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*Original Article*

# Effects of Vitamin B 12 Supplementation on Cognitive Function in Survivors of Hemorrhagic Stroke

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## ABSTRACT

Background: Hemorrhagic stroke often leads to significant cognitive deficits in survivors. Vitamin B12 plays a crucial role in neurological functions, suggesting its potential in cognitive recovery post-stroke. This retrospective cohort study explored the impact of Vitamin B12 supplementation on cognitive function in hemorrhagic stroke survivors, a subject that holds substantial importance in stroke rehabilitation and patient care.

Objective: The primary objective was to evaluate the effectiveness of Vitamin B12 supplementation in improving cognitive function, as measured by MMSE and MoCA scores, in adults who have recently survived a hemorrhagic stroke.

Methods: The study included 75 adults diagnosed with hemorrhagic stroke within the last six months. Participants were administered a daily oral dose of 1000 mcg of Vitamin B12 for three months. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) at the start and end of the supplementation period. Additionally, Vitamin B12 levels were measured at baseline and after three months to gauge the physiological uptake of the supplement.

Results: The study observed significant improvements in cognitive function, with the MMSE score increasing by an average of 2.2 ($p=0.0463$) and the MoCA score by 5.8 ($p=0.0410$). There was also a notable average increase of 400 pg/mL in Vitamin B12 levels ($p<0.05$). The supplementation was generally well-tolerated, with only 8% of participants reporting minor adverse effects, a rate not statistically significant ($p>0.05$).

Conclusion: The study provides preliminary evidence that Vitamin B12 supplementation may positively impact cognitive function in survivors of hemorrhagic stroke. However, due to the study's limitations, further extensive research is necessary to corroborate these findings and to deepen our understanding of the role of Vitamin B12 in post-stroke cognitive recovery.

Keywords: Cognitive Function, Hemorrhagic Stroke, Mini-Mental State Examination, Montreal Cognitive Assessment, Vitamin B12 Supplementation.

## INTRODUCTION

Hemorrhagic stroke, a critical neurological emergency, arises from sudden and catastrophic bleeding within or near brain tissues due to cerebral blood vessel rupture. Although it constitutes roughly 15% of all strokes, hemorrhagic strokes are notably more fatal and debilitating than ischemic strokes, leading to increased mortality and disability rates (1,2). These strokes primarily occur as intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), both capable of causing severe disability or death. ICH happens when blood seeps directly into brain tissue, delivering a double blow to the brain: the initial hemorrhage deprives brain tissue of oxygen and nutrients, causing mechanical damage to surrounding cells, while the secondary assault involves harmful byproducts of blood degradation and the body's inflammatory response (3-5).

Despite medical progress, the prognosis for hemorrhagic stroke remains dismally poor, with almost half of the patients succumbing within the first two days. Prompt diagnosis and treatment are essential for improving survival rates and reducing long-term disabilities. Treatment varies depending on the cause, location, and severity of the hemorrhage, ranging from conservative medical management to surgical interventions (6). Understanding hemorrhagic stroke involves unraveling various risk factors, neurovascular

structures, and the body's response to this medical emergency. Intensive research is crucial for enhancing prevention, refining diagnosis, improving treatment, and bolstering rehabilitation protocols, thereby improving patient outcomes (7-8).

Vitamin B12 (cobalamin) plays a pivotal role in brain and nervous system function, being essential for neurotransmitter synthesis, myelin formation, and methylation processes. Deficiency in vitamin B12 can lead to severe cognitive impairment, memory loss, and even neurodegenerative disorders. Recent investigations into the effects of vitamin B12 supplementation on cognitive function in hemorrhagic stroke survivors have sparked hope for their recovery and health improvement (9).

Post-stroke, survivors often endure severe cognitive and physical impairments, manifesting as difficulties with memory, attention, language, or problem-solving, significantly impacting their independence and comfort. While traditional rehabilitation therapy aids in regaining lost functions, the potential benefits of adjuvant therapies like vitamin supplementation are increasingly under exploration (10-11).

Stroke triggers a series of biochemical reactions leading to neuronal death and cognitive deficits, partially mediated by oxidative stress and inflammation. Vitamin B12, known for its antioxidant properties, may offer neuroprotective effects by combating oxidative stress, promoting neuronal repair, and facilitating neuroplasticity. Its role in neurotransmitter synthesis also suggests a direct impact on cognitive functions (12).

Multiple studies have established a correlation between low vitamin B12 levels and poor cognitive performance, supporting its potential as a supplement for stroke survivors. However, the relationship between vitamin B12 and cognitive function in stroke recovery warrants further investigation (13). Current research focuses on cognitive evaluations before and after supplementation to determine the impacts of vitamin B12 on cognitive function in survivors of hemorrhagic stroke, underscoring the need for continued scientific inquiry in this domain.

## MATERIAL AND METHODS

In this retrospective cohort study, conducted between May and August 2023, 75 patients who had presented at the outpatient department of a tertiary care center in Islamabad, Pakistan, were enrolled. The study targeted adults who had survived a hemorrhagic stroke within the previous six months, providing a relevant population for examining the effects of Vitamin B12 supplementation on cognitive recovery post-stroke.

During the intervention phase, participants, who had all experienced a hemorrhagic stroke within the last six months, were prescribed a daily oral dose of 1000 mcg of Vitamin B12 for a three-month period (14). Baseline characteristics, including cognitive function, were initially recorded at Day 0. Subsequently, their improvement in cognitive function was monitored over the course of the three months.

Criteria for inclusion in the study were adults aged 18 and above, who had received a confirmed diagnosis of hemorrhagic stroke within the past six months and were medically stable following the stroke. The ability to provide informed consent was also a prerequisite for participation. Exclusion criteria were multifaceted: individuals with a history of allergic reactions or intolerance to Vitamin B12 or related compounds were excluded. Those who had used or intended to use Vitamin B12 supplements during the study period, or who had been diagnosed with cognitive disorders prior to their stroke or severe psychiatric disorders impacting cognitive function evaluation, were also excluded. Participants with significant concurrent illnesses such as terminal cancer, uncontrolled diabetes, severe cardiovascular disease, or any condition that might interfere with adherence to study protocols or pose an additional risk, were not included. Pregnant or lactating women were excluded due to potential unknown effects of high doses of Vitamin B12 on fetuses or infants. Additionally, participants unable to complete cognitive tests due to severe visual, auditory, or severe language impairments were excluded, as were those unwilling or unable to comply with the study protocol.

Cognitive function assessment was a central component of the study. Participants were administered the Mini-Mental State Examination (MMSE) at baseline and then again after three months. This test evaluated five aspects of cognitive function: orientation, immediate and delayed recall, attention or concentration, language, and visuospatial skills, with memory constituting about 20% of the test's total weight (15). Cognitive impairment was defined as a score below 24 on the MMSE, measured at least twice after the intervention and three months following the qualifying stroke event. Cognitive decline was indicated by a decrease of three or more points on the MMSE compared to the baseline assessment conducted at least six months post-stroke and recorded at least twice during the follow-up period.

The primary outcome measure was the alteration in cognitive function scores after one year of supplementation, as measured by the MMSE and the Montreal Cognitive Assessment (MoCA). Blood assays were utilized to assess Vitamin B12 levels at baseline and at the end of three months. Secondary outcomes included changes in specific cognitive domains, such as memory, attention, and problem-solving, the optimal dosage of Vitamin B12, and any adverse effects or contraindications.

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In terms of data analysis, categorical and continuous variables were presented as figures, percentages, means, and standard deviations. Student's t-test was used to evaluate the differences in data, and Pearson's correlation coefficient assessed the correlation between changes in Vitamin B12 levels and cognitive function scores (SPSS 24.0).

The study received ethical approval from the Institutional Review Board and was conducted in accordance with the principles set out in the Helsinki Declaration.

## RESULTS

The table provided a comprehensive overview of Day 0 baseline characteristics of 75 participants. The participants' average age was approximately 59.85 years, 62.67% of the population was male, compared to 37.33% of female population. 76.0 percent of participants were diagnosed with hypertension, 30.66% had diabetes mellitus, and 70.66% were affected by hyperlipidemia. Moreover, 18.66% of the participants were smokers. MMSE and MoCA were used to evaluate their cognitive abilities, yielding mean scores of 26.3 (SD=2.3) and 22.9 (SD2.5), respectively. The participants' average basal Vitamin B12 concentration was 228 pg/ml with no statistically significant differences between these baseline characteristics of patients ($p>0.05$) (Table 1).

After three months, patients' mean MMSE score was 28.5. The odds ratio was 1.30 (with 95% CI of 1.10 to 1.55) and p-value was 0.9159, indicating that MMSE scores did not change significantly ($p>0.05$). In contrast, mean MoCA score was 28.7, odds ratio was 1.50 (with 95% CI: 1.20 to 1.88), and p-value was 0.8752, indicating that MoCA scores also did not change significantly ($p>0.05$). Observing change in MMSE and MoCA scores from the baseline to three months, however, revealed distinct outcomes. The MMSE score change was 2.2 and odd ratio was 1.20 (95% CI: 1.03 to 1.40). The p-value was 0.0463, indicating that the improvement in MMSE scores was statistically significant ($p<0.05$). Likewise, change in MoCA scores was 5.8, and the odds ratio was 1.40 (95% CI: 1.15 to 1.61). The p-value was 0.0410, indicating that MoCA scores improved statistically significantly after the 3-month intervention ($p<0.05$) (Table 2).

Following 3-month intervention, average Vitamin B12 level in participants was 850 pg/mL. The odds ratio was 4.0 (95% CI: 3.3-5.0) ($p<0.05$). This indicated that Vitamin B12 levels increased significantly after the intervention. Changes in Vitamin B12 levels between baseline and end of 03 months were also statistically significant ($p<0.05$). Vitamin B12 levels rose by an average of 400 pg/mL. The odds ratio for this change was a staggering 38 (95% CI: 30.2 to 47.8), and p-value was 0.0001, indicating statistically significant increase in Vitamin B12 levels over the 3-month period ($p<0.05$). Eight percent of participants reported experiencing adverse effects. The odds ratio for this event was 6.5 (95% CI: 0.8-54.3). However, associated p-value was 0.2269, indicating that the incidence of adverse effects in patients was not statistically significant ($p>0.05$). This indicated that the intervention was typically well-tolerated by the subjects (Table 3).

Table 1. Participants' baseline characteristics at Day 0

| S. No | Characteristics | Intervention group (n=75) | F-value | p-value |
|---|---|---|---|---|
| 1 | Age (Mean±SD) years | 59.85±10.31 | 0.0001 | 0.9942 |
| 2 | Gender n (%)<br>Male<br>Female | <br>47 (62.67)<br>28 (37.33) | <br>0.0133<br>0.0314 | <br>0.9082<br>0.8593 |
| 3 | Hypertension n(%) | 57 (76.0) | 0.0054 | 0.9413 |
| 4 | Diabetes mellitus n(%) | 23 (30.66) | 0.2662 | 0.6058 |
| 5 | Hyperlipidemia n(%) | 53 (70.66) | 0.0086 | 0.9260 |
| 6 | Smoking n(%) | 14 (18.66) | 0.0010 | 0.9745 |
| 7 | Baseline MMSE Score (Mean±SD) | 26.3±2.3 | 0.0077 | 0.9302 |
| 8 | Baseline MoCA Score (Mean±SD) | 22.9±2.5 | 0.0070 | 0.9335 |
| 9 | Baseline Vitamin B12 Level (Mean±SD) pg/ml | 228±56 | 0.0557 | 0.8134 |

Table 2. Comparing cognitive function scores after 3 months of intervention

| Outcome Measures | Intervention Group (Mean ± SD) | Odds ratio (95% CI) | p-value |
|---|---|---|---|
| MMSE Score (3 months) | 28.5 ± 2.8 | 1.30 (1.10 to 1.55) | 0.9159 |
| MoCA Score (3 months) | 28.7 ± 3.4 | 1.50 (1.20 to 1.88) | 0.8752 |
| Change in MMSE Score (Baseline to 3 months) | 2.2±0.5 | 1.20 (1.03 to 1.40) | 0.0463* |
| Change in MoCA Score (Baseline to 3 months) | 5.8±0.9 | 1.40 (1.15 to 1.70) | 0.0410* |

*Indicated that the value is significant at p<0.05; CI: Confidence interval

Table 3: Comparison of vitamin b12 levels and adverse effects after 3 months of intervention

| Outcome Measures | Intervention Group (Mean ± SD) | Odds ratio (95% CI) | p-value |
|---|---|---|---|
| Vitamin B12 Level (3 months) pg/mL | 850 ± 100 | 4.0 (3.3 to 5.0) | 0.0001* |
| Change in Vitamin B12 Level (Baseline to 3 months) pg/mL | +400 ± 60 | 38.0 (30.2 to 47.8) | 0.0001* |
| Adverse Effects (%) | 6 (8) | 6.5 (0.8 to 54.3) | 0.2269 |

*Indicated that the value is significant at p<0.05

## DISCUSSION

This retrospective cohort study delved into the effects of Vitamin B12 supplementation on cognitive function in survivors of hemorrhagic stroke. The results shed light on the potential benefits and challenges associated with this supplementation in such patients. Initially, the study population exhibited a diverse range of cognitive abilities, as reflected in their mean MMSE and MoCA scores. While there were no significant differences in these scores at the onset, a notable improvement was observed over the three-month supplementation period. Post-intervention, both MMSE and MoCA scores registered statistically significant gains, with MMSE scores increasing by 2.2 (p=0.0463) and MoCA scores by 5.8 (p=0.0410). This improvement suggests that Vitamin B12 supplementation can lead to measurable enhancements in cognitive functions.

Vitamin B12's crucial role in myelin synthesis and regeneration, as well as its involvement in homocysteine metabolism, may underpin its impact on cognitive recovery post-stroke. Elevated homocysteine levels have been associated with cognitive decline, underscoring the importance of Vitamin B12 in maintaining cognitive function (16). Post-intervention, a significant increase in Vitamin B12 levels was observed, with an average increase of 400 pg/mL, indicating effective absorption of the supplement. Notably, the supplementation was generally well-tolerated, as evidenced by the non-significant incidence of adverse effects reported by eight percent of the participants (p=0.2269).

The study aligns with existing literature indicating that B vitamins are pivotal in a metabolic network that integrates nutritional signals with processes such as biosynthesis, redox homeostasis, and epigenetics. Clinical data analytics suggest that Vitamin B12 deficiency is a risk factor for stroke and may influence its outcome. However, the exact mechanisms by which Vitamin B12 deficiency increases stroke risk and affects outcomes remain to be fully elucidated (17). Additionally, the administration of B vitamin supplements, particularly the combination of folic acid and vitamin B6, has been associated with a reduced risk of stroke, although the efficacy varies across different B vitamins and their combinations in stroke prevention (18).

The findings also resonate with a meta-analysis of randomized controlled trials assessing the impact of Vitamin B12 supplementation on cognitive function, depressive symptoms, and fatigue in patients without advanced neurological disorders. While Vitamin B12 is often used to improve cognitive function and alleviate depressive symptoms, evidence supporting its efficacy in these areas is still limited (19). Another investigation highlighted the association between Vitamin B12 deficiency and cognitive impairment. In dementia patients deficient in Vitamin B12, supplementation led to a significant increase in MMSE scores and a decrease in homocysteine levels, further supporting the link between Vitamin B12 levels and cognitive function (20).

Despite these promising findings, the study has limitations. The sample size was relatively small, and the study was limited to a single tertiary care center, which may affect the generalizability of the results. Additionally, the retrospective design limits the ability to establish causality. Future research should consider larger, multicenter, prospective studies to validate these findings and explore the long-term effects of Vitamin B12 supplementation on cognitive recovery post-stroke.

This study contributes to the growing body of evidence suggesting the potential benefits of Vitamin B12 supplementation in improving cognitive function in hemorrhagic stroke survivors. The significant increase in cognitive scores post-supplementation, coupled with the well-tolerated nature of the treatment, underscores the potential role of Vitamin B12 in stroke recovery protocols. However, further research is needed to fully understand the mechanisms at play and to confirm these findings in broader populations.

## CONCLUSION

Current study revealed that Vitamin B12 supplementation potentially enhances cognitive function in individuals recovering from hemorrhagic stroke. Over a period of three months, we noted statistically significant improvements in both MMSE and MoCA scores, alongside a marked increase in Vitamin B12 levels. Despite these encouraging findings, the limitations of current study, including its scope and design, highlight the need for further investigation. Future research, ideally encompassing comprehensive, prospective studies with larger participant groups and prolonged monitoring, is essential. Such studies would not only offer a more profound understanding of the impact of Vitamin B12 on cognitive recuperation post-stroke but also inform and refine rehabilitation strategies for these patients.

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