Use of a cysteine-rich whey protein isolate (Immunocal®) in post COVID-19 cognitive impairment

Abstract

Background: Post-COVID-19 cognitive impairment (PCCI), characterized by deficits in attention, memory, and executive functioning, remains a significant challenge among long COVID patients. Oxidative stress is a key contributor to this condition. Cysteine-rich whey protein isolate (CRWPI), such as Immunocal®, enhances intracellular glutathione production and may offer neuroprotective benefits.

Objective: To evaluate the efficacy of Immunocal® supplementation on cognitive function—particularly attention and memory—and functional performance in individuals with PCCI.

Methods: A randomized, controlled, parallel-group trial was conducted in Cali, Colombia, with 120 adults recovering from COVID-19 with mild to moderate cognitive impairment. Participants were randomly assigned to three groups: (1) immune® supplementation (CRWPI) (20 g/day), (2) neuropsychological rehabilitation, or (3) no intervention (control), for 12 weeks. Cognitive outcomes were assessed using the Montreal Cognitive Assessment (MoCA) and the NEUROPSI attention and memory test. Clinical outcomes and physical endurance were measured using a medical assessment form that took into account the physical symptoms presented, and a physical test for 30 seconds standing (STST). **Results**: Both the Immunocal® and neurorehabilitation groups showed statistically significant improvements in all attention subdomains and memory types compared to the control. Immunocal® produced greater gains in divided attention and working memory, suggesting a specific advantage in cognitive domains sensitive to oxidative stress. Performance and clinical symptoms of STST were also significantly improved in the Immunocal group compared to the control group.

Conclusion: Immunocal® supplementation significantly improves cognitive performance, comparable to structured neurorehabilitation, in individuals with ICCP. It also shows potential to improve physical endurance, reduce fatigue and initial clinical symptoms. These findings support the integration of Immunocal® as a non-pharmacological intervention for cognitive dysfunction related to long COVID.

Introduction

The COVID-19 pandemic has had unprecedented effects on global health, not only in terms of acute respiratory manifestations but also in long-term sequelae (Long COVID) affecting various systems. The two symptoms recently rated as the most severe in patients with long COVID persisting more than 4 weeks are fatigue and “brain fog”, also referred to as post-COVID-19 Cognitive Impairment (PCCI).[1] PCCI encompasses deficits in attention, working memory, verbal fluency, executive functioning, and processing speed,[2]

while post-COVID fatigue is defined as post-exertional neuroimmune exhaustion.[3] Both post-viral symptoms limit a person's ability to carry out physical and mental ordinary daily activities.[4-6]

Oxidative stress and mitochondrial dysfunction are known contributors to both age-related and post-infectious cognitive decline.[7] Viral infections may accelerate neurodegeneration by increasing reactive oxygen species, promoting neuronal senescence, and inducing neuroinflammation.[8] In fact, emerging evidence suggests that excessive oxidative stress may be one of the key mechanisms associated with the cognitive impairment observed in patients with SARS-CoV and SARS-CoV-2 infections.[9] In response, research has turned toward neuroprotective and antioxidant interventions. Cysteine, a precursor to intracellular glutathione (GSH), plays a critical role in defending against oxidative damage.[2,10-11]

Although there are few evidence-based recommendations regarding protein intake for cognitive health, consumption of whey protein isolates (WPI) have been associated with cognitive performance improvements in both cross-sectional and longitudinal cohort studies.[12-15] N-acetyl cysteine (NAC) and bovine WPI are rich in cysteine and undenatured WPI in cystine, the disulfide form of cysteine. This amino acid is the most important precursor for the synthesis of intracellular glutathione, a critical biomolecule in reducing oxidative stress.[16] Oral supplementation of a cysteine-rich WPI (CRWPI) with a very high biological value (BV), PER (protein efficiency ratio) and PDCAAS (protein digestibility-corrected amino acid score) has been associated with increased intracellular GSH synthesis and neuroprotective properties.[17]

The primary objective of this study was to assess the efficacy of supplementation with a cysteine-rich whey protein isolate (CRWPI, Immunocal®) on cognitive function—specifically memory and attention—in individuals with post-COVID cognitive impairment (PCCI). A secondary aim was to compare these outcomes with those achieved through neurocognitive rehabilitation, and to evaluate the effects of Immunocal® on functional performance and fatigue using the sit-to-stand test (STST).

Methods

Study Design and Participants

This randomized, controlled, parallel-group trial included subjects at least 18 years of age in Cali, Colombia, who recovered from COVID-19 infection and presented with a mild-to-moderate cognitive impairment and no prior history of administration of Immunocal.

Subjects with a history of cerebrovascular or cardiovascular disease and current or previous use of Immunocal were excluded from selection. Ethical approval was obtained from Universidad Libre's IRB, and informed consent was secured.

Sampling and Protocol

A non-probabilistic consecutive sampling was performed. For this study, a target sample of 120 subjects was selected to achieve a 95% confidence level. A double-blind randomization process was used to divide the subjects into three groups of 40 participants as follows: 1. CRWPI (Immunocal®) supplementation; 2. Structured neuropsychological rehabilitation (Neurorehabilitation), and no intervention (control).

A group of neuropsychologists with expertise on the application of cognitive tools and neuropsychological rehabilitation were responsible for the evaluation and management of the neuropsychological phase of the study. The neuropsychological rehabilitation consisted of 45-minute face-to-face group sessions that took place three times weekly for a period of 12 weeks. After 12-weeks, a neuropsychological evaluation was completed on every subject.

The CRWPI Immunocal® (Immunotec ™) was administered at a dose of 20 grams (2 sachets once daily) for 12 weeks consecutive months. The research team delivered the Immunocal directly to subjects and instructed them how to mix it and self-administer.

Pre-test cognitive functioning was evaluated using the NEUROPSI attention and memory[18] while only the NEUROPSI attention and memory were used to assess the same cognitive domains at 12-weeks.

The main goal of the NEUROPSI Attention and Memory is to evaluate a wide spectrum of cognitive functions, including spatial, temporal and personal orientation; attention and concentration; working memory; verbal and visual memory, and executive and motor functions. The NEUROPSI Attention and Memory test considers age and schooling for the acquisition of both quantitative and qualitative data and classifies amnesic and attentional alterations in four different categories.

The 30-second sit-to-stand test (STST) is a widely used assessment designed to evaluate lower body strength and functional endurance.[19] It measures how many full stands a person can complete from a seated position in 30 seconds, without using their arms for support. This test provides valuable insight into muscle strength and balance, making it a practical tool for monitoring physical performance and the effectiveness of interventions such as exercise programs or nutritional supplementation. The STST is often used to

evaluate fatigue in lower limb and trunk muscles.[20] This test was performed to all available participants after the intervention period was completed.

Statistical Analysis

A data collection instrument was designed using Excel to tabulate the information of the participants. Qualitative variables were reported in their absolute and relative frequencies. After normality analysis, according to Kolmogorov-Smirnov procedure, quantitative variables were expressed as median with interquartile range or as mean with standard deviation. The comparison of the two groups was performed using the chi2 test or Fisher's exact test for qualitative variables and Student's t-test or Mann-Whitney U-test for quantitative variables. Multivariate logistic regression was applied to evaluate the improvement in scores of the neuropsychological tests applied to compare the data between the two groups. Relative risk (RR) was be reported with their 95% confidence interval (95% CI). A $p<0.05$ was considered for statistical significance. Post hoc comparisons were performed using Tukey's test. A p-value < 0.05 was considered statistically significant. Randomization integrity and baseline equivalence were checked for age and cognitive scores. Data were analyzed using SPSS v25.

Results

A total of 120 subjects were randomly assigned to the three groups. Most participants were women (n = 77; 64.2%) and only a few subjects came from rural areas (n = 2; 6.7%). While all 120 subjects had a diagnosis of COVID-19, only 62.5% of them reported a positive test. In terms of level of education, the largest group had a technical degree (n=40; 33.3%), followed by undergraduate education (n=32; 26.7%). More than 80% of participants experienced daily post-COVID symptoms. The most common post-COVID symptoms were musculoskeletal, followed by headache and fatigue. More than 60% of subjects reported attention and memory deficits. In the evaluation of the physical results, it was found that 67% showed a physical performance between poor and very poor in the STST test (30 seconds). Table 1 provides additional demographic comparisons between groups.

Table 1. Demographic information

	CRWPI (n=40)	Neurorehabilitation (n=40)	Control (n=40)
Age (SD)	33.3 (10.9) *	47.6 (12.9) *	41.8 (14.8)
Gender			
Male	37.5%	40.0%	30.0%
Female	62.50%	60.0%	70.0%
Vaccinated	87.5%	87.5%	97.5%
1 dose	22.50%	8.6%	15.4%
2 doses	45.7%	42.9%	33.3%
3 or more doses	31.1%	48.6%	51.3%
Level of Education			
High school	25.0%	25.0%	20.0%
Associate's degree	45.0%	30.0%	30.0%
Undergraduate	20.0%	35.0%	35.0%
Other	10.0%	10%	15%
Post-COVID Symptoms			
Musculoskeletal	87.5%	87.5%	75.0%
Headache	65.0%	57.5%	62.5%
Fatigue	52.5%	60.0%	62.5%
Respiratory	37.5%	57.5%	47.5%
Digestive	32.5%	35.0%	46.7%
Depression	25.0%	17.5%	32.5%
Daily symptoms	75.0%	85.0%	85.0%
STST (30sec)	13.5*$\pm$	16.4*+	14.3+$\pm$
Attention deficit	78.9%*	41.7%*	69.2%
Memory deficit	78.9%*	58.3%*	65.4%

STST (30sec): Sit-to-stand test in 30 seconds.

Age: * P < 0.001 95% CI [7.39, 21.16]; ‡ P = 0.012 CI [1.57, 15.33]; † P = 0.115 CI [-12.71, 1.06].

STST: * p = 0.001; + p = 0.06; $\pm$ p = 0.62

Attention and memory: * P < 0.001

A one-way ANOVA performed to compare the mean age and revealed a statistically significant difference among the three groups. Given the mean rankings (Immunocal > Control > Neurorehabilitation), this suggests a gradient effect or systematic group variation (Figure 1). The effect size, measured by Cohen's d, was 0.65, suggesting a moderate to large difference between CRWPI and control groups. On the other hand, when comparing participants taking CRWPI and those undergoing neurorehabilitation a Cohen's of 1.20 indicates that the difference between the two groups is not only statistically significant but also practically meaningful.

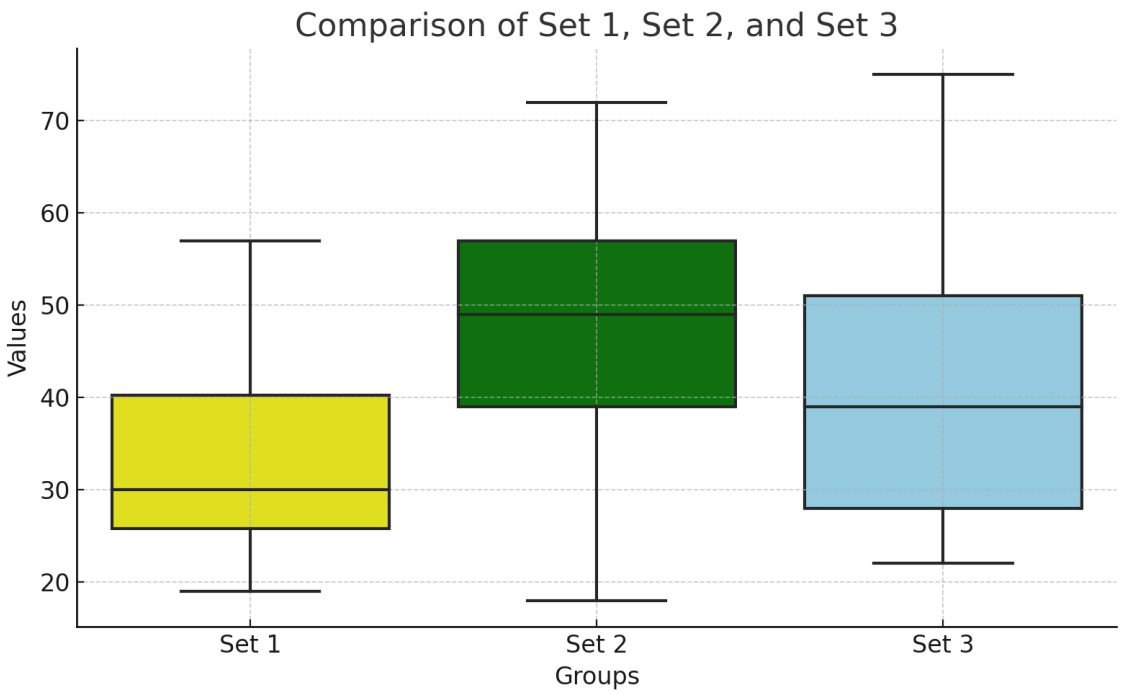

Figure 1. Boxplot showing differences between mean age in the three groups. Set 1 = CRWPI; set 2 = neurorehabilitation; set 3 = control.

More than two thirds of the subjects (78.9%) in the Immunocal group had either a severe (5.3%) or mild (73.7%) baseline attention disorder. However, after administration of Immunocal, every subject had a normal attention score (P<0.001). In the neurorehabilitation group, 41.7% of the subjects had either a had either a severe (2.8%) or mild (38.9%) baseline attention disorder. After the rehabilitation program, there were no subjects with severe impairment and 94.4% of them had a normal attention score (P=0.001). More than half of the subjects (69.2%) in the control group had either a severe (11.5%) or mild (57.7%) baseline attention disorder. Only 30.8% had a normal score. No changes were observed in the attention scores after the study period. (P=0.89).

As shown in Figure 1, total attention increased 42.6% in the Immunocal group and 23.7% in the rehabilitation group. The control group remained essentially unchanged (6.51 to 6.44).

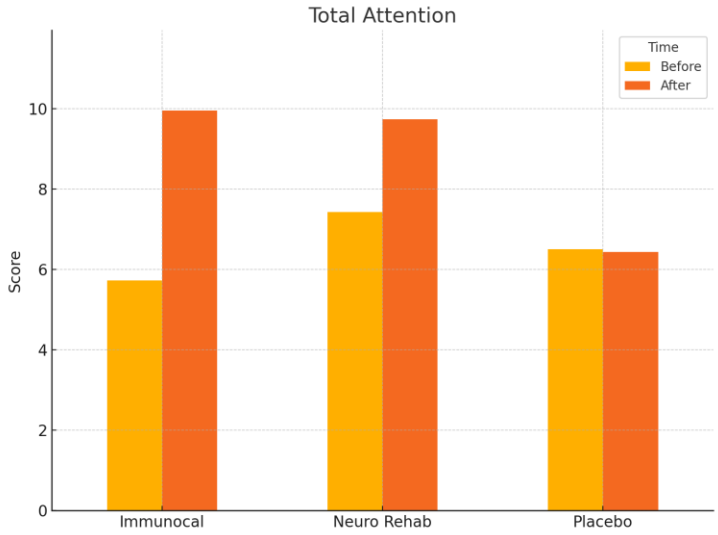

Figure 1. Total Attention Scores Before and After Intervention

More than two thirds of the subjects (78.9%) in the Immunocal group had either a severe (5.3%) or mild (52.6%) baseline selective attention disorder. However, there was a statistically significant change in the number of subjects who after administration of Immunocal scored either normal (81.6%) or above normal (13.2%) ($P<0.001$). A similar finding was present in the neurorehabilitation group where before intervention, 8.3% of the subjects had a severe or mild (36.1%) baseline selective attention disorder and improved to either a normal (97.2%) or above normal (2.8%) ($P<0.001$).

Overall, selective attention improved markedly post-intervention in the active treatment groups (Figure 2). Scores increased 48.9% (Immunocal; $P<0.001$) and 27.8% (Rehabilitation; $P<0.001$) while the control group showed a decline ($P = 0.37$).

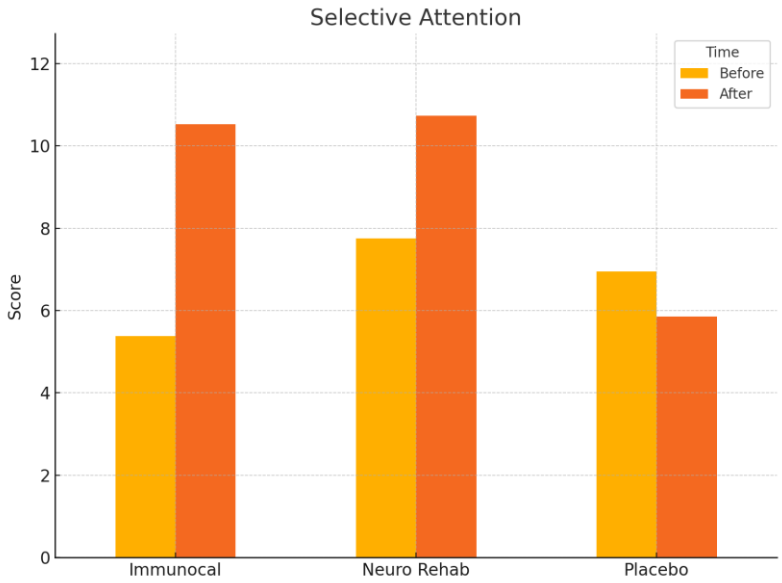

Figure 2. Variable: Selective Attention – summarized by average

Before intervention, the subjects on the Immunocal group had either a severe (36.84%) or mild (39.47%) baseline sustained attention disorder. After completing the intervention, only 13.2% of the subjects had a mild disorder while 86.8% scored normal (P=0.000). Subjects in the neurorehabilitation group had a severe (19.4%) or mild (36.1%) baseline disorder. Almost half of participants (44.4%) had a normal baseline score. After the intervention, 80.6% of the subjects had a normal or above normal score (5.56%) (P=0.01). Figure 3 shows that overall, Immunocal group scores improved 50.2% (P< 0.001), and the rehabilitation by 30.2% (P= 0.001). The control group remained almost unchanged (P=0.92).

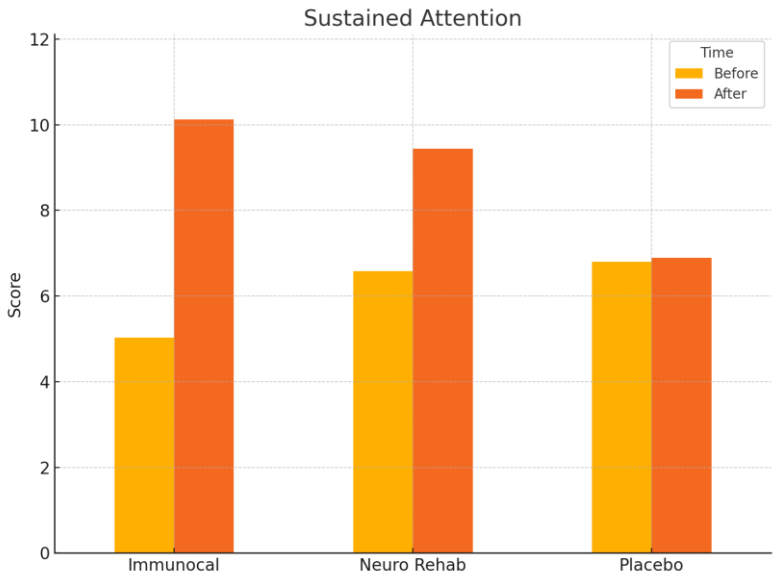

Figure 3. Sustained Attention Scores Before and After Intervention

Subjects on the Immunocal group had either a severe (2.6%), mild (47.4%) or normal (50%) baseline divided attention scores. After completing the intervention, only 5.3% of the subjects had a mild disorder while 94.8% scored normal (P< 0.001). Participants in the neurorehabilitation group had a severe (2.8%), mild (27.8%) or normal (69.4%) baseline scores. There was minimal change on the mild alteration scores after intervention (25%). More than half of participants (72.2%) had a normal baseline score while a small percent scored above normal (2.8%). These changes were not statistically significant (P=0.56).

In summary, Immunocal was the only group that reported a statistically significant improvement post intervention (26.3%; P< 0.001) (Figure 4).

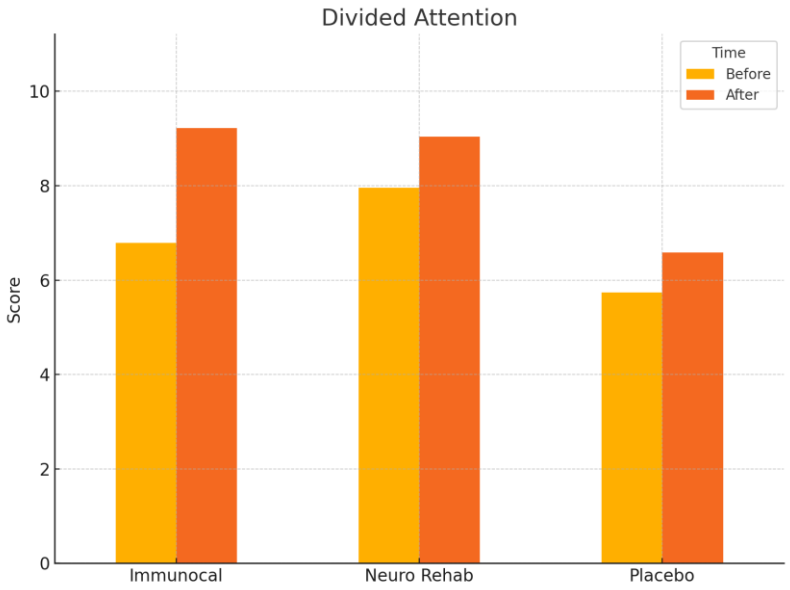

Figure 4. Divided Attention Scores Before and After Intervention

More than two thirds of the subjects (78.9%) in the Immunocal group had either a severe (5.3%) or mild (73.7%) baseline memory disorder. After administration of Immunocal, 100% of subjects had either a had a normal attention score (97.4%) or above normal (2.6%) (P< 0.001). In the neurorehabilitation group, more than half of the subjects (58.3%) had either a had either a severe (5.6%) or mild (52.8%) baseline memory disorder. After the rehabilitation program, while there were no subjects with severe impairment, 83.3% of them had a normal attention score and 2.8% had an above normal score (P=0.001).

In the control group, 65.4% of the had either a severe (3.9%) or mild (61.5%) baseline attention disorder. Only 34.6% had a normal score. Interestingly, 19.2% of them had a severe memory disorder after the study period. (P=0.89).

Total memory scores (Figure 5) improved significantly by 46.7% (P< 0.001) and 33.6% (P= 0.001), respectively. The control group remained unchanged (P=0.19).

Figure 5. Total Memory Scores Before and After Intervention

Working memory (Figure 6) significantly increased by 46.6% with Immunocal (P< 0.001) and 37.4% with rehabilitation (P< 0.001). Conversely, the control group dropped slightly from 6.89 to 6.07 (P=0.006).

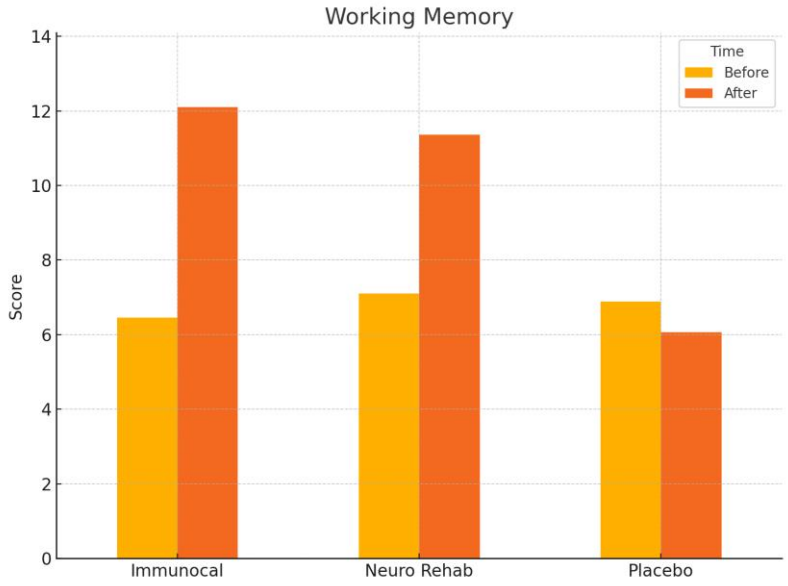

Figure 6. Working Memory Scores Before and After Intervention

Short-term verbal memory (Figure 7) improved significantly in the Immunocal (64.9%; P< 0.001) and the Rehabilitation groups (40.2%; P< 0.001), whereas the control group showed only minor change (11.3%; P= 0.77).

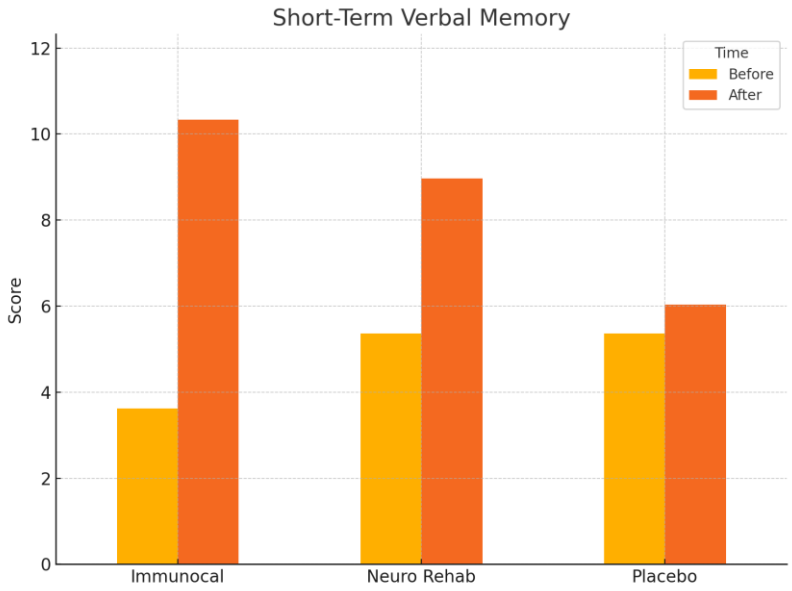

Figure 7. Short-Term Verbal Memory Scores

Short-term visual memory (Figure 8) scores rose 58.4% in the Immunocal group (P< 0.001) and 58.5% in the rehabilitation group (P= 0.001), while the control group remained in the same ranges (P=0.26).

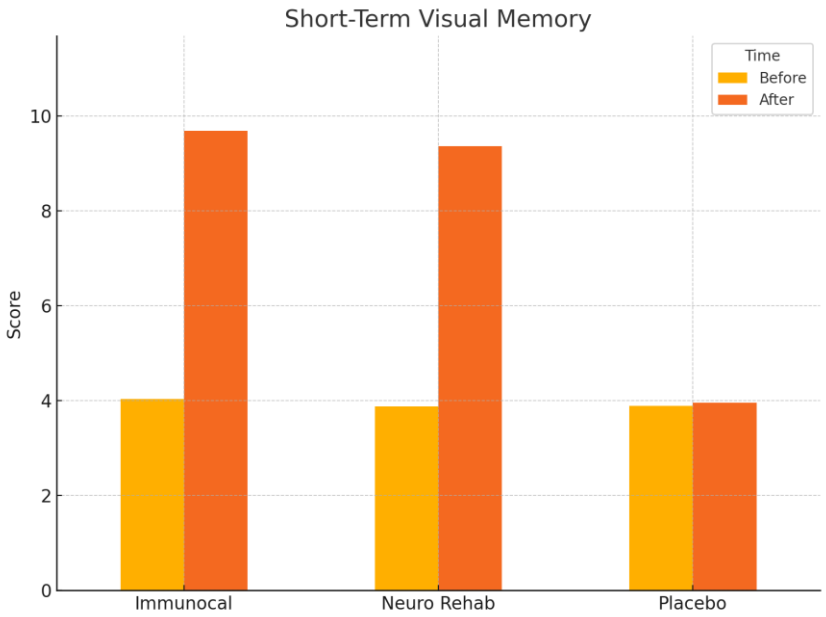

Figure 8. Short-Term Visual Memory Scores

Long-term verbal memory (Figure 9) increased 49.7% (Immunocal) and 29.8% (rehabilitation). The control group changes were minimal (6.21 to 6.28).

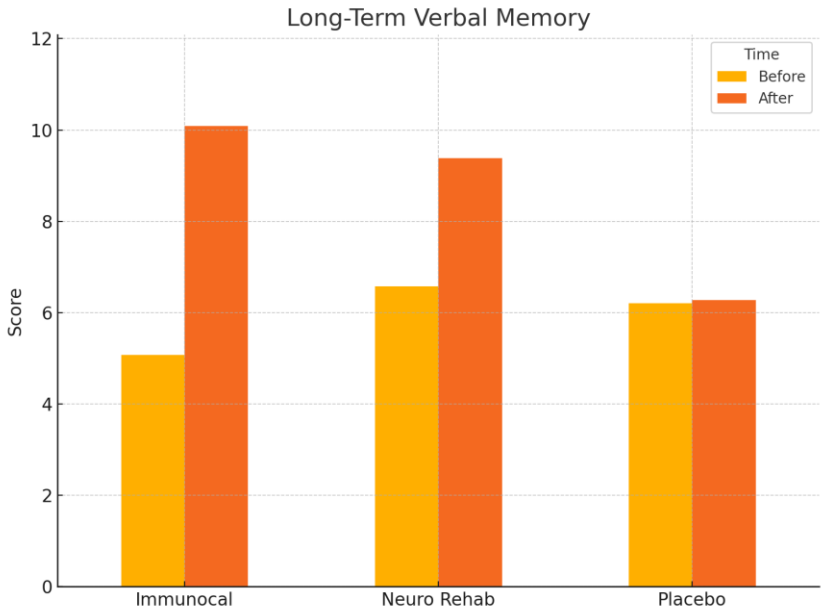

Figure 9. Long-Term Verbal Memory Scores

Long-term visual memory (Figure 10) showed modest improvement across all groups. The Immunocal group improved 12.4% (P< 0.001), the rehabilitation 12.1% (P=0.08), and the control group from 10.18 to 10.32 (P=0.94).

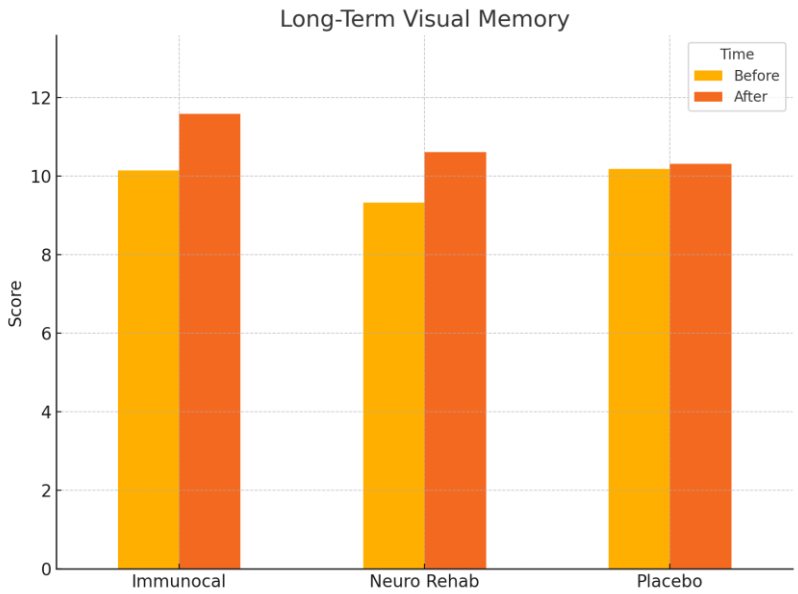

Figure 10. Long-Term Visual Memory Scores

While a 30-second sit-to-stand test (STST) was performed in 122 subjects before randomization (mean 14.9±4.6), only 27 subjects were available for the test after the intervention period had ended. The mean age for these 27 subjects was 45.9 (±12.5) and the STST before intervention was 16.9 (±5.4), which is consistent with an average performance. Twenty-two subjects on the CRWPI group were available for the postintervention STST. While baseline mean STST for the CRWPI group was not significantly different to the other two groups (16±5.1; P=0.32), post intervention mean STST was significantly higher than the other two groups (18±8.1; P=0.042).

Discussion

The statistical analysis demonstrated that both a cysteine-rich whey protein isolate **(**Immunocal®) and neuropsychological rehabilitation yielded significant improvements in the cognitive domains evaluated—attention and memory—in patients with post-COVID-19 cognitive impairment (PCCI)**.** There were no significant differences between the two active interventions, a finding that is consistent with prior reports where neurorehabilitation programs have been shown to significantly improve global cognition and memory in patients with mild cognitive impairment (MCI) and post-viral cognitive deficits.[2,21]

These results support the hypothesis that administration of a CRWPI like Immunocal has comparable efficacy to structured cognitive rehabilitation in subjects with PCCI.[4] Previous studies in animal models[22,23]and human subjects[24,25] have demonstrated that supplementation with cysteine-rich whey protein isolates or other glutathione precursors[26] significantly preserves brain glutathione levels and ameliorates cognitive impairments associated with oxidative stress, neuroinflammation and mitochondrial dysfunction.[27] The results of the current study are also consistent with a recent study by Li and colleagues who demonstrated in a randomized controlled trial that a12-month use of whey protein improved cognitive function in older adults with MCI. They reported a significant change on cognitive scores, which is consistent with our results.[25]

In this study, all subdomains of attention (selective, sustained, divided) improved significantly in the CRWPI group. Importantly, a statistical difference was observed between the CRWPI and neurorehabilitation groups when compared for divided attention, favoring Immunocal. It is possible that divided attention and executive function improvements are particularly sensitive to oxidative stress modulation.[26,27] When compared with placebo, both active intervention groups significantly improved across all attention subdomains, whereas the placebo group showed negligible changes, reinforcing the conclusion that improvements were probably due to active intervention rather than spontaneous recovery.

Regarding memory performance, both treatment groups showed improvements across all memory dimensions—total, working, verbal short-term and long-term, visual short-term and long-term memory. However, visual long-term memory (VLTM) changes were more modest, indicating a potential resistance of this domain to short-term interventions. This observation is consistent with previous studies suggesting that visual memory—especially long-term visual retention—can respond more slowly to interventions such as antioxidant therapies and cognitive retraining compared to verbal

and working memory improvements.[28] Schurgin and Flombaum also concluded that VLTM performance suffers as more variability is introduced when individuals are tested while visual working memory performance is better after interventions.[29]

When evaluating baseline memory scores before interventions across all three groups, significant group differences were found, with the placebo group having significantly lower average scores. Nevertheless, no significant differences were found between the Immunocal and neuropsychological rehabilitation groups at baseline, indicating well-matched groups for initial cognitive status. Following the interventions, statistically significant differences persisted. The placebo group remained significantly lower in memory performance, while CRWPI and neurorehabilitation groups showed comparable outcomes. These findings align with the results of a recent systematic review by Gorenshtein et al where structured cognitive rehabilitation improved post-COVID-19 cognitive impairment.[30]

The 30-second chair stand test has been used to evaluate subject's functional performance. Administration of a CRWPI has been shown to enhance muscular performance during short-duration exertion tests, like the STST. A clinical study evaluating young adults who consumed the same amount of Immunocal used in our study (20 g/day) for the same period (3 months) reported significant increases in peak power and total work capacity during a 30-second exertion, compared to a placebo group that showed no improvements.[31] These benefits are attributed to increased intracellular glutathione levels—a key antioxidant that combats oxidative stress and delays muscle fatigue. Glutathione and its precursors can contribute to muscle recovery, maintenance of muscle mass, and better muscle performance. Although no studies specifically assess the impact of Immunocal on the STST, the evidence suggests that its use may enhance performance in such tests by improving muscular endurance and reducing fatigue. Our study results are similar to a recent study where subjects of similar age (44 years old) and long COVID were evaluated for persistency of symptoms and quality of life with the STST.[32] Nunez-Cortes and colleagues found that 79 participants scored an average of 11.5 repetitions, which correlated well with higher severity of symptoms and worse functional performance.[33]

This study has several strengths and limitations. This study compared two active treatments—Immunocal supplementation and neuropsychological rehabilitation—against a placebo control. The use of two distinct therapeutic strategies enhances the rigor of the findings and allows meaningful comparisons between biological and cognitive-behavioral interventions. The assessment of attention (including selective, sustained, and divided subdomains) and memory (working, verbal, visual, short- and long-

term) provided a comprehensive overview of cognitive functions typically impaired in post-COVID-19 cognitive impairment (PCCI). The use of objective statistical methods allowed robust statistical comparisons between groups and adjustment for multiple comparisons, increasing the reliability of detected differences. The interventions evaluated—dietary supplementation and structured rehabilitation—are accessible and scalable therapies with potential for broad application in post-COVID-19 care programs.

There are also several limitations. Each intervention group included only 40 participants, which may limit the power to detect more subtle effects, especially in subgroup analyses (e.g. age-specific effects or specific memory domains). The study was conducted in a single city**,** which narrowed the generalizability of the findings to broader populations. Regional, ethnic, and health care access differences may influence cognitive recovery trajectories. Despite the potential outcomes associated with CRWPI, some subjects in the Immunocal group may not fully adhere to the prescribed supplementation regimen, which could affect the size of the total effect of the intervention. Neuropsychological rehabilitation sessions were offered only twice a week instead of the three times a week initially planned. This lower intensity could have attenuated the potential benefits of the cognitive rehabilitation program.
Future research should aim to address the limitations identified in this study by conducting larger multicenter randomized trials with more diverse populations to improve the generalizability of the findings. Ensuring age-matched cohorts and implementing stricter monitoring of intervention adherence, particularly with respect to CRWPI intake, would help clarify the true efficacy of cysteine-rich whey protein supplementation. In addition, optimizing the intensity and frequency of neuropsychological rehabilitation protocols to reflect standard cognitive training regimens could produce more robust comparative data and explore the long-term durability of cognitive improvements with extended follow-up periods. In addition, research of biomarkers of oxidative stress and brain glutathione levels along with cognitive outcomes could provide mechanistic insights into the role of antioxidant therapies such as Immunocal in postviral cognitive rehabilitation.

Conclusion

This study demonstrates that both a cysteine-rich whey protein isolate (Immunocal™) and structured neuropsychological rehabilitation significantly improve attention and memory in patients with post-COVID-19 cognitive impairment (PCCI). In particular, Immunocal showed a specific advantage in improving divided attention, suggesting that antioxidant support may offer unique cognitive benefits through modulation of oxidative stress. These findings support the use of Immunocal as a viable, non-pharmacological intervention with efficacy comparable to established cognitive training protocols.

Beyond cognitive improvements, preliminary data from functional assessments suggest that Immunocal may also help reduce fatigue and improve muscle endurance, which could improve overall recovery in patients with long COVID. While more research is needed with larger and more diverse populations, these results highlight the potential of combining nutritional and neurocognitive rehabilitation interventions to address the multidimensional impact of PCCI.

Conflict of Interest Statement

This study was supported by Immunotec, Inc. AA, GD, JG, and RR are independent consultants to Immunotec. JG and HP serve on Immunotec's Scientific Advisory Board. The rest of the authors declare that they have no conflicts of interest. All findings, conclusions, or recommendations expressed in this manuscript are those of the authors and do not reflect the views of Immunotec.

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