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Медицинские новости Грузии

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SAFETY AND EFFICACY OF THYMIC PEPTIDES IN THE TREATMENT OF HOSPITALIZED COVID-19 PATIENTS IN HONDURAS


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Introduction.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (Covid-19) global pandemic, continues to spread rapidly with increasing daily hospitalizations and deaths worldwide [1]. Even though vaccine platforms are expected to significantly reduce the burden of disease [2], the amount of active Covid-19 cases continue to demand the development of effective treatments. Emerging viral variants [3,4] and vaccination hesitancy [5,6] may extend or aggravate this problem, particularly in developing countries where access to vaccines is already limited [7].

The pathogenesis of Covid-19 is thought to be driven by SARS-CoV-2 replication in the early stages of the disease, while a dysregulated immune/inflammatory response appears to promote tissue damage in later phases [8]. Therefore, the use of thymic peptides might improve immunomodulation and clinical outcomes in the complex management of COVID-19 in moderate-to-severe cases. We report a nonrandomized phase 2 clinical trial with historical controls, using propensity score matching (PSM) from the registry data of the Hospital Santa Bárbara Integrado, to evaluate the safety and efficacy of oral thymic peptides in the treatment of hospitalized Covid-19 patients in Honduras. The trial protocol was approved by the Catholic University of Honduras IRB in Tegucigalpa and registered by the General Directorate for Regulatory Framework Surveillance of the Ministry of Health of Honduras. Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent. ClinicalTrials.gov ID: NCT04771013.

Materials and methods.

Hospitalized patients aged ≥ 21 years with confirmed Covid-19 by detection of viral nucleic acid (RNA) using reverse transcription polymerase chain reaction (RT-PCR), viral antigen, or IgM antibodies to the virus were eligible for enrollment. Unfortunately, there were no laboratories in Honduras that performed analyses for specific viral variants. Patients were required to present with at least one of the following: oxygen saturation level below 94%; complete blood count showing lymphopenia, neutrophilia, or both; positive C-reactive protein; and chest radiography or computed tomography scan with ground-glass opacities. All patients were hospitalized with oxygen by mask or nasal prongs, which corresponds to a score of 5 according to the World Health Organization (WHO) clinical progression scale [9]. Pregnant and breastfeeding women, as well as organ transplant recipients, were not eligible.

Thymic peptides were isolated from 25 thymus glands of 6- to 10-month-old calves bred in an organic production system through acid lysis. The entire cervical and thoracic thymus gland portions were used to obtain 100 g of the lyophilized product. Thymic peptides were administered orally once a day by trained physicians either one hour before or two hours after a meal, in a 250-mg dose, dissolved in 50 mL of water, until hospital discharge or death within a 20-day period. The dose used was in accordance with previous clinical safety reports and trials that have used oral thymic peptides in respiratory infections, the elderly, and other conditions [10,11], and the availability of calves in our production system to cover a maximum of 20 days of treatment for each patient.
Outcomes.

Patients were evaluated daily during hospitalization from days 1 through 20. The primary outcome measures included the time to recovery and number of participants with treatment-related adverse events and side effects. The first primary endpoint of this study was measured in days to clinical recovery, defined as the first day, during the 20 days after enrollment, on which a patient met the criteria for categories 1, 2, or 3 on an eight-category ordinal scale (as described by Beigel et al.) [12]. The categories were as follows: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or other medical conditions); 5, hospitalized, requiring supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, death. Adverse events ≥ Grade 3 were evaluated using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) and side effects were defined by the Generic Assessment of Side Effects in Clinical Trials (GASE).

The secondary outcome measure was overall survival, defined as the time from the start of treatment until death for any reason in the 20-day period. The average length of hospital stay was analyzed as a complementary analysis using the Kaplan-Meier method.

Statistical analysis.

For the comparison group, propensity score matching using IBM SPSS ver.25 (IBM Co., Armonk, NY, USA) was performed based on registry data. Heatmap and dimensional reduction techniques using principal component analysis were applied to determine the global comparison between the two groups.

Analyses of time to recovery, mortality, length of hospital stay, and time to supplemental oxygen withdrawal were estimated using the Kaplan-Meier method. Cumulative incidence curves were compared between the two groups using the log-rank test. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). For time to recovery, data for patients who died or did not recover were censored on day 20. For mortality, patients who did not die were censored on day 20. For length of stay, patients who were not discharged on day 20 and those who died were censored on day 20. For supplemental oxygen withdrawal, patients who still required oxygen therapy after day 20 and those who died were censored at day 20.

Differences in base drug treatments among groups were analyzed using the chi-square test or Fisher’s exact test, when appropriate. Safety analysis findings are descriptive in nature and not based on formal statistical hypothesis testing. The number of patients who presented with adverse events in the prospectively treated group, which was ≥ Grade 3 according to CTCAE v5.0, and the number that manifested side effects according to GASE, were considered. All P-values were two-sided, and all analyses were performed according to the intention-to-treat principle.

Results.

A total of 44 patients were analyzed in this study: 22 in the thymic peptide group and 22 in the standard care group (Figure 1). Between February 10, 2021, and April 12, 2021, patients were prospectively assessed for eligibility for the intervention group. For the comparison group, registry data from June 2020 to February 2021 were considered, as the standardization of the therapeutic management of the Honduran national guideline for the entire study period occurred in May 2020 [13]. Within the thymic peptide group, acute infection for COVID-19 was confirmed by antigen detection in 86.4% (19/22), RT-PCR in 4.5% (1/22), and IgM in 9.1% (2/22) of participants. Within the standard care group, acute infection for COVID-19 was confirmed by RT-PCR in 63.6% (14/22), antigen detection in 31.8% (7/22), and IgM in 4.5% (1/22) of patients. Dimensionality reduction by principal component analysis demonstrated the overlapping of both groups, and heatmap analysis showed homogeneous baseline characteristics (Figure 2). Together, these results indicate that the groups were globally similar in their severity indices after matching.

Demographic and clinical characteristics of the patients at baseline are shown in Table 1. The median number of days between symptom onset and hospitalization/enrollment was 11.5 (interquartile range: 9–13) in the intervention group and 10 (interquartile range: 9–14) in the standard care group. In the thymic peptide and standard care groups, 15 (68.2%) and 13 (59.1%) were men, and the mean (±SD) age was 52±16 years and 57±17 years, respectively. All patients were mestizo. Most patients had one or more comorbidities (75%), mainly hypertension (36.4%) and diabetes (31.8%). Notably, 61.4% of patients in both groups had elevated liver enzyme or creatinine levels at admission. All patients were WHO clinical progression score 5 at hospitalization/enrollment, and most (86.4%) had an oxygen saturation of ≥91%.

The median time to recovery in the thymic peptide group was 6 days, compared with 12 days of standard care. Kaplan-Meier analysis revealed a significantly shorter time to recovery in the intervention group (log-rank test, P=0.002) (Figure 3). The hazard ratio for recovery was 2.75, with a 95% confidence interval of 1.34 to 5.62. No side effects or adverse events related to thymic peptides were reported during the 20-day follow-up hospitalization period. This is in accordance with previous literature of thymic peptide safety and toxicity studies [11,14,15].

No deaths occurred in the thymic peptide group by day 20. In contrast, the Kaplan-Meier estimate of mortality for the standard care group by day 20 was 24% (Figure 4). This difference was statistically significant (log-rank, test P=0.02). Kaplan-Meier analysis showed a median time to oxygen therapy withdrawal of 4 days in the thymic peptide group, as compared with 10 days in the standard care group (hazard ratio, 2.3; 95% CI, 1.13 to 4.67; log-rank P=0.01). Patients in the intervention group had a shorter length of in-hospital stay (median, 6 days, compared with 12 days; hazard ratio for discharge, 2.34; 95% CI, 1.16-4.75; log-rank P=0.01), which may have influenced the lack of side effects and adverse events reported in the intervention group.
Table 1. Demographic and clinical characteristics of the patients at baseline. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thymic peptides (N=22)</th>
<th>Standard care (N=22)</th>
<th>Total (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean -yr</td>
<td>52±16</td>
<td>57±17</td>
<td>54±16</td>
</tr>
<tr>
<td>Distribution - no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 years</td>
<td>15 (68.2)</td>
<td>12 (54.5)</td>
<td>27 (61.4)</td>
</tr>
<tr>
<td>61-64 years</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>5 (22.7)</td>
<td>7 (31.8)</td>
<td>12 (27.3)</td>
</tr>
<tr>
<td><strong>Sex – no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (31.8)</td>
<td>9 (40.9)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (68.2)</td>
<td>13 (59.1)</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td><strong>Race - no. (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestizo</td>
<td>22 (100)</td>
<td>22 (100)</td>
<td>44 (100)</td>
</tr>
<tr>
<td><strong>Median no. of days since symptom onset (IQR)</strong></td>
<td>11.5 (9-13)</td>
<td>10.0 (9-14)</td>
<td>10.5(9-13)</td>
</tr>
<tr>
<td><strong>No. of comorbidities</strong></td>
<td>2±1</td>
<td>2±2</td>
<td>2±1</td>
</tr>
<tr>
<td><strong>Coexisting conditions - no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes ‡</td>
<td>11 (50)</td>
<td>3 (13.6)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (31.8)</td>
<td>9 (40.9)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 (9.1)</td>
<td>4 (18.2)</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (4.5)</td>
<td>1 (4.5)</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Organ damage (other than lung) §</td>
<td>12 (54.5)</td>
<td>15 (68.2)</td>
<td>27 (61.4)</td>
</tr>
<tr>
<td>WHO clinical progression score 5 - no. (%)</td>
<td>22 (100)</td>
<td>22 (100)</td>
<td>44 (100)</td>
</tr>
<tr>
<td><strong>Heart rate distribution- no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-90 beats/min</td>
<td>14 (63.6)</td>
<td>10 (45.5)</td>
<td>24 (54.5)</td>
</tr>
<tr>
<td>91-110 beats/min</td>
<td>6 (27.3)</td>
<td>10 (45.5)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>111-130 beats/min</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure distribution- no. (%)</strong></td>
<td>22 (100)</td>
<td>22 (100)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>90-219 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate distribution- no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-24 breaths/min</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>≥ 25 breaths/min</td>
<td>20 (90.9)</td>
<td>19 (86.4)</td>
<td>39 (88.6)</td>
</tr>
<tr>
<td><strong>Oxygen saturation distribution- no. (%)</strong></td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>92-93%</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>≤91%</td>
<td>19 (86.4)</td>
<td>19 (86.4)</td>
<td>38 (86.4)</td>
</tr>
<tr>
<td>Temperature distribution- no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.6-37.9 °C</td>
<td>19 (86.4)</td>
<td>19 (86.4)</td>
<td>38 (86.4)</td>
</tr>
<tr>
<td>38-39 °C</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>≥39.1 °C</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>SARS-CoV-2 positive test result- no. (%)</td>
<td>22 (100)</td>
<td>22 (100)</td>
<td>44 (100)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, COPD Chronic obstructive pulmonary disease, WHO World Health Organization, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† Race was recorded in the patient’s electronic health record.

‡ There was a significant (P=0.01) difference in the percentage of diabetic patients between the thymic peptide group and the standard care group, but there were no significant differences between the groups in any other baseline characteristic.

§ Liver damage was defined as elevated liver enzymes, and kidney damage as elevated creatinine level.
Figure 1. Enrollment and Propensity Score Matching.

31 Patients were assessed for eligibility for intervention group

9 declined to participate

462 Patients were assessed for eligibility for control group

425 were excluded
   241 Were not confirmed Covid-19 cases by RNA, antigen, or antibody detection
   177 Full records were not digitally available
   6 Did not meet Stage IIb or WHO score 5 at hospital admission
   1 Was under the age of 21

37 Underwent propensity score matching

22 Were matched to participants of the intervention group

No randomization

22 Received thymic peptides

20 Completed the trial
   2 Requested self-discharge
     1 Manifested clinical improvement and did not want to continue hospitalization
     1 Manifested clinical improvement and left to care for other sick members of the household
     0 Died at 20-day follow-up
     18 Recovered during 20-day follow-up
     0 Adverse events were reported
     0 Side effects were reported
     11 Were lost to follow-up after medical discharge

22 were analyzed in the intention to treat approach

22 Received standard care

21 Completed at least 20 days of hospitalization
   1 Manifested clinical improvement but was referred to another hospital before day 20 to continue therapeutic management due to shortage of beds for more severe cases
   5 Died at 20-day follow-up
   14 Recovered at 20-day follow up

22 were analyzed in the intention to treat approach
Figure. 2. Principal component analysis (PCA) and hierarchical heat map cluster of group characteristics. The percentage of variation explained by each component is indicated in parenthesis in panel A. PCA considered the following variables: confirmatory covid test, number of comorbidities, sex, WHO clinical progression score, need for oxygen therapy, age distribution, heart rate distribution, systolic blood pressure distribution, respiratory rate distribution, oxygen saturation distribution, temperature distribution, and presence of diabetes, hypertension, obesity, overweight, chronic obstructive pulmonary disease, heart failure, organ damage, and dyspnea. Hierarchical heat map cluster of baseline patient characteristics and outcomes is shown in panel B. AgeClass indicates age distribution, TempClass temperature distribution, COPD Chronic obstructive pulmonary disease, HRClass heart rate distribution, No. Comorb number of comorbidities, O2SatClass oxygen saturation distribution, RespRateClass respiratory rate distribution, O2Omitted time to oxygen withdrawal by day 20, Days Hosp time to discharge by day 20.

Figure. 3. Kaplan-Meier estimates of time to recovery by day 20. The Kaplan-Meier method was used to estimate the cumulative proportion of patients and the log-rank test was used to compare the two groups. The Cox proportional-hazard model was used to estimate the hazard ratio and 95% confidence interval. Vertical dashes indicate censored data.
Conclusion.

In conclusion, given that a dysregulated immune/inflammatory response promotes tissue damage in the later phases of COVID-19, the use of thymic peptides should be further examined and considered to improve immunomodulation and clinical outcomes in the complex management of the disease. A daily oral dose of 250 mg of thymic peptides proved to be safe in a hospitalized Covid-19 group of patients in Honduras, reporting no deaths by day 20. When compared with registry data after PSM, shorter times to oxygen therapy withdrawal, recovery, and length of stay as well as a reduction in mortality were identified. This study’s results suggest that administration of thymic peptides should be considered at hospitalization of patients with a WHO clinical progression score of 5, although benefits since symptom onset should be evaluated in future research. Trials with larger populations are required to confirm our findings and further describe efficacy with other oral thymic peptide doses. Our group is preparing a more extensive double-blind randomized controlled trial of oral thymic peptides in Covid-19 patients.

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Disclosure of interest.

HMRZ, KGRP, and HAAA designed the modified protocol for isolation of thymic peptides, which is patent pending. HMRZ receives a grant for education from the Universidad Católica de Honduras not related to this study. The rest of the authors declare no competing interests.

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