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Coenzyme Q10 as a promising supplement for traumatic brain injury: a randomized, double-blind, placebo-controlled study

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ABSTRACT

Purpose: In cases of traumatic brain injury (TBI), oxidative stress is recognized as a major factor in neuronal cell damage. This study was conducted to assess the effects of coenzyme Q10 (CoQ10), a powerful antioxidant, on oxidative stress biomarkers and clinical outcomes in patients with TBI.
Methods: In this randomized controlled trial, patients with moderate or severe TBI (n = 40) admitted to the ICU received either CoQ10 tablets at a dose of 600 mg/day or a placebo for three consecutive days within the first 72 hours post-injury. Serum malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity were assessed at baseline and again three days after the intervention. The Glasgow Coma Scale (GCS) was evaluated daily until day 5. The Glasgow Outcome Scale (GOS) was assessed at the time of discharge from both the ICU and hospital, and the Sequential Organ Failure Assessment (SOFA) score was determined on days 1, 3, and 5. Mortality rates and the length of ICU and hospital stays were also recorded.
Results: CoQ10 had no significant effect on MDA levels, SOD activity, or duration of hospitalization compared with the placebo ($P > 0.05$). However, GCS scores showed significant improvement from days 3 to 5 in the CoQ10 group compared with the placebo ($P = 0.017$, $P = 0.007$, and $P = 0.006$, respectively). In addition, GOS scores demonstrated significant improvement at discharge from both the ICU and hospital ($P = 0.005$ and $P < 0.001$, respectively). In the CoQ10 group, the SOFA score declined significantly by day 5 compared with the placebo group ($P = 0.023$). In-hospital mortality was also significantly lower in the CoQ10 group ($P = 0.002$).
Conclusion: Supplementation with CoQ10 in patients with TBI did not affect MDA levels, SOD activity, or length of hospital stay. However, it improved GCS, GOS, and SOFA scores and reduced in-hospital mortality. CoQ10 may serve as a promising adjunctive therapy in TBI patients, although further research is required (IRCT registration number: IRCT20231017059754N1).

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Introduction

Traumatic brain injury (TBI) is a leading contributor to mortality and persistent disability worldwide; affecting millions of people each year.[1] The pathophysiology of TBI is multifaceted, involving both primary and secondary injury mechanisms. The initial damage is caused by mechanical forces at the time of impact, whereas secondary injury evolves through a complex cascade of biochemical and molecular events, including elevated oxidative stress, mitochondrial dysfunction, and neuroinflammation. Oxidative stress-induced neuronal damage is considered one of the key mechanisms contributing to injury progression and poor neurological outcomes.[2] After TBI, oxidative stress primarily results from the excessive accumulation of reactive oxygen species (ROS). Although the brain contains endogenous antioxidant enzymes—such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase—these defense systems are often unable to adequately counteract the extensive oxidative damage associated with TBI.[1]

Mitochondria are critical organelles that regulate neuronal function and energy production. Mitochondrial dysfunction represents a central event in secondary brain injury, leading to increased ROS production, disrupted calcium homeostasis, and activation of apoptotic pathways.[3,4]

Given the central role of oxidative stress in TBI pathophysiology, the development of therapeutic strategies aimed at mitigating oxidative damage has become a major focus of research. Several antioxidant compounds have been proposed as potential neuroprotective agents for TBI, including N-acetyl-L-cysteine (NAC),[5] vitamins C and E,[6,7] and coenzyme Q10 (CoQ10),[8,9] among others. CoQ10, also known as ubiquinone, is a fat-soluble compound primarily localized within the inner mitochondrial membrane.[10] It serves as a crucial cofactor in cellular energy production by functioning as an electron carrier in the mitochondrial electron transport chain.[11] CoQ10 has attracted considerable attention due to its potent antioxidant properties and its role in mitochondrial bioenergetics.[12] This compound has demonstrated significant neuroprotective effects in several neurodegenerative disorders and brain injuries, including stroke and TBI.[13–15] Preclinical studies in TBI models have shown that CoQ10 supplementation can attenuate oxidative stress, preserve mitochondrial function, and promote neurological recovery.[5,8,15] Despite these promising preclinical findings, clinical evidence regarding the efficacy of CoQ10 in patients with TBI remains limited. Accordingly, this study was designed to evaluate the effects of CoQ10 supplementation on oxidative stress biomarkers as well as clinical outcomes in individuals with moderate or severe TBI.

Materials and Methods

This research was conducted as a randomized, double-blind, placebo-controlled clinical trial between December 2023 and June 2025. Ethical approval was obtained from the Ethics Committee of Semnan University of Medical Sciences (approval code: IR.SEMUMS.REC.1402.147). The study was also registered in the Iranian Registry of Clinical Trials under the registration number IRCT20231017059754N1. Written informed consent was obtained from the legal guardians of all participants before enrollment. Participants were recruited from patients hospitalized at Kowsar Hospital, affiliated with Semnan University of Medical Sciences, and Imam Hossein Hospital, affiliated with Shahid Beheshti University of Medical Sciences, in Iran.

Patients were considered eligible for inclusion if they satisfied all of the following conditions: age 16 years or older; a verified diagnosis of moderate or severe TBI, defined by a Glasgow Coma Scale (GCS) score ranging

from 3 to 12; admission to the intensive care unit (ICU) within 72 hours after injury; and adequate gastrointestinal function to allow for oral drug administration. Exclusion criteria included an ICU length of stay shorter than three days; a history of hypersensitivity or allergy to CoQ10; pregnancy or lactation; concurrent use of warfarin; presence of sepsis; advanced hepatic impairment (Child–Pugh class C); dialysis-dependent end-stage renal disease; or severe heart failure (NYHA class III–IV).

Random Assignment

After obtaining written informed consent, eligible participants were assigned to the treatment or placebo group using a block randomization method. Treatment allocation was blinded to the patients, medical staff, and the researcher responsible for evaluating study outcomes.

Treatment Protocol

The treatment group received 200 mg of CoQ10 (manufactured under license by Golden Life, Darman Yab Darou Co., Tehran, Iran) three times daily (600 mg/day) for three consecutive days, starting within 72 hours of TBI. A dose of 600 mg/day of CoQ10 was selected based on evidence that higher doses are generally safe and may be more effective in acute conditions,[16] and it was administered for 3 days to target the period of peak oxidative stress in the early phase of TBI. The placebo group received an identical placebo, prepared in the pharmaceutical laboratory of Mazandaran University of Medical Sciences, which was matched in appearance and dosage but contained no active CoQ10. Medication compliance was evaluated by tablet counts at each follow-up visit. Participants whose adherence to the treatment regimen was below 80% were excluded from the final analysis set.

Outcome Measures

The primary aim of this study was to evaluate the effects of CoQ10 on oxidative stress markers after three days of intervention, as well as its influence on neurological outcomes, in comparison with a placebo. Venous blood samples (5 mL) were collected from participants in both groups at baseline, prior to administration of the study medication or placebo, and again after completion of the treatment period. Samples were centrifuged at 3,000–4,000 rpm for 10–15 minutes, and the separated serum samples were aliquoted into labeled microtubes and stored at −80 °C pending analysis.

Oxidative stress was assessed by measuring serum levels of malondialdehyde (MDA), an indicator of lipid peroxidation, using a commercial assay kit (Kushan Zist Azma Co., Tehran, Iran). Additionally, the activity of SOD, an important antioxidant enzyme, was determined with a commercially available SOD assay kit from the same manufacturer, following the provided protocol.

Neurological status was assessed using the GCS, which was evaluated daily until day 5, and the Glasgow Outcome Scale (GOS), which was measured at the time of discharge from both the ICU and hospital. The GCS is a widely used scoring system ranging from 3 (deep coma) to 15 (fully conscious) and assesses the level of consciousness, while the GOS is a 5-point scale ranging from “death” to “full recovery” for evaluating neurological recovery.

Secondary outcomes included the Sequential Organ Failure Assessment (SOFA) score measured on days 1, 3, and 5, along with length of ICU and hospital stay, and overall mortality, to evaluate the clinical effects of CoQ10 on patient recovery.

A comprehensive checklist capturing all relevant demographic and clinical data was completed by a medical student. In addition, cognitive and functional evaluations were performed under the guidance of a trained and experienced nurse. Adverse events were actively monitored during the study through regular clinical assessments and patient follow-up.

Sample Size Calculation

In a systematic review and meta-analysis of randomized clinical trials, Dai et al[16] demonstrated that CoQ10 supplementation significantly lowered MDA levels by 0.77 μmol/L compared with placebo. Based on these findings, the required sample size was calculated assuming a 5% significance level (α), 80% power (1 - β), and a standard deviation (SD) of 0.87 for both groups. Sample size calculations showed that 20 participants per group would be adequate to detect a significant difference in biomarker levels. To account for an anticipated dropout rate of 20%, the sample size was adjusted to 24 participants per group.

Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Variables with a normal distribution are reported as mean ± SD, while non-normally distributed data are presented as the median with the first and third quartiles (Q1-Q3). Between-group differences in normally distributed variables were assessed using the independent-samples t-test, while within-group changes were examined with the paired-samples t-test. When variables were non-normally distributed or ordinal, between-group differences were assessed with the Mann–Whitney U test, and within-group analyses were performed using either the Wilcoxon signed-rank test or the Friedman test, as appropriate. Categorical variables are presented as counts and percentages, and differences between groups were analyzed using the chi-square test or Fisher's exact test, when indicated. Statistical significance was defined as a p-value < 0.05. All analyses were performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA).

Results and Discussion

Of the 145 patients with TBI assessed for eligibility, 49 were randomly assigned to the study groups (25 patients to the CoQ10 group and 24 patients to the placebo group) in a 1:1 ratio. A total of 20 patients in each group completed the study. The causes of study discontinuation are shown in Figure 1.

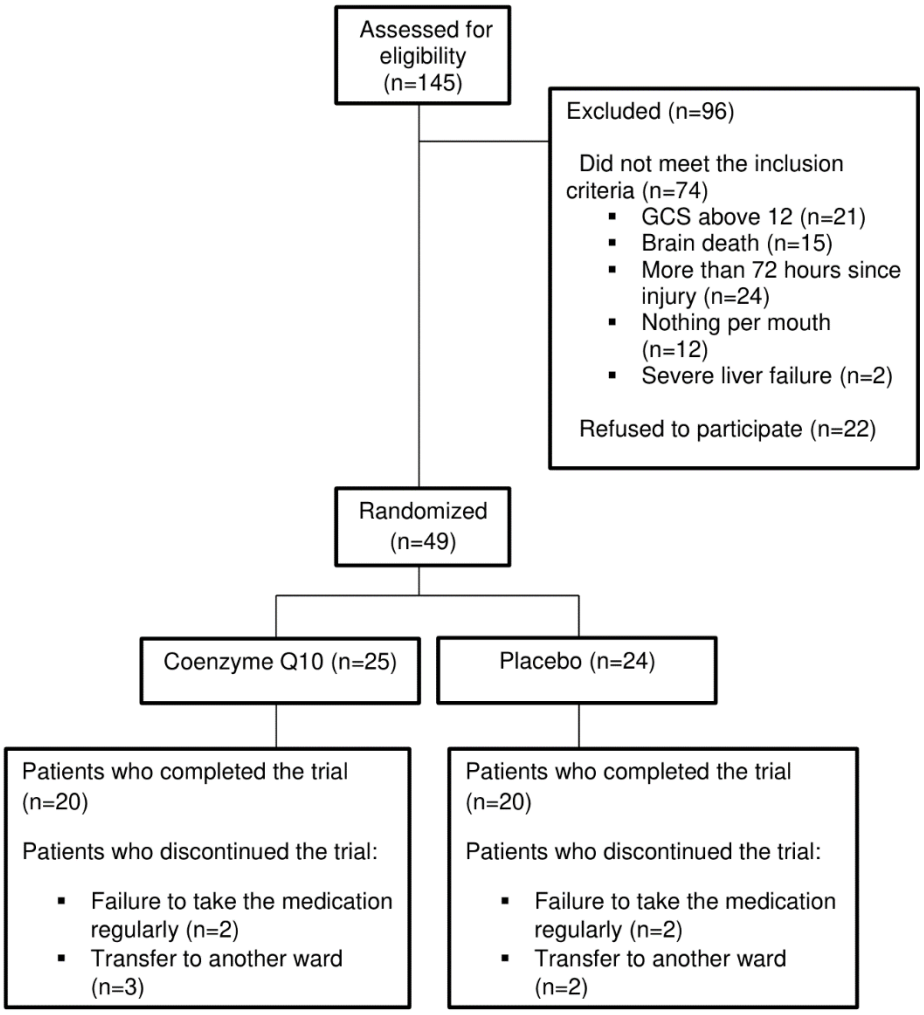

Figure 1. Progress through the stages of the trial

Table 1 summarizes the participants' baseline demographic and clinical characteristics. There were no significant differences between the two groups in age, gender, or baseline clinical parameters, including GCS and SOFA scores.

Table 1. Demographic and clinical characteristics of the study participants

Variable	Coenzyme Q10 (n=20)	Placebo (n=20)	*P* value*
Gender, n (%)			
Male	17 (85)	17 (85)	1.000
Female	3 (15)	3 (15)	
Age, years, mean ± SD	33.95 ± 10.85	34.69 ± 16.34	0.874
Type of TBI, n (%)			
Contusion	11 (55)	12 (60)	0.861
SDH	2 (10)	2 (10)	
TSAH	4 (20)	3 (15)	
EDH	1 (5)	0	
Diffuse axonal injury	1 (5)	1 (5)	
Skull base fracture	1 (5)	2 (10)	
Laboratory parameters (unit), mean ± SD/ median (Q1-Q3)			
Creatinine (mg/dL)	0.95 (0.80-1.10)	1.15 (0.92-1.30)	0.063
WBC (10^3/mm^3)	11.10 (6.62-15.35)	12.25 (8.95-17.97)	0.283
Hb (g/dL)	12 (10.37-13.10)	12.40 (10.50-13.10)	0.531
Platelets (10^3/mm^3)	208.03 ± 80.71	217.70 ± 80.82	0.711
Sodium (mEq/L)	140 (138.75-142)	139 (137.25-141.75)	0.393
Potassium (mEq/L)	3.81 ± 0.52	3.95 ± 0.56	0.432
Albumin (g/dL)	3.27 ± 0.66	3.04 ± 0.81	0.503
INR	1 (1-1.10)	1.10 (1-1.20)	0.063
GCS, median (Q1-Q3)	8 (6-10)	6.50 (4.25-10.25)	0.355
GCS, n (%)			
3-8	11 (55)	15 (75)	0.185
9-12	9 (45)	5 (25)	
MAP, mean ± SD	95.15 ± 16.00	91± 18.69	0.455
SOFA score, median (Q1-Q3)	7 (6-9)	8 (6.25-10.50)	0.369

TBI: Traumatic brain injury; SDH: Subdural hematoma; TSAH: Traumatic subarachnoid hemorrhage; EDH: Epidural hematoma; WBC: White blood cell; Hb: Hemoglobin; INR: International normalized ratio; GCS: Glasgow coma scale; MAP: Mean arterial pressure; SOFA: Sequential organ failure assessment.
*Independent-samples *t*-test and Mann-Whitney U test were used to compare parametric and nonparametric values, respectively. Chi-square/Fisher's exact test was performed to compare categorical values.

Table 2 illustrates the impact of the interventions on the measured biomarkers after three days. As shown, CoQ10 significantly increased SOD activity compared with baseline values (P = 0.013). However, this increase did not reach statistical significance in comparison with the placebo group. In addition, CoQ10 did not significantly affect MDA levels relative to placebo.

Table 2. The effects of interventions on the measured biomarkers in the study participants

Biomarker (Unit)	Time	Coenzyme Q10 (n=20)	Placebo (n=20)	*P* value (between groups)
MDA (µmol/L)	Baseline	18.06 ± 15.03	14.97 ± 12.42	0.701*
	End	18.93 ± 10.50	14.88 ± 9.84	0.322**
	P value	0.841***	0.985****	0.872**
SOD (U/mL)	Baseline	14.46 ± 5.47	15.63 ± 3.11	0.672**
	End	16.54 ± 3.65	16.43 ± 4.15	0.961**
	P value	0.013****	0.361****	0.273**

MDA: malondialdehyde; SOD: Superoxide dismutase.
The values are presented as mean ± standard deviation; *Mann-Whitney U test; **Independent-samples *t*-test; ***Wilcoxon signed-rank test (within-group comparison); ****Paired-samples *t*-test (within-group comparison).

Table 3 presents the impact of the interventions on the clinical scores. GCS scores demonstrated significant improvements from days 3 to 5 in the CoQ10 group compared with the placebo group (P = 0.017, P = 0.007, and P = 0.006, respectively). Moreover, GOS scores showed significant improvements at the time of discharge from

both the ICU and the hospital (P = 0.005 and P < 0.001, respectively). In the CoQ10 group, SOFA scores significantly declined by day 5 compared with the placebo group (P = 0.023).

Table 3. The effects of interventions on the clinical scores in the study participants

Clinical score	Time	Coenzyme Q10 (n=20)	Placebo (n=20)	*P* value*
GCS	Day 1	8 (6-10)	6.5 (4.25-10.25)	0.355
	Day 2	8 (7-11)	6.5 (5-9.75)	0.068
	Day 3	9 (8-12)	6.5 (4-10.50)	0.017
	Day 4	10 (8.25-14)	6 (4-11.75)	0.007
	Day 5	10.5 (9-15)	6 (3.25-13.50)	0.006
	P value**	<0.001	0.823	
SOFA	Day 1	7 (6-9)	8 (6.25-10.50)	0.369
	Day 3	7 (5.25-7.75)	8 (6-9)	0.201
	Day 5	6 (4.25-7)	8 (6.25-8.75)	0.023
	P value**	<0.001	0.252	
GOS	ICU discharge	4 (3-4)	3 (2-3)	0.005
	Hospital discharge	4.5 (3.25-5)	1 (1-3)	<0.001

GCS: Glasgow coma scale; SOFA: Sequential organ failure assessment; GOS: Glasgow outcome scale.
Data are presented as median (first and third quartiles); *Mann-Whitney U test (between-group comparison); **Friedman test (within-group comparison).

No significant differences were observed between the groups regarding the duration of ICU or total hospital stay. However, the in-hospital mortality rate was significantly lower in the CoQ10 group compared with the placebo group (10% vs. 55%; P = 0.002; Table 4).

Table 4. The effects of interventions on length of stay in ICU and hospital, and mortality in the study participants

Outcome	Coenzyme Q10 (n=20)	Placebo (n=20)	*P* value
ICU length of stay, median (Q1-Q3)	10 (4-17)	7 (5-13)	0.665*
Hospital length of stay, median (Q1-Q3)	13 (10-26)	12 (6-37)	0.624*
ICU Mortality, n (%)	2 (10)	3 (15)	1.000**
Hospital Mortality, n (%)	2 (10)	11 (55)	0.002**

*Mann-Whitney U test; **Chi-square/Fisher's exact test.

There were significant differences in the frequency of favorable outcomes (GOS > 3) between the CoQ10 and placebo groups at the time of discharge from both the ICU (60% vs. 10%; P = 0.001) and the hospital (75% vs. 10%; P < 0.001; Table 5). No adverse effects were reported in either the CoQ10 or placebo groups.

Table 5. Comparison of favorable status between the study groups at ICU and hospital discharge

Outcome	Coenzyme Q10 (n=20)	Placebo (n=20)	*P* value*
GOS>3 at ICU discharge, n (%)	12 (60)	2 (10)	0.001
GOS>3 at hospital discharge, n (%)	15 (75)	2 (10)	<0.001

GOS: Glasgow outcome scale.
*Chi-square test.

In this randomized, placebo-controlled study, adults with moderate or severe TBI were administered oral CoQ10 (600 mg/day), initiated within 72 hours of injury and continued for three days, in addition to standard treatment. CoQ10 was associated with improvements in key clinical outcomes, including neurological status, organ function, and patient survival; however, it did not significantly affect oxidative stress biomarkers or the length of hospital

stay. Previous studies have reported reduced CoQ10 levels in neurodegenerative diseases and acute brain disorders such as ischemic stroke and TBI. CoQ10 is a key component of the mitochondrial electron transport chain, and its deficiency can lead to impaired mitochondrial function, decreased energy production, elevated oxidative stress, and progression of neuronal injury.[13–15] Given the central role of mitochondria in neuronal survival and organ function homeostasis,[2] CoQ10 supplementation could be considered a targeted strategy to enhance mitochondrial function and mitigate oxidative neuronal damage in patients with TBI.

The observed improvement in organ function, as reflected by lower SOFA scores in the CoQ10 group, is consistent with the current understanding of the underlying pathophysiological mechanisms of TBI. Mitochondria are among the earliest structures affected in the acute phase of brain injury, and impaired electron transport chain function, accumulation of ROS, and reduced ATP production can predispose patients to multi-organ failure. Studies in septic[17] and critically ill trauma patients[18]—conditions in which mitochondrial dysfunction and oxidative stress play a central role in the injury process—have shown that stabilizing mitochondrial function with CoQ10 can help prevent the progression of organ failure. However, inconsistent findings have been reported in other studies, particularly those using lower doses or delayed initiation of therapy with CoQ10,[19,20] suggesting that early administration at an adequate dose may be critical for effectively modifying the course of injury.

In this study, CoQ10 administration was associated with improved patients' GCS scores, which is consistent with findings reported by Valizadeh-Hasanloei et al,[18] who demonstrated the antioxidant effects of CoQ10 in critically ill trauma patients. However, it is worth noting that, although a statistically significant improvement in the GCS was observed in the CoQ10 group in our study, the magnitude of change (median increase from 8 to 10.5 points) represents a relatively modest clinical effect. This degree of improvement may correspond to only limited neurological recovery, and its clinical relevance should be interpreted in the context of broader patient outcomes.

Beyond impairments in consciousness, TBI also affects patients' functional status, ultimately impacting their quality of life.[21] In the current study, the impact of CoQ10 supplementation on functional status was evaluated using the GOS. The substantial improvement in functional outcomes (GOS > 3) at hospital discharge in the CoQ10 group (75% versus 10% in the placebo group) underscores the potential for long-term benefits of CoQ10 supplementation. These results, which are consistent with research on other conditions characterized by oxidative stress and mitochondrial dysfunction—such as reported improvements in neurological and functional outcomes after acute ischemic stroke[22] and cardiac arrest[23]—suggest that CoQ10 may act by decreasing oxidative stress and neuroinflammation, supporting mitochondrial function, and reducing cell death.

Following TBI, ROS levels increase, and the balance between the antioxidant defense system and free radicals is disrupted, resulting in oxidative stress and progressive brain injury.[2] CoQ10 has been proposed as a potential neuroprotective agent in neurological disorders. Its protective effects against oxidative stress—through reductions in biomarkers of oxidative damage and preservation of antioxidant enzymes—have been demonstrated in several studies.[13] Valizade-Hasanloei et al[18] investigated the impact of CoQ10 supplementation on oxidative stress in mechanically ventilated trauma patients in the ICU. They found that administering 400 mg of CoQ10 daily for one week to patients with a GCS score of 7 or higher significantly reduced MDA levels and was associated with shorter ICU and hospital stays. In contrast, in our study, CoQ10 did not significantly alter MDA levels, SOD activity, or the length of ICU or hospital stay. Differences in study populations, baseline levels of consciousness, and the dose and duration of CoQ10 therapy may account for these observed discrepancies. It appears that a longer

duration of supplementation may be required to achieve detectable effects on oxidative stress biomarkers, as the antioxidant and mitochondrial effects of CoQ10 are likely to develop gradually over time and with sustained administration. Furthermore, length of stay is influenced by multiple factors, including local care protocols and clinical decisions made by the treatment team. It should be noted that during the intervention, patients did not receive additional antioxidant supplementation aside from CoQ10.

Consistent with our findings, Ramezani et al[22] reported that daily supplementation with 300 mg of CoQ10 for four weeks in patients with acute ischemic stroke did not significantly affect oxidative stress markers, including MDA and SOD. However, Mojaver et al[24] demonstrated that a higher daily dose of CoQ10 (600 mg), administered for the same 30-day period, resulted in a significant reduction in MDA levels alongside a significant elevation in SOD activity relative to the placebo group in patients with acute ischemic stroke. Considering the shared pathophysiological mechanisms at the subcellular level between ischemic stroke and TBI, it is plausible that higher doses and longer treatment durations may be required to achieve more pronounced effects on oxidative stress in TBI.

Similarly, not all clinical trials have demonstrated positive effects of CoQ10 across all evaluated endpoints. Soltani et al[19] assessed CoQ10 in patients with early-phase sepsis. In that trial, CoQ10 administered at a dose of 100 mg twice daily for seven days as an adjunct to standard care in ICU patients with sepsis did not significantly affect GPx levels, SOFA scores, or ICU length of stay; however, it did reduce MDA, TNF-α, and in-hospital mortality. A cross-sectional study reported lower serum CoQ10 levels in patients admitted to the ICU.[25] Moreover, CoQ10 supplementation in trauma patients during their ICU stay was found to increase plasma CoQ10 levels.[18] One of the key findings of our study is the significant decrease in in-hospital mortality observed in the CoQ10 group. Although mortality is a complex outcome influenced by multiple factors, the convergence of our results with similar observations in septic patients[19] and individuals with chronic heart failure[26] suggests that CoQ10 may reduce mortality by exerting protective effects through modulation of systemic inflammation, impaired cellular energy metabolism, and organ dysfunction.

Human studies to date indicate that CoQ10 supplementation is generally well tolerated[16] and appears safe even at high doses.[27] Consistent with these reports, no treatment-related adverse events attributable to CoQ10 supplementation were observed in our study.

To our knowledge, this represents the first randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of CoQ10 on both clinical and biochemical outcomes in TBI patients. The study has several important strengths. The intervention was initiated very early after injury, when secondary injury pathways are most susceptible to modulation. Repeated assessments of organ function enabled evaluation of the dynamic trajectory of patient status, rather than reliance on a single time point. In addition, validated, patient-centered outcome measures, including the GCS, GOS, and SOFA, were used to assess treatment effects.

The principal limitations of the present study include the small sample size and the limited intervention period, which may have been insufficient to produce significant changes in oxidative stress biomarkers. Although the study met the a priori minimum sample size, the final sample (n = 20 per group) may have limited statistical power to detect smaller treatment effects, so larger future studies are needed to confirm the findings.

Another limitation of this study is the lack of baseline CoQ10 measurements, which may have influenced the observed treatment response and limited the ability to assess individual deficiency or identify subgroups that benefit most; future studies should include baseline CoQ10 level assessments. Moreover, potential confounders such as rehabilitation interventions, which may influence clinical outcomes, were not evaluated or controlled for.

Conclusion

In conclusion, in patients with moderate or severe TBI, oral CoQ10 administered at a dose of 600 mg for 3 days and initiated within 72 hours after injury did not significantly affect MDA levels, SOD activity, or length of stay, but was associated with improvements in the GCS, GOS, and SOFA scores, as well as a reduction in mortality. Taken together, these findings provide supporting evidence for a potential role of CoQ10 as an adjunctive therapy in the management of patients with TBI. Nonetheless, additional trials using higher doses of CoQ10, larger participant numbers, and extended treatment and follow-up periods are needed to more comprehensively evaluate its effects in this patient population.

Authors' contribution:

Conceptualization: BH
Data curation: MS, BH
Formal analysis: BH
Investigation: MS, KP, EH, SS
Methodology: BH, BB
Project administration: BH
Supervision: BH, BB
Validation: BH, MS
Writing–original draft: BH, MS
Writing–review & editing: BH

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Competing interests: None to be declared.

Data availability statement: The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical approval: This study was approved by the Ethics Committee of Semnan University of Medical Sciences with the code IR.SEMUMS.REC.1402.147.

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