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Original Article

Effects of combined atorvastatin calcium and hyperbaric oxygen therapy on postoperative recovery in patients with traumatic brain injury

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Abstract: Objective: To evaluate the combined effect of atorvastatin calcium and hyperbaric oxygen therapy (HBOT) on postoperative functional recovery in patients with traumatic brain injury (TBI). Methods: We retrospectively analyzed 179 TBI patients who underwent surgery at the First Affiliated Hospital of Chongqing Medical College from March 2021 to October 2024. Patients were divided into two groups. An atorvastatin group (n=87), receiving standard neurosurgical care plus atorvastatin, and a combination group (n=92), receiving atorvastatin and HBOT. Both groups followed a 14-day treatment protocol. Outcomes, including cognitive function, limb performance, quality of life, neurological status, cerebral hemodynamics, and serum biomarkers, were assessed at 7 and 14 days post-treatment. Results: The combination group showed significantly better cognitive scores, higher Fugl-Meyer Assessment scores for both limbs, and improved Quality of Life after Brain Injury scores (all $P<0.05$). They also demonstrated greater reductions in National Institutes of Health Stroke Scale scores and increases in Glasgow Coma Scale scores (both $P<0.001$). Brain injury markers were lower in this group ($P<0.001$), with neuron-specific enolase differing only on Day 7. Hemodynamically, the combination group had higher flow velocity and peak systolic velocity, and lower pulsatility index (all $P<0.05$). Conclusion: Combined atorvastatin and HBOT therapy significantly enhances cognitive and limb recovery, improves neurological outcome, regulates cerebral hemodynamics, and reduces brain tissue damage. Thus, it shows substantial value in early TBI rehabilitation.

Keywords: Traumatic brain injury, atorvastatin calcium, hyperbaric oxygen therapy, cognitive function, cerebral hemodynamics

Introduction

Traumatic brain injury (TBI) is one of the most common and severe emergencies in neurosurgical practice, typically caused by traffic accidents, falls, or blunt trauma. It poses a high risk of long-term disability and mortality [1]. Studies show that TBI remains a leading cause of disability globally, with over 10 million cases reported in 2021, especially among young and middle-aged men [2]. The complex pathophysiology of TBI involves not only immediate mechanical damage but also progressive secondary injuries, including cerebral hypoperfusion, programmed cell death, neuroinflammation, oxidative stress, and blood-brain barrier dysfunction, all contributing to long-term cognitive deficits, motor impairment, and reduced community reintegration [3].

Traditional neurosurgical interventions primarily focus on reducing intracranial pressure, evacuating hematomas, and relieving brain tissue compression. However, postoperative recovery of neurological and cognitive functions requires multifactorial synergistic interventions [4]. Current standard of care for TBI emphasizes stabilization, neurotrophic support, and homeostasis maintenance, but these measures offer limited benefits in restoring multidimensional function [5]. Consequently, there is a lack of standardized protocols for comprehen-

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sive post-surgery rehabilitation, making it essential to identify effective adjunctive therapies with broader and more sustained benefit in neurorehabilitation.

Atorvastatin calcium, a widely used statin and selective 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, is primarily used for lipid-lowering purposes [6]. Emerging evidence suggests that atorvastatin has neuroprotective properties beyond lipid reduction, modulating recovery mechanisms such as neurotrophic factor regulation and cytokine suppression [7-9]. Additionally, brain tissue retains considerable plasticity after TBI, and some rehabilitation strategies can promote early recovery of brain function [10]. Hyperbaric oxygen therapy (HBOT) has emerged as a widely accepted adjunctive therapy, enhancing neural cell proliferation, increasing cerebral oxygenation, improving perfusion in ischemic areas, and supporting restoration of neural function [11]. HBOT has also been shown to inhibit platelet aggregation, facilitate endothelial repair, and provide metabolic support to damaged neurons [12, 13].

Although both atorvastatin and HBOT have demonstrated potential in TBI treatment, few studies have explored their combined effects. The lack of empirical data on their synergistic mechanisms limits their integrated application. Therefore, this study aimed to investigate systematically the combined effects of atorvastatin calcium and HBOT on postoperative functional recovery in TBI patients, with the goal of establishing a practical and evidence-based therapeutic framework for individualized neurorehabilitation.

Materials and methods

Study design and participants

This retrospective study used clinical records from the First Affiliated Hospital of Chongqing Medical College, spanning March 2021 to October 2024. Patient data were anonymized following privacy regulations, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical College.

Patients were stratified into two treatment groups: the Atorvastatin group (n=87), received atorvastatin monotherapy, and the Combination group (n=92), received atorvastatin calcium plus adjunctive HBOT. Inclusion criteria included adults aged 18 to 70 years with confirmed TBI on cranial CT [14], a Glasgow Coma Scale (GCS) score of 3-8 on admission, and a postoperative GCS >8 within 24 hours. Exclusion criteria included severe hepatic/renal insufficiency, prior neurodegenerative diseases or TBI, psychotropic/immunosuppressive drug use, incomplete follow-up, and contraindications to HBOT.

Treatment protocol

All patients enrolled in this study underwent one of the following neurosurgical procedures before treatment initiation: decompressive craniectomy, burr hole drainage, or external ventricular drainage. Decompressive craniectomy was performed for cases with diffuse cerebral edema or medically refractory intracranial hypertension. This procedure involved the removal of the frontotemporoparietal bone flap or a craniotomy, adjusted according to the lesion location, to relieve intracranial pressure [15]. Burr hole drainage was performed in patients with chronic subdural hematoma or select cases of epidural hematoma, using a cranial burr hole to establish a closed drainage system for hematoma evacuation [16]. External ventricular drainage was used in patients with intraventricular hemorrhage or hydrocephalus, where a catheter was inserted into the frontal horn of the lateral ventricle through a burr hole placed at Kocher's point to facilitate cerebrospinal fluid diversion [17]. All surgeries were performed by experienced neurosurgeons following standardized institutional protocols. Subsequent therapeutic interventions were initiated only after patients exhibited stable vital signs and intracranial pressure for at least 24 hours postoperatively. Baseline clinical evaluations were performed prior to therapeutic intervention.

All patients received standard nursing interventions, including maintaining a 30° head elevation, continuous intracranial pressure monitoring, strict infection prevention, fluid and electrolyte balance management, and nutritional and psychological support.

Patients in the atorvastatin group received 20 mg of atorvastatin calcium (H20133127; Lepu

Pharmaceutical Technology Co., Ltd.) daily for 14 days, while the Combination group also received HBOT. HBOT was conducted at 1650 mmHg, with each session consisting of 20 minutes of pressurization, 30 minutes of oxygen inhalation, a 10-minute break, another 30 minutes of oxygenation, and a 30-minute decompression phase. Sessions were conducted daily for 14 days.

Outcome measures

Clinical indicators were assessed at baseline, 7 days, and 14 days post-treatment. Cognitive performance was measured using the Lowenstein Occupational Therapy Cognitive Assessment (LOTCA) [18], Mini-Mental State Examination (MMSE) [19], and Montreal Cognitive Assessment (MoCA) [20], with higher scores indicating better cognitive functioning. Quality of life was measured using the Quality of Life after Brain Injury (QOLIBRI) scale [21]. Higher QOLIBRI scores reflect better perceived quality of life.

Neurological condition was measured by the National Institutes of Health Stroke Scale (NIHSS) and GCS scores. Limb function recovery was measured with the Fugl-Meyer Assessment (FMA) for both upper and lower limbs [22]. Cerebral hemodynamics were monitored by transcranial Doppler ultrasonography, assessing mean flow velocity (Vm), peak systolic velocity (Vs), and pulsatility index (PI) in the middle cerebral artery.Peripheral venous blood (5 mL) was drawn in the early morning. Serum was isolated by centrifugation at 3000 rpm for 10 min at 4°C and stored at -80°C for batch testing. The neuronal injury markers including S100β, glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), and neuron-specific enolase (NSE), were measured using ELISA kits (Elabscience, Wuhan, China). Inflammatory and lipid metabolism indicators such as high-sensitivity C-reactive protein (hs-CRP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and total cholesterol (TC) were assessed using the Beckman Coulter AU2700 automated chemistry analyzer (Tokyo, Japan).

Statistical analysis

Data analysis was performed using SPSS 22.0. Continuous variables were tested for normality with the Kolmogorov-Smirnov test and expressed as mean ± standard deviation ($\bar{x} \pm s$), compared using t-tests. Categorical variables were summarized as counts and percentages [n (%)] and analyzed using the chi-square (χ^2) test. A *P*-value of <0.05 was considered significant. Graphical representations were created using GraphPad Prism.

Results

Comparison of general characteristics

Baseline demographic and clinical characteristics are summarized in **Table 1**. There were no significant differences between the two groups in sex distribution, age, BMI, cause of injury (traffic accidents, falls, or blunt trauma), or type of surgical intervention (decompressive craniectomy, burr hole drainage, or external ventricular drainage) (all P>0.05). Prevalence of hypertension (P=0.369) and diabetes (P=0.058) was also comparable, ensuring good baseline balance for subsequent comparisons.

Comparison of clinical findings

The combination group demonstrated significantly lower subdural effusion volume, shorter time to normalization of intracranial pressure, and a reduced length of hospital stay compared to the Atorvastatin group (all P<0.01), suggesting enhanced clinical recovery (**Table 2**).

Comparison of LOTCA scores

LOTCA scores in the combination group were consistently higher across all domains (all P<0.05). While no significant difference was observed in spatial perception on day 7 post-treatment, a significant improvement emerged by day 14 (P=0.002) (**Table 3**).

Comparison of MMSE and MoCA scores

Post-treatment assessment demonstrated that the combination group scored significantly higher than the atorvastatin group on both the MMSE and MoCA (both P<0.05). These differences became more pronounced by Day 14 (MMSE: 24.69±2.35 vs. 26.85±1.85; MoCA: 24.07±2.85 vs. 26.38±2.15 (both P<0.05)), indicating that combination therapy more effectively facilitated cognitive recovery after TBI (**Table 4**).

Table 1. Comparison of general characteristics

	Atorvastatin group (n=87)	Combination group (n=92)	t/χ^2	*P*
Sex			0.025	0.874
Male	51 (58.6)	55 (59.8)		
Female	36 (41.4)	37 (40.2)		
Age	47.62±8.10	49.39±8.24	1.449	0.149
Cause of injury			0.492	0.782
Traffic accident	52 (59.8)	57 (62.0)		
Fall from height	28 (32.2)	30 (32.6)		
Blunt trauma	7 (8.0)	5 (5.4)		
BMI (kg/m^2)	23.37±2.38	22.79±2.24	1.655	0.100
Surgical approach			0.256	0.880
Decompressive craniectomy	35 (40.2)	36 (39.1)		
Burr hole drainage	33 (37.9)	33 (35.9)		
External ventricular drainage	19 (21.8)	23 (25.0)		
Hypertension			0.807	0.369
Yes	28 (32.2)	24 (26.1)		
No	59 (67.8)	68 (73.9)		
Diabetes mellitus			3.600	0.058
Yes	9 (10.3)	19 (20.7)		
No	78 (89.7)	73 (79.3)		

Table 2. Comparison of clinical data

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
Subdural effusion volume (mL)	4.21±1.63	3.58±1.35	2.822	0.005
Days to normalization of intracranial pressure	13.28±2.36	11.30±2.64	5.258	<0.001
Length of hospital stay (d)	30.47±6.12	26.55±6.31	4.213	<0.001

Table 3. Comparison of LOTCA scores

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
Visual perception				
Pre-treatment	7.85±1.69	8.02±1.25	0.768	0.444
Day 7	8.82±2.04	9.47±1.93	2.196	0.029
Day 14	10.53±2.16	12.27±2.05	5.531	<0.001
Thinking operations				
Pre-treatment	13.25±2.04	13.79±2.17	1.713	0.088
Day 7	15.91±2.53	16.62±2.05	2.070	0.040
Day 14	18.44±3.35	21.11±3.05	6.193	<0.001
Praxia				
Pre-treatment	4.81±1.15	5.05±1.63	1.132	0.259
Day 7	5.49±1.52	6.01±1.54	2.257	0.025
Day 14	7.94±1.61	9.23±1.41	5.699	<0.001
Visuomotor organization				
Pre-treatment	11.52±1.93	12.01±2.27	1.552	0.123
Day 7	13.26±2.80	15.01±2.64	4.293	<0.001
Day 14	16.51±2.93	19.53±2.80	7.065	<0.001

Orientation				
Pre-treatment	3.62±1.34	3.95±1.12	1.791	0.075
Day 7	4.25±1.17	4.64±1.05	2.332	0.021
Day 14	5.69±1.11	6.84±0.91	7.583	<0.001
Spatial perception				
Pre-treatment	5.68±1.25	5.42±1.64	1.188	0.236
Day 7	6.28±1.56	6.73±1.74	1.830	0.069
Day 14	8.35±1.47	9.07±1.58	3.153	0.002

LOTCA: Lowenstein Occupational Therapy Cognitive Assessment; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

Table 4. Comparison of MMSE and MoCA scores

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
MMSE				
Pre-treatment	19.35±2.16	19.74±1.90	1.284	0.201
Day 7	21.53±1.85	22.12±1.53	2.334	0.021
Day 14	24.69±2.35	26.85±1.85	6.846	<0.001
MoCA				
Pre-treatment	19.22±2.84	18.87±2.74	0.839	0.403
Day 7	20.16±3.24	21.99±2.92	3.970	<0.001
Day 14	24.07±2.85	26.38±2.15	6.146	<0.001

MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

Comparison of neurological function and brain injury biomarkers

The combination group outperformed the atorvastatin group in NIHSS, GCS, S100β, GFAP, and MBP, with significant differences observed on Day 14 (all P<0.001). A difference in NSE was noted on Day 7 (P=0.039), but this disappeared by Day 14 (P>0.05). Overall, these results indicate that combination therapy improved neurological function and reduced brain tissue damage (**Table 5**).

Comparison of FMA scores

FMA scores showed significantly greater motor recovery in both upper and lower limbs in the combination group compared to the atorvastatin group. Significant differences were observed on both Day 7 and Day 14 (both P<0.01), suggesting that combination therapy enhanced early-stage motor rehabilitation (**Table 6**).

Comparison of inflammatory and lipid metabolism indicators

By Day 14, the combination group exhibited significantly lower levels of hs-CRP, LDL-C, TG, and TC (all P<0.05), while HDL-C levels were significantly higher (P<0.001) compared to the atorvastatin group (**Table 7**). These findings suggest that combination therapy was more effective in reducing systemic inflammation and optimizing lipid metabolism.

Comparison of cerebral hemodynamic indices

On both Day 7 and Day 14, patients in the combination group exhibited significantly higher Vm and Vs values compared to those in the atorvastatin group, indicating enhanced cerebral perfusion. Additionally, PI values decreased significantly in the combination group at both time points, suggesting improved cerebrovascular resistance and more favorable cerebral hemodynamic patterns (**Figures 1**, **2**).

Comparison of QOLIBRI scores

As shown in **Table 8**, the combination group achieved significantly higher scores across all six dimensions of the QOLIBRI compared to the atorvastatin group. These findings suggest that combination therapy may significantly enhanced perceived quality of life and overall patient satisfaction during early rehabilitation following traumatic brain injury.

Table 5. Comparison of neurological function and brain injury biomarkers

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
NIHSS				
Pre-treatment	10.87±1.10	11.12±1.24	1.424	0.156
Day 7	9.41±2.14	8.68±2.08	2.312	0.022
Day 14	6.20±1.93	4.30±1.54	7.259	<0.001
GCS				
Pre-treatment	8.46±0.87	8.29±0.57	1.555	0.122
Day 7	8.87±0.52	9.03±0.48	2.120	0.035
Day 14	12.70±2.15	14.15±0.98	5.855	<0.001
S100β (μg/L)				
Pre-treatment	1.30±0.33	1.35±0.41	0.896	0.372
Day 7	1.25±0.28	1.10±0.25	3.857	<0.001
Day 14	1.02±0.35	0.72±0.22	7.253	<0.001
GFAP (ng/L)				
Pre-treatment	551.84±10.26	554.41±11.34	1.587	0.114
Day 7	521.74±14.84	539.33±17.96	7.121	<0.001
Day 14	287.45±9.18	174.27±7.67	89.708	<0.001
MBP (μg/L)				
Pre-treatment	1.62±0.26	1.60±0.34	0.440	0.660
Day 7	1.48±0.32	1.20±0.29	5.971	<0.001
Day 14	1.15±0.28	0.88±0.23	6.976	<0.001
NSE (μg/L)				
Pre-treatment	21.93±3.75	22.84±2.79	1.849	0.066
Day 7	18.26±2.28	17.53±2.40	2.084	0.039
Day 14	15.36±2.58	15.21±1.47	0.449	0.654

NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, GFAP: glial fibrillary acidic protein, MBP: myelin basic protein, NSE: neuron-specific enolase; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

Table 6. Comparison of FMA scores

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
Upper extremity				
Pre-treatment	26.45±5.84	27.38±5.32	1.115	0.267
Day 7	30.68±6.86	33.87±6.14	3.283	0.001
Day 14	41.32±7.20	49.55±6.95	7.785	<0.001
Lower extremity				
Pre-treatment	14.63±4.87	15.84±4.15	1.792	0.075
Day 7	17.17±4.53	19.47±4.12	3.550	<0.001
Day 14	24.21±4.34	28.92±3.32	8.188	<0.001

FMA: Fugl-Meyer Assessment; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

Table 7. Comparison of Inflammatory and lipid metabolism indicators

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
hs-CRP (mg/L)				
Pre-treatment	5.12±0.70	5.05±0.62	0.709	0.479
Day 7	4.31±0.84	4.23±0.79	0.654	0.514
Day 14	2.98±0.64	2.62±0.51	4.157	<0.001

LDL-C (mmol/L)				
Pre-treatment	3.68±0.74	3.59±0.81	0.775	0.440
Day 7	3.29±0.61	3.06±0.58	2.587	0.011
Day 14	2.24±0.54	1.65±0.46	7.962	<0.001
HDL-C (mmol/L)				
Pre-treatment	1.12±0.36	1.15±0.25	0.651	0.516
Day 7	1.19±0.34	1.30±0.36	2.118	0.036
Day 14	1.42±0.18	1.68±0.23	8.912	<0.001
TG (mmol/L)				
Pre-treatment	2.31±0.67	2.25±0.61	0.627	0.531
Day 7	2.16±0.73	1.89±0.75	2.440	0.016
Day 14	1.89±0.47	1.63±0.42	3.915	<0.001
TC (mmol/L)				
Pre-treatment	5.74±0.58	5.65±0.49	1.124	0.263
Day 7	5.38±0.64	5.21±0.48	2.132	0.034
Day 14	4.30±0.35	4.18±0.31	2.429	0.016

hs-CRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides, TC: total cholesterol; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

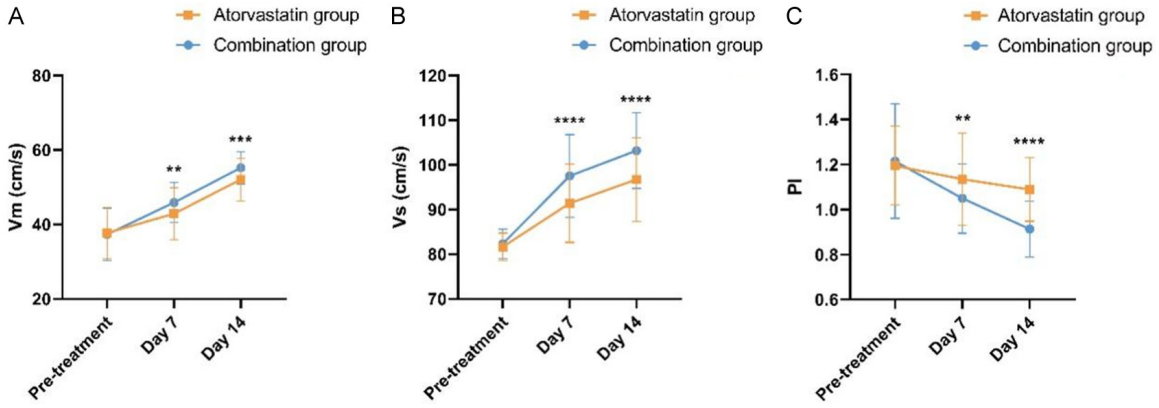

Figure 1. Comparison of cerebral hemodynamic indices. Vm: mean flow velocity, Vs: peak systolic velocity, PI: pulsatility index; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively; ***P*<0.01, ****P*<0.001, *****P*<0.0001.

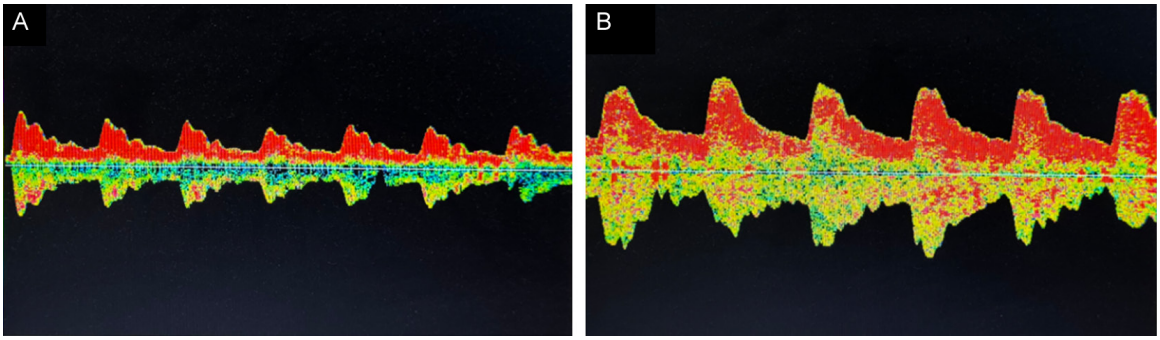

Figure 2. Representative TCD waveforms 14 days after treatment. A. A 56-year-old male patient from the Atorvastatin group showing Vs of 56.5 cm/s, Vm of 33.6 cm/s, and PI of 1.25. B. A 60-year-old male patient from the Combination group showing Vs of 76.6 cm/s, Vm of 43.8 cm/s, and PI of 1.13. TCD: transcranial Doppler, Vm: mean flow velocity, Vs: peak systolic velocity, PI: pulsatility index.

Table 8. Comparison of QOLIBRI scores in atorvastatin vs. combination groups

	Atorvastatin group (n=87)	Combination group (n=92)	*t*	*P*
Cognition				
Pre-treatment	52.16±7.58	53.98±8.62	1.497	0.136
Day 7	58.34±9.12	63.12±8.64	3.597	<0.001
Day 14	66.40±8.73	72.91±7.58	5.338	<0.001
Self-concept				
Pre-treatment	54.83±8.16	56.25±8.27	1.156	0.249
Day 7	60.11±8.87	65.84±7.92	4.559	<0.001
Day 14	68.52±7.95	75.60±7.11	6.289	<0.001
Emotions				
Pre-treatment	48.09±7.84	49.77±7.55	1.460	0.146
Day 7	58.89±9.01	62.33±11.35	3.539	<0.001
Day 14	65.26±8.19	72.45±5.44	6.942	<0.001
Physical function				
Pre-treatment	40.43±8.97	42.12±9.06	1.253	0.212
Day 7	55.75±10.13	60.02±9.77	2.873	0.005
Day 14	63.08±9.31	70.82±8.94	5.670	<0.001
Social relationships				
Pre-treatment	55.25±6.38	56.92±7.29	1.627	0.106
Day 7	60.41±7.96	64.77±11.40	2.949	0.004
Day 14	67.51±5.84	73.38±6.90	6.130	<0.001
Overall satisfaction				
Pre-treatment	52.79±9.65	53.64±10.74	0.556	0.579
Day 7	61.20±8.73	66.35±9.16	3.848	<0.001
Day 14	74.13±9.05	77.05±7.32	2.387	0.018

QOLIBRI: Quality of Life after Brain Injury; Day 7 and Day 14 refer to the 7th and 14th days after treatment initiation, respectively.

Discussion

Traumatic brain injury (TBI) remains a major global public health issue. The mechanical impact from trauma induces widespread cerebral contusions and hemorrhagic lesions, leading to secondary complications such as cerebral edema, elevated intracranial pressure, and compromised cerebral perfusion [23]. Current research highlights the complex pathologic and physiologic mechanisms of TBI, which include abnormal energy metabolism, calcium overload, microcirculation disorders, and inflammatory response. These mechanisms are closely linked to various cytokines and signaling pathways [24]. Despite early interventions such as surgical decompression, pharmacologic therapy, and mild hypothermia, many survivors continue to experience persistent impairments in consciousness, motor function, speech, and cognition, severely affecting their physical, psychological, and overall quality of life [25].

Recent studies suggest that with timely external interventions and appropriate neural stimulation, the brain's ability to reorganize and repair itself can be significantly supported [26]. Synnot et al. reported that early and targeted interventions can reduce skeletal muscle spasticity, indirectly improving motor recovery and reducing complications like muscle contractures [27]. On another front, extensive preclinical studies have demonstrated that HBOT, by elevating arterial oxygen tension, can suppress lipid peroxidation and excessive reactive oxygen species generation, reduce excitatory neurotransmitter release and neuronal apoptosis, and attenuate central neuroinflammation [28, 29]. These mechanisms contribute to the preservation of blood-brain barrier integrity, promotion of axonal regeneration, and enhancement of neural repair. Clinical findings support these mechanisms. For instance, Ablin et al. reported that HBOT improved pain and cognitive-related symptoms more effectively than pharmacologi-

cal interventions in post-TBI fibromyalgia patients, suggesting that HBOT benefits extend beyond motor recovery to broader neurological function [30]. Ren et al. also found that HBOT reduced oxidative stress markers and increased nerve growth factor expression in craniocerebral injury patients, enhancing cognitive and motor outcomes [31].

Our study aligns with these reports: patients receiving combined drug therapy and HBOT showed superior neurological and cognitive improvements compared to the control group, reinforcing HBOT's clinical utility [32, 33]. Notably, spatial perception showed no significant improvement at Day 7, but improved markedly by Day 14, suggesting a delayed recovery trajectory that may require a longer therapeutic duration.

S-100β and GFAP, two astrocyte-derived proteins, play critical roles in neuronal repair and structural maintenance. Under normal conditions, their serum levels remain low, but they rapidly enter circulation following brain damage. Elevated S-100β levels reflect altered neuronal membrane permeability, while GFAP increases correlate with glial cell injury severity [34, 35]. In our study, the Combination group showed a significantly sharper decline in both markers, suggesting that the therapy may have suppressed glial activation and promoted healthier neuron-glia interactions. We also examined MBP, a key structural protein of the myelin sheath. Elevated MBP levels are indicative of myelin damage or compromised blood-brain barrier function [36]. The Combination group showed significantly greater reductions in MBP, suggesting that HBOT may play a critical role in restoring blood-brain barrier integrity. Atorvastatin may also have supported recovery by improving endothelial function and contributing to a more stable neurovascular environment [37].

There is growing consensus that single therapeutic strategies may be insufficient for addressing the complex pathology of brain injury. In contrast, combination therapies appear better suited to deliver broad-spectrum benefits, modulating metabolism, reducing inflammation, and improving cerebral perfusion simultaneously [13, 38-40]. Our findings strongly support this approach.

Notably, while most markers showed distinct differences between the two groups, NSE exhibited a more complex pattern of change. NSE, a glycolytic enzyme primarily found in neuronal cell bodies, is rapidly released after acute brain injury and has long been used as an indicator of early neuronal damage [41]. In our study, NSE levels differed significantly between the groups on Day 7 but converged by Day 14, suggesting a transient response to intervention. This finding aligns with previous research. Zhang et al. reported that while NSE can identify early septic encephalopathy or post-traumatic brain dysfunction, its diagnostic and prognostic value can fluctuate over time, influenced by non-neurological factors such as inflammatory responses and metabolic status [42]. Moreover, Bandyopadhyay et al. highlighted that NSE shows significant baseline differences and high inter-individual variability, which can limit its consistency and reliability in cross-phase and cross-population efficacy assessments [43]. Based on these findings, we recommend interpreting NSE alongside other neuronal injury biomarkers to enhance diagnostic precision and clinical applicability.

Hemodynamic disturbances are characteristic of TBI, often manifesting as reduced cerebral blood flow velocity. Continuous monitoring of cerebral hemodynamic parameters is crucial for guiding management in TBI patients [44]. In our study, patients in the combination group demonstrated higher Vm and Vs, along with significantly lower PI values, indicating improved cerebral perfusion and reduced vascular resistance. Elevated Vm and Vs reflect enhanced middle cerebral artery perfusion, while reduced PI suggests better vascular compliance and elasticity [45]. These improvements may result from the combined effects of HBOT, which enhances oxygen delivery efficiency, alleviates cerebral vasospasm, and regulates autonomic nervous tone [46]. Additionally, atorvastatin - beyond its lipid-lowering action as an HMG-CoA reductase inhibitor - exhibits vascular-protective and anti-inflammatory effects through upregulation of eNOS and activation of the AKT/eNOS signaling pathway. These actions enhance vasodilation and microvascular regulation, contributing to the restoration of cerebral hemodynamic stability in the postoperative setting [47].

Patients recovering from TBI surgery often experience varying degrees of limb motor dysfunction, which worsens their quality of life

and social function recovery. Our data revealed superior limb function and quality of life metrics in the combination therapy group compared to the atorvastatin monotherapy group. Notably, the combination group also had significantly shorter hospital stays and quicker intracranial pressure recovery times, suggesting that it accelerates postoperative recovery and reduces medical resource burdens, demonstrating substantial practical significance. Furthermore, the reduction in postoperative subdural effusion volume indirectly confirms the treatment's effect on alleviating brain tissue inflammatory exudation. However, several limitations should be acknowledged. First, the present study adopted a retrospective, single-center design, which may restrict the external validity of the findings. Future investigations should therefore be conducted as prospective, multicenter trials with larger patient cohorts to strengthen the reliability and generalizability of the conclusions. Second, HBOT was administered for only 14 days, and outcome assessments were confined to short-term follow-up. As a result, the durability of treatment effects remains uncertain. Subsequent studies should consider prolonging both the therapeutic course and the observation period to clarify whether extended HBOT provides more sustained improvements in neurological function and cognitive recovery.

In conclusion, our results are robust, showing that HBOT offers superior outcomes compared to medication alone in several areas. This supports the idea that HBOT is a valuable treatment for TBI and underscores the importance of a multi-faceted approach in clinical studies.

Disclosure of conflict of interest

None.

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References

[1] Bernhardt K, McClune W, Rowland MJ and Shah A. Hypertonic saline versus other intracranial-pressure-lowering agents for patients with acute traumatic brain injury: a systematic review and meta-analysis. Neurocrit Care 2024; 40: 769-784.

[2] Yan J, Wang C and Sun B. Global, regional, and national burdens of traumatic brain injury from 1990 to 2021. Front Public Health 2025; 13: 1556147.

[3] Brett BL, Gardner RC, Godbout J, Dams-O'Connor K and Keene CD. Traumatic brain injury and risk of neurodegenerative disorder. Biol Psychiatry 2022; 91: 498-507.

[4] Roberts CJ, Barber J, Temkin NR, Dong A, Robertson CS, Valadka AB, Yue JK, Markowitz AJ, Manley GT, Nelson LD; Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) Investigators; Badjatia N, Diaz-Arrastia R, Duhaime AC, Feeser VR, Gopinath S, Grandhi R, Jha R, Keene CD, Madden C, McCrea M, Merchant R, Ngwenya LB, Rodgers RB, Schnyer D, Taylor SR and Zafonte R. Clinical outcomes after traumatic brain injury and exposure to extracranial surgery: a TRACK-TBI study. JAMA surg 2024; 159: 248-259.

[5] Hossain I, Rostami E and Marklund N. The management of severe traumatic brain injury in the initial postinjury hours - current evidence and controversies. Curr Opin Crit Care 2023; 29: 650-658.

[6] Yuan W, Fan H, Yang H, Tang L, Liu Z, Ouyang F, Luo W and Yan Y. Effect and mechanism of HMG-CoA reductase inhibitor on the improvement of elderly essential hypertension-induced vascular endothelial function impairment based on the JAK/STAT pathway. Diagn Pathol 2023; 18: 108.

[7] Adamičková A, Chomaničová N, Gažová A, Maďarič J, Červenák Z, Valášková S, Adamička M and Kyselovic J. Effect of atorvastatin on angiogenesis-related genes VEGF-A, HGF and IGF-1 and the modulation of PI3K/AKT/mTOR transcripts in bone-marrow-derived mesenchymal stem cells. Curr Issues Mol Biol 2023; 45: 2326-2337.

[8] Hashemizadeh S, Alaee E, Aghajani N, Azizi H and Semnanian S. Atorvastatin facilitates extinction and prevents reinstatement of morphine-induced conditioned place preference in rats. Biomed Pharmacother 2024; 181: 117639.

[9] Alarfaj SJ, El-Haggar SM, Hegazy SK, Maher MM, Bahgat MM, Elmasry TA, Alrubia S, Alsegiani AS and Bahaa MM. Effect of a high dose atorvastatin as adjuvant therapy to mesalamine in attenuating inflammation and symp-

toms in patients with ulcerative colitis: a randomized controlled pilot study. Front Med (Lausanne) 2024; 11: 1490178.
[10] Godoy DA, Murillo-Cabezas F, Suarez JI, Badenes R, Pelosi P and Robba C. "THE MANTLE" bundle for minimizing cerebral hypoxia in severe traumatic brain injury. Crit Care 2023; 27: 13.
[11] Alashram AR, Padua E, Romagnoli C and Annino G. Hyperbaric oxygen therapy for cognitive impairments in patients with traumatic brain injury: a systematic review. Appl Neuropsychol Adult 2023; 30: 602-613.
[12] Forner L, Berkowicz A, Dickmeiss E, Hyldegaard O, Jansen EC and Fischer-Nielsen A. Only minor stem cell mobilization in head and neck irradiated patients treated with hyperbaric oxygen. Diving Hyperb Med 2019; 49: 175-185.
[13] Xiu G, Li X, Li Q, Yin Y, Tang Q, Li J, Ling J, Ling B and Yang Y. Role of hyperbaric oxygen therapy in PDGF-BB-mediated astrogliosis in traumatic brain injury rats associated with ERK1/2 signaling pathway inhibition. Eur J Med Res 2023; 28: 99.
[14] Kulesza B, Litak J, Mazurek M and Nogalski A. Initial factors affecting 6-month outcome of patients undergoing surgery for acute posttraumatic subdural and epidural hematoma. Folia Med (Plovdiv) 2020; 62: 94-104.
[15] Hawryluk GWJ, Rubiano AM, Totten AM, O'Reilly C, Ullman JS, Bratton SL, Chesnut R, Harris OA, Kissoon N, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Lumba-Brown A and Ghajar J. Guidelines for the management of severe traumatic brain injury: 2020 update of the decompressive craniectomy recommendations. Neurosurgery 2020; 87: 427-434.
[16] Bellut D, Woernle CM, Burkhardt JK, Kockro RA, Bertalanffy H and Krayenbühl N. Subdural drainage versus subperiosteal drainage in burr-hole trepanation for symptomatic chronic subdural hematomas. World Neurosurg 2012; 77: 111-118.
[17] Chung DY, Olson DM, John S, Mohamed W, Kumar MA, Thompson BB and Rordorf GA. Evidence-based management of external ventricular drains. Curr Neurol Neurosci Rep 2019; 19: 94.
[18] Katz N, Bar-Haim Erez A, Livni L and Averbuch S. Dynamic lowenstein occupational therapy cognitive assessment: evaluation of potential to change in cognitive performance. Am J Occup Ther 2012; 66: 207-214.
[19] Arevalo-Rodriguez I, Smailagic N, Roqué I Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X and Cullum S. Mini-mental state examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2015; 2015: CD010783.
[20] Bruijnen CJWH, Dijkstra BAG, Walvoort SJW, Budy MJJ, Beurmanjer H, De Jong CAJ and Kessels RPC. Psychometric properties of the Montreal cognitive assessment (MoCA) in healthy participants aged 18-70. Int J Psychiatry Clin Pract 2020; 24: 293-300.
[21] Chang FH, Chen CY, Liang WM and Lin MR. Validating the quality of life after brain injury through rasch analysis. J Head Trauma Rehabil 2017; 32: E11-E18.
[22] Gladstone DJ, Danells CJ and Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair 2002; 16: 232-240.
[23] Figaji A. An update on pediatric traumatic brain injury. Childs Nerv Syst 2023; 39: 3071-3081.
[24] El Baassiri MG, Raouf Z, Badin S, Escobosa A, Sodhi CP and Nasr IW. Dysregulated brain-gut axis in the setting of traumatic brain injury: review of mechanisms and anti-inflammatory pharmacotherapies. J Neuroinflammation 2024; 21: 124.
[25] Hassett L. Physiotherapy management of moderate-to-severe traumatic brain injury. J Physiother 2023; 69: 141-147.
[26] Park E, Lyon JG, Alvarado-Velez M, Betancur MI, Mokarram N, Shin JH and Bellamkonda RV. Enriching neural stem cell and anti-inflammatory glial phenotypes with electrical stimulation after traumatic brain injury in male rats. J Neurosci Res 2021; 99: 1864-1884.
[27] Synnot A, Chau M, Pitt V, O'Connor D, Gruen RL, Wasiak J, Clavisi O, Pattuwage L and Phillips K. Interventions for managing skeletal muscle spasticity following traumatic brain injury. Cochrane Database Syst Rev 2017; 11: CD008929.
[28] Sakas R, Dan K, Edelman D, Abu-Ata S, Ben-Menashe A, Awad-Igbaria Y, Francois-Soustiel J and Palzur E. Hyperbaric oxygen therapy alleviates memory and motor impairments following traumatic brain injury via the modulation of mitochondrial-dysfunction-induced neuronal apoptosis in rats. Antioxidants (Basel) 2023; 12: 2034.
[29] Li C, Wu Z, Chen F, Dai C, Yang X, Ye S, Shi M, Chen P, Liu X and Liu F. Regulation of Nrf2/GPX4 signaling pathway by hyperbaric oxygen protects against depressive behavior and cognitive impairment in a spinal cord injury rat model. CNS Neurosci Ther 2025; 31: e70421.
[30] Ablin JN, Lang E, Catalogna M, Aloush V, Hadanny A, Doenyas-Barak K, Finci S, Polak N, Fishlev G, Korin C, Tzidky RY, Meir Genuth O and Efrati S. Hyperbaric oxygen therapy com-

pared to pharmacological intervention in fibromyalgia patients following traumatic brain injury: a randomized, controlled trial. PLoS One 2023; 18: e0282406.
[31] Ren B, Ye H, Shan W, Tao X and Ye Z. Effect of hyperbaric oxygen intervention on oxidative stress and expression of nerve growth factor in patients with craniocerebral injury. J Inflamm Res 2023; 16: 4925-4932.
[32] Dong Q, Wu M and Hu W. Efficacy and association of hyperbaric oxygen therapy combined with butylphthalide and oxiracetam with serum levels of inflammatory markers in vascular cognitive impairment after acute ischemic stroke. Pak J Med Sci 2023; 39: 829-834.
[33] Hadanny A, Rittblat M, Bitterman M, May-Raz I, Suzin G, Boussi-Gross R, Zemel Y, Bechor Y, Catalogna M and Efrati S. Hyperbaric oxygen therapy improves neurocognitive functions of post-stroke patients - a retrospective analysis. Restor Neurol Neurosci 2020; 38: 93-107.
[34] Bantis LE, Young KJ, Tsimikas JV, Mosier BR, Gajewski B, Yeatts S, Martin RL, Barsan W, Silbergleit R, Rockswold G and Korley FK. Statistical assessment of the prognostic and the predictive value of biomarkers-A biomarker assessment framework with applications to traumatic brain injury biomarker studies. Res Methods Med Health Sci 2023; 4: 34-48.
[35] Lanzilao L, Bianchi I, Grassi S, Defraia B, Brogi M, Da Ros M, Biagioli T, Fanelli A, Pinchi V and Focardi M. Biomarkers of traumatic brain injury in vitreous humor: a pilot study. Forensic Sci Int 2023; 350: 111782.
[36] Bohnert S, Wirth C, Schmitz W, Trella S, Monoranu CM, Ondruschka B and Bohnert M. Myelin basic protein and neurofilament H in postmortem cerebrospinal fluid as surrogate markers of fatal traumatic brain injury. Int J Legal Med 2021; 135: 1525-1535.
[37] Liu S, Li X, Jiang S, Liu D and Wang J. A review of advances in multimodal treatment strategies for chronic disorders of consciousness following severe traumatic brain injury. Int J Gen Med 2025; 18: 771-786.
[38] Wang HC, Wang PM, Lin YT, Tsai NW, Lai YR, Kung CT, Su CM and Lu CH. Effects of hyperbaric oxygen therapy on serum adhesion molecules, and serum oxidative stress in patients with acute traumatic brain injury. J Pers Med 2021; 11: 985.
[39] Chen Y, Wang L, You W, Huang F, Jiang Y, Sun L, Wang S and Liu S. Hyperbaric oxygen therapy promotes consciousness, cognitive function, and prognosis recovery in patients following traumatic brain injury through various pathways. Front Neurol 2022; 13: 929386.
[40] Liang F, Kang N, Li P, Liu X, Li G and Yang J. Effect of hyperbaric oxygen therapy on polarization phenotype of rat microglia after traumatic brain injury. Front Neurol 2021; 12: 640816.
[41] Zarei H, Roshdi Dizaji S, Toloui A, Yousefifard M and Esmaeili A. Diagnostic and prognostic values of S100B versus neuron specific enolase for traumatic brain injury; a systematic review and meta-analysis. Arch Acad Emerg Med 2024; 12: e29.
[42] Zhang Q, Zhang X, Li Y, Zeng L, Zhu R, Xin Y, Liu L, Hu Z and Huo Y. Combined cerebral oxygen saturation and neuron-specific enolase evaluation for diagnosis and prognosis of sepsis-associated encephalopathy. Sci Rep 2025; 15: 15369.
[43] Bandyopadhyay S, Hennes H, Gorelick MH, Wells RG and Walsh-Kelly CM. Serum neuron-specific enolase as a predictor of short-term outcome in children with closed traumatic brain injury. Acad Emerg Med 2005; 12: 732-738.
[44] Lapointe AP, Ware AL, Duszynski CC, Stang A, Yeates KO, and Dunn JF. Cerebral hemodynamics and microvasculature changes in relation to white matter microstructure after pediatric mild traumatic brain injury: an A-CAP pilot study. Neurotrauma Rep 2023; 4: 64-70.
[45] Dzierzęcki S, Ząbek M, Zaczyński A and Tomasiuk R. Prognostic properties of the association between the S-100B protein levels and the mean cerebral blood flow velocity in patients diagnosed with severe traumatic brain injury. Biomed Rep 2022; 17: 58.
[46] Barata P, Camacho O, Lima CG and Pereira AC. The role of hyperbaric oxygen therapy in neuroregeneration and neuroprotection: a review. Cureus 2024; 16: e62067.
[47] Zhou Y, Tashiro J, Kamatani S, Irie N, Suzuki A, Ishikawa T, Warita K, Oltvai ZN and Warita T. HMG-CoA reductase degrader, SR-12813, counteracts statin-induced upregulation of HMG-CoA reductase and augments the anticancer effect of atorvastatin. Biochem Biophys Res Commun 2023; 677: 13-19.