27] in his retrospective study reported shorter ICU LOS in treatment group vs control (7.1 vs 15.6 p=0.04). The vasopressor use in days was shorter in the intervention group vs control with no statistical significance (2 vs 3 days p=0.19), this was also evaluated in the VICTAS trial [28] vasopressor free days difference of -1 day between grupos p = 0.85.

In our prospective trial, only hydrocortisone demonstrated to have an association with survival, this was the only statistical difference between groups; 50% of control group patients had this treatment accordingly to GCP. Vitamin C, Complex B and Hydrocortisone had no association with survival o organic failure this is concordant with prior clinical trials; ACTS trial [29] found that treatment with vitamin C, thiamine, and hydrocortisone did not reduce SOFA score or mortality. The VITAMINS trial [25] found that the combination did not increase days alive and free of vasopressors.

This trial has several limitations: First the population evaluated is small, even though this was limited by ICU capacity of only two beds during the protocol. Second, a fixed dose of vitamin C was tested; a higher dose or dosing based on plasma vitamin C concentrations might yield different results. Third, clinicians were allowed to administer corticosteroids at their discretion. Fourth we didn't assessed time to treatment and its association with our outcomes.

Conclusion

In septic patients administration of Vitamin C, Complex B and Hydrocortisone + standard treatment vs standard treatment alone was no associated with a statistical difference in Hospital survival, organic failure or vasopressor use.

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