



Impact of CIGB-258 on the survival of severely ill patients with COVID-19

Impacto de CIGB-258 en la supervivencia de pacientes graves con COVID-19

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ABSTRACT

Introduction: COVID-19 causes an acute respiratory disease with high morbidity and mortality. CIGB-258 monitors inflammatory response, survival and favorable impact on predictive model variables.

Objective: Showing the impact of CIGB-258 on the survival of patients with COVID-19.

Methods: Descriptive study retrospective, in 69 severe patients with COVID-19, at the “Salvador Allende” Hospital, since March to May 2020, the sample selected by inclusion criteria and by random assignment, grouped into two groups, Group 1: 37 patients treated with a standardized protocol and Group 2: 32 patients with a standardized protocol and CIGB-258. The model was used to stratify

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the risk of death and survival from admission to discharge and death of the patients. The variables age, sex, and gender were operationalized. Frequency respiratory, creatinine, systolic and diastolic blood pressure, oxygen pressure, hemoglobin and sodium, history of arterial hypertension, diabetes and obesity. It was determined means, medians, Levene's Test, the test Bartholomew's, Student's T; standard deviation complied with the principles of biomedical research.

Results: With the use of CIGB-258, the evolution was satisfactory in 72 hours, the time from admission to discharge was 6-9 days, time between admission and death of 10-12 days, decrease to low risk of death according to model and elderly survival in patients

Conclusions: CIGB-258 peptide reduces time to discharge and lowers risk of death. Model shows impact of treatment on survival of COVID-19 patients.

Keywords: COVID-19; CIGB-258; survival.

RESUMEN

Introducción: La COVID-19, produce una enfermedad respiratoria aguda con elevada morbilidad y mortalidad. El CIGB-258 controla la respuesta inflamatoria, supervivencia e impacto favorable en las variables del modelo predictivo.

Objetivo: Mostrar el impacto del CIGB-258 en la supervivencia de pacientes con COVID-19

Métodos: Estudio descriptivo retrospectivo, en 69 pacientes graves con COVID-19, en el Hospital "Salvador Allende", desde marzo a mayo del 2020, la muestra seleccionada por criterios de inclusión y por asignación

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aleatoria, agrupados en dos grupos, Grupo 1: 37 pacientes tratados con protocolo estandarizado y Grupo 2: 32 pacientes con protocolo estandarizado y CIGB-258. Con el modelo se estratificó el riesgo de muerte y supervivencia desde el ingreso al alta y deceso de los pacientes. Se operacionalizaron las variables edad, frecuencia respiratoria, creatinina, presión arterial sistólica y diastólica, presión de oxígeno, hemoglobina y sodio, antecedentes de hipertensión arterial, diabetes y obesidad. Se determinaron medias, medianas, el Test de Levene, la prueba de Bartholomew, T Student, desviación estándar. Se cumplió

con los principios de las investigaciones biomédicas.

Resultados: Con el uso del CIGB-258, la evolución fue satisfactoria en 72 horas, el tiempo del ingreso al alta de 6-9 días, tiempo entre el ingreso y la muerte de 10-12 días, disminución a bajo riesgo de muerte según modelo y mayor supervivencia en los pacientes

Conclusiones: El péptido CIGB-258 reduce el tiempo hasta el alta de los pacientes y menor riesgo de muerte. El modelo muestra el impacto del tratamiento en la supervivencia de pacientes con COVID-19.

Palabras clave: COVID-19; CIGB-258; supervivencia.

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INTRODUCTION

The SARS-CoV-2 coronavirus causes the disease known as COVID-19, which was “declared by the World Health Organization (WHO) as a global health emergency, “denomination who retired in May 2023. The epidemic claimed the lives of more than 2 million patients and exposed the weaknesses of health systems around the world. The impact on health services has been complex, sometimes overwhelmed by the influx of serious and critical patients.⁽¹⁾

COVID-19 causes an acute respiratory disease. It is reported in the literature that it progresses very quickly to severe phases. It is associated with high morbidity and mortality, resulting from acute respiratory distress syndrome (ARDS) and multisystem organ failure (MOF).^(2, 3, 4)

The binding of the S protein of the virus to the angiotensin converting enzyme (ACE) receptor is involved, which constitutes the initial step of the pathogenesis.⁽⁵⁾ Knowledge of the disease has revolutionized the traditional approach to the treatment of diseases caused by respiratory viruses.⁽⁶⁾ Currently, it is considered that one of the pathophysiological alterations is mediated by endothelial damage associated with lung damage; with episodes of microthrombosis in the microvasculature due to platelet activation.^(7, 8, 9)

COVID-19 is considered a systemic disease, related to multisystem inflammatory syndrome.^(10, 11) Hyperinflammation is a characteristic of COVID-19 patients who progress to a severe or critical stage.⁽¹²⁾

Mortality due to COVID-19 is also associated with a high inflammatory and procoagulant state,⁽¹³⁾ age is a risk factor for death and is determined by the high susceptibility of the elderly to the emergence of complications due to the disease, something that has been evidenced by several authors.^(14, 15, 16)

The peptide CIGB-258 is an altered peptide ligand (APL) derived from cellular stress protein 60 (HSP60) and has well-proven anti-inflammatory properties.⁽¹⁷⁾ It is used in the treatment protocol

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for seriously ill COVID-19 patients. As it is a novel drug, it is necessary to show the impact on the different variables that are studied in patients affected by the SARS-CoV-2 virus.

The results obtained in preclinical models and clinical trials, the anti-inflammatory effects and the increase in the activity of regulatory T cells (Treg) stand out, ^(18, 19) which brought with it the prior authorization by the regulatory entity (CECMED), of its compassionate use in serious and critically ill patients with COVID-19, extended to other hospitals in the country on April 27, 2020 and subsequently issued emergency use authorization, with encouraging results. ⁽¹⁹⁾

For this reason, the present research was carried out, with the aim of showing the impact of the CIGB-258 peptide on the survival of seriously ill patients with COVID-19 admitted to a health institution from the application of a validated mathematical model.

METHODS

A retrospective descriptive study was carried out at the Salvador Allende Hospital from March 2020 to May 2020, with prior authorization from the regulatory entity: Cuban State Control Center for Medical Equipment (CECMED) for the compassionate use of the peptide in critically ill and seriously ill patients with COVID-19, after the excellent results obtained in preclinical studies and clinical trials carried out. The universe consisted of 69 patients who met the inclusion criteria of being positive for SARS-CoV-2 using real-time polymerase chain reaction (RT-PCR) and were randomly assigned to two treatment groups.

Group 1: (37) serious patients who were admitted to the serious care area and treated with a current standardized treatment protocol with steroids, multivisceral protection, anticoagulation, antiviral (Kaletra) and chloroquine.

Group 2: (32) critically ill patients who were admitted to the critically ill care area and treated according to the current standardized protocol with steroids, multivisceral protection, anticoagulation, antiviral (Kaletra), chloroquine and the administration of the CIGB-258 peptide

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was added at a dose of 1 mg every 12 hours intravenously (IV) for three to five days and until the parameters were normalized according to the risk model used.

Inclusion criteria

- Seriously ill patients admitted to critical care with a diagnosis of COVID-19 pneumonia with symptoms of sustained fever of more than 38 °C, disnea, polypnea greater than 25 ventilations per minute, requiring oxygen therapy.

Exclusion criteria

- Presence of comorbidities such as AIDS, malignant hematological diseases, treated with cytostatics or steroids in doses greater than 20 mg of prednisone per day or its equivalent for at least one month within the 6 months prior to admission and the patient is dying.

Exit criteria

- Patient who was transferred to another health center without completing the study.

The patients' medical records were reviewed and the information collection form was filled out. The result of the previously validated mathematical predictive model of mortality ⁽²⁰⁾ was then calculated for all patients in both groups, with the data collected at admission and on a daily basis with the variables described in the model.

Mathematical Model= $3 * (\text{age} + \text{Creatinine}) + (\text{RR} * \text{HR}) + 2 * (140 - \text{Na}) - (\text{SBP} + 2 * \text{DBP}) / (\text{PO}_2 + \text{Hb})$.

Where:

FR: respiratory rate measured in breaths per minute; serum creatinine in mmol/liter; chronological age measured in years; SBP: systolic blood pressure; DBP: diastolic blood

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pressure; PO2: partial pressure of oxygen measured by arterial blood gas analysis; Hb: hemoglobin measured in grams per liter; Na (serum sodium measured in mmol/liter).

The risk was stratified according to the results of the predictive model calculated in tertiles: lower, middle and upper tertile with cut-off points and their correspondence with the prediction of the risk of death.

1. Lower tertile up to 2300 points (Corresponds to a low risk)
2. Median tertile: 2301-3300 points (corresponds to a medium risk)
3. High tertile: more than 3301 points (Corresponds to a high risk)

The means and medians of the variables were determined to verify the differences between the study groups, standard deviation, the analysis through the statistic (t Student) for independent samples with 95 % reliability and the two statistical assumptions for its use were met. The association was assessed through the test Bartholomew's for ordinal qualitative variables, Levene's test was used to assess equality of variance for the study groups.

According to the risk category assigned by the predictive model, in each study group, the medians were determined in the assessment of patient survival according to the time elapsed from admission to discharge and according to patient death.

The percentage of mortality was represented in proportion and the impact of the use of the CIGB-258 peptide was determined according to the survival of patients in days, after applying the treatment and their evolution with the result in the predictive model used. The principles of medical ethics set out in the Declaration of Helsinki and approval by the research ethics committee were followed.

RESULTS

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Overall mortality was in the order of 20 % with 14 patients deceased, (Group 1= 9) for 64 % of deaths and (Group 2= 5) for the remaining 36 %, All of them were at medium risk of death on admission. Discharge was achieved in 55 patients, representing an 80% of the total. The groups had a behavior of (group 1-37): 73 % for 27 patients discharged and (group 2 -32): 87 % for a total of 28 patients discharged. The average age in both groups was 61 years and the presence of a personal history of hypertension in 78 % (32 patients in group 1 and 22 in group 2), diabetes in 42 % (17 in group 1 and 12 in group 2), and obesity in 8.2 % (two patients in group 1 and three in group 2).

Table 1 shows the similarity between the groups based on the model result. There are similar means that place the groups in the median tertile (Group 1 - 2510) and (Group 2 - 2527) and stratified between low and medium risk, t Student=0.698. This guarantees that there are no differences between the group means. On the other hand, the Levene test guarantees equality between the variances of both groups. That is to say, the patients are at a very similar distance from the group means, which translates into homogeneity of the individuals between each group, where the demographic variables and background in both groups are included.

Table 1. Behavior of the study group means according to the result of the predictive model

Study group	N	Average \bar{x}	Standard deviation	T. Students	Levene's test for equality of variances
1	37	2510	214.9	0.698	0.003
2	32	2527	143.3		

Table 2 shows the distribution of the study groups according to the results of the risk given by the mathematical model upon admission. The parity that exists between them in each of the risk

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groups is evident. The Bartholomew statistical test for ordinal qualitative variables such as a gradient of significance showed that there is no independence of the groups in relation to the risk upon admission of the patients.

Table 2. Distribution of patients in the study groups according to the risk assigned at admission

Study groups		At-risk group		Total
		Low	Half	
Cluster	1	6	31	37
	2	4	28	32
Total		10	59	69

Bartholomew's test - 0.656

Table 3 shows the results of the analysis of survival using a mortality table. It is evident that in the group of patients with low risk of death, the median time from admission to discharge is higher in patients in group 1 with a total of nine deaths (low risk - 8.50) and (medium risk - 13.10). In the case of patients belonging to group 2, treated with CIGB 258, the time from admission to discharge was lower (low risk - 6.00) and (medium risk - 9.54), with a total of five deaths.

Table 3. Survival analysis according to risk of death and time from admission to discharge in the study groups

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Study groups		Risk of death		Median time from admission to discharge
Groups	1	Risk	Low	8.50
			Half	13,10
	2	Risk	Low	6.00
			Half	9.54

Table 4 shows the time to death in patients. It is evident that in group 1, where the CIGB-258 peptide was not used, nine of the 31 patients with a medium risk of death died within a time elapsed from admission to fatal outcome of 6 to 10 days, which is less than the time elapsed in patients in group 2 treated with CIGB-258, out of a total of 28 patients with a medium risk of death, five died within a time of 10-12 days.

Table 4. Analysis of survival according to risk of death and the occurrence of death in the study groups

Study groups		Deceased with medium risk of death	Median time since admission until death
Cluster	1	9	6-10
	2	5	10-12

Fig.1 shows the impact of Treatment applied according to mortality in both study groups with medium risk of death. The percentage of mortality was represented in proportion, where 0.85 (85 %, representing a total of 23 patients) survived after four days, with a longer time between admission and death of the patients (between 8 and 12 days) and a significant decrease in the <http://revcimeq.sld.cu/index.php/imq> revinmedquir@infomed.sld.cu

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clinical humoral parameters in group 2 treated with CIGB-258. In group 1, deaths were reported (54 %, for a total of five deaths) before the fourth day of starting treatment, with a lower survival rate of the patients (only four patients survived to the fourth day of treatment) and a shorter time (between six and 10 days) from admission to death. No adverse effects were reported with the use of CIGB-258.

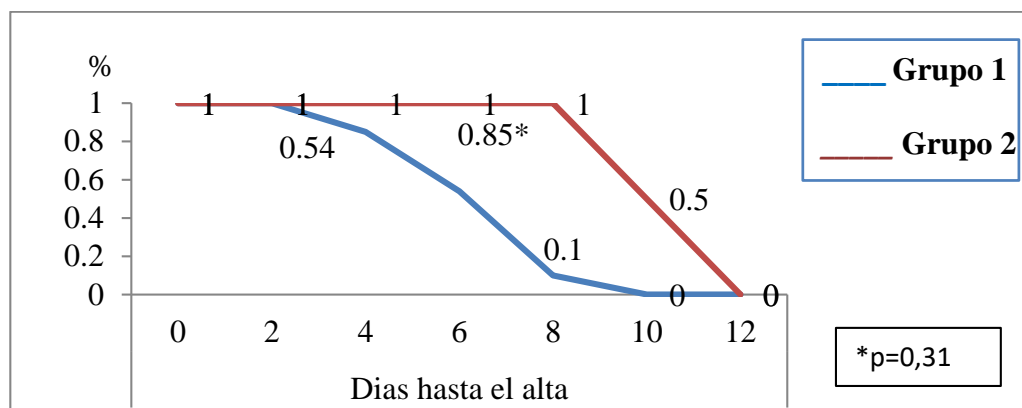


Fig.1-Patient mortality according to treatment impact and days from admission to discharge through the predictive model

DISCUSSION

The CIGB-258 peptide is obtained from a human stress protein, and has well-evidenced anti-inflammatory properties. ⁽¹⁷⁾ It is used in the treatment protocol for severe and critically ill patients with COVID-19. ^(18, 19) Being a novel drug, it is necessary to evaluate the impact on the different variables that are studied in patients affected by the SARS-CoV-2 virus.

The similarity between the study groups and the variables included in the model allowed the risk of the patients to be stratified to calculate the group means. It should be noted that the clinical and humoral state of the patients was homogeneous. This point is important, considering that the

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objective of the work was precisely to show the impact of the use of the CIGB-258 peptide, from the perspective of the result of the validated mathematical model.⁽²⁰⁾ There were no patients with a high risk of death in either group because patients in that range were excluded.

In both groups, comorbidities such as high blood pressure, diabetes, and chronic diseases linked to pro-inflammatory processes are present, which imply a higher risk for severe clinical presentation in patients with COVID-19, with a 3.5-fold increase in risk being described.⁽²¹⁾

According to the risk assigned at admission, it was the same as before, that is, to demonstrate the equality of the distribution of the risk group between the study groups. The demonstration of similarity, in the opinion of the authors, is important as evidence prior to the evaluation of the drug's efficacy. In this way, it is guaranteed that the results found are due to the true effect of the drug and are not a product of the heterogeneity of the study groups.

When analyzing in the study groups the risk of death and time from admission to discharge, the results demonstrate the difference in time from admission to discharge of patients, which was shorter in those where the CIGB-258 peptide was used.

This finding coincides with that reflected in the literature on the subject,^(17,19,22,23) where they grant the peptide a great capacity to reduce inflammatory parameters (not measured in the study, although the literature⁽²¹⁾ reports that the comorbidities described are associated with increased levels of pro-inflammatory cytokines such as IL-6, IL-17, among others) and improved oxygenation parameters. The study reflects an improvement in the clinical and humoral condition of the patients (group 2), oxygenation and serum markers such as creatinine and sodium. It is considered that discharge occurs when there is improvement in both elements, so it is not surprising that the period from admission to discharge is considered lower in this group of patients.

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In the analysis of survival according to the risk of death and the time elapsed from admission to death of the patients, it was found that in group 1 patients, deaths began early, while in group 2 they occurred late with a longer evolution time. Clinical observation showed satisfactory progress in group 2 patients during the first 72 hours of treatment, symptoms disappeared and they did not require oxygen supplementation. The results coincide with a study carried out in severe patients ⁽¹⁹⁾ where clinical and humoral improvement was evident after 48-72 hours of treatment with CIGB-258 and they were discharged after seven days.

Pharmacokinetic and biodistribution studies of the peptide support that, through the intravenous route, it reaches its maximum concentration in blood after half an hour and its clearance occurs in 6 hours and is biodistributed to multiple organs, including the lungs. ^(19, 24)

In the analysis of mortality according to the impact of the drug, it was observed that at admission both groups of patients have similar values, determined by the clinical state of the patient, evaluated in the variables of the model. ⁽²⁰⁾ At the beginning of the treatment in group 2 with CIGB-258, the curves of both groups begin to differentiate, determined by the reduction of the value of the model, translated into the improvement of the clinical and humoral parameters included. The discharge of the patients was early and had a higher survival rate, while in group 1 the discharge was prolonged with a lower survival rate of the patients.

The average increase occurred when the result was below 2,300 points, according to the model used. The results correspond to what is reported in the literature ^(18, 19, 20) where the use of the CIGB-258 peptide produces regulation in the inflammatory response and improvement in the evaluated parameters, with a greater survival rate of the patients. No adverse effects were recorded with the use of CIGB-258.

Treatment with the CIGB-258 peptide has been safe for patients and has reduced mortality in critical and severe patients with COVID-19. One of the health policies to confront the COVID

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19 pandemic in the world and in Cuba was the design of vaccines with a positive impact on reducing the incidence, hospitalizations, severity and mortality from the disease. ^(19, 25, 26)

CONCLUSIONS

The use of the CIGB-258 peptide reduces the time from admission to discharge of patients, and patients die in less time when they do not receive this drug. The application of the mathematical model constitutes a working tool to evaluate the impact of the treatment and the evolution of the seriously ill patient infected with the SARS-CoV-2 virus.

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Conflicts of interest

The authors report no conflicts of interest.

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