TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2016) 46: 1-5

doi:10.3906/sag-1404-125

Simvastatin's effects on survival and outcome in traumatic brain injury patients: a comparative study

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Received: 21.04.2014 • **Accepted/Published Online:** 17.10.2014 • **Final Version:** 05.01.2016

Background/aim: Mortality and morbidity still remain high in patients with traumatic brain injuries. Understanding the role of new treatments in these patients is critical. The aim of this study was to determine the effect of simvastatin on survival and outcome in traumatic brain injury patients.

Materials and methods: Forty-four patients were assigned to receive either simvastatin or a placebo. The serum interleukin-6 and C-reactive protein levels were measured at the first 24 h and 48 h after trauma. All data, including the Glasgow Coma Scale score, survival at discharge, length of intensive care unit stay, and duration of mechanical ventilation, were collected. The effect of simvastatin on the collected data was then investigated.

Results: The Glasgow Coma Scale level at discharge was significantly higher in the simvastatin group. The overall mortality rate, duration of mechanical ventilation, and length of intensive care unit stay were similar between the 2 groups. The C-reactive protein concentration 48 h after trauma was significantly lower in the simvastatin group, but there was no significant difference according to the interleukin-6 level 48 h after trauma between the 2 groups.

Conclusion: Simvastatin could be suggested as an adjunctive therapy in traumatic brain injury patients.

Key words: Simvastatin, traumatic brain injury, outcome, survival

1. Introduction

Traumatic brain injuries (TBIs) are a leading cause of morbidity and mortality. Recent evidence suggests that TBIs accounted for the majority of trauma deaths in Europe. This situation is comparable in the United States and is even worse in developing countries (1). Despite recent improvements in the management of patients with TBI in intensive care, mortality and morbidity in these patients still remain high (2). Therefore, understanding the role of new treatments in TBI outcome and mortality is critical. An acute inflammatory response occurs within the central nervous system (CNS) after severe TBI. This response leads to brain damage following traumatic injury (3). Many studies have revealed that the intracranial inflammatory response in injured brain patients results in an adverse outcome after head injury (4). After TBI several cytokines and chemokines are released, which, if not controlled, lead to secondary insults. The inflammatory response within the injured brain can exacerbate the damage following TBI. Many studies have demonstrated that limiting neuroinflammation is necessary for brain repair. Based on this fact, the role of antiinflammatory agents as a treatment drug in TBI has been investigated in several studies (5).

Statins are characterized as reductase inhibitors and have 3-hydroxy-3-methylglutaryl coenzyme activity. A wide variety of advantages of statins has been proven through recent research. Antiinflammatory actions, the direct activation of heme oxygenase, direct interference in leukocyte–endothelial interactions, and direct inhibition of major histocompatibility complex class II are the effects of statins that are independent of their lipid-lowering ability (6).

Preinjury statin use and postinjury statin treatment have been shown by many new studies to have beneficial properties in patients suffering general trauma, TBI, and burns. A well-designed clinical trial is required to determine the therapeutic efficacy in improving outcomes in this patient population (7). Many studies confirm the need for randomized, controlled trials to verify the relationship

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between statin therapy and observed outcomes (6). In this respect, a comparative study was designed to indicate whether acute statin treatment following TBI was able to reduce inflammatory cytokines and improve survival and outcome in humans.

2. Materials and methods

2.1. Study design

After approval by the local ethics committee, 44 patients were enrolled in this double-blind randomized clinical trial study. The trial was registered with the Iranian Registry of Clinical Trials (IRCT201305075363N3). Valid informed written consent was obtained from all patients or their relatives.

2.2. Study participants

Between June 2012 and August 2013, 44 patients who were admitted to the intensive care unit (ICU) of our tertiary health care institution within 24 h of head trauma were screened for eligibility for enrollment in the trial. The patients were divided into 2 groups, with 22 patients in each group.

Patients were included if their age was older than 18 years; if they were not receiving NSAIDs, statins, or corticosteroid drugs; if they had no allergy to statins; if there was no other kind of trauma (except for head trauma); and if they had no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic, or renal diseases.

Exclusion criteria were sepsis during the first 72 h of admittance and if patients did not survive for at least 72 h after admittance.

2.3. Randomization and blinding

Patients who met the inclusion criteria were randomly assigned to receive either simvastatin (Hakim, 20 mg, tablet) at a dose of 80 mg on the first day followed by 40 mg daily, or a placebo (lactose).

The patients were allocated to 1 of the 2 groups according to a randomization code list in a randomly permuted block design generated using a computer program. Investigators were unaware of the treatment groups.

2.4. Data extraction

Within the initial 24 h after the head trauma, age, sex, chronic diseases, and severity of trauma according to the Injury Severity Score (ISS) (8), Glasgow Coma Scale (GCS), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (9) were recorded. The serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels were measured at the first 24 h and 48 h after trauma. A previous study showed that IL-6 concentration increased 24 h after accidental trauma and continued to be present for >5 days in injured patients (10). Another investigation revealed that peak concentration of CRP occurred on day 2 or 3 after trauma in most cases (11). Based on those results the times were chosen for measuring the inflammatory factors in this study.

As clinical features, all data of the GCS at discharge, the outcome at discharge (dead or alive), the length of ICU stay, and the duration of mechanical ventilation were collected. Finally, the effect of simvastatin on the collected data was investigated.

2.5. Biomarker selection and assays

Blood samples were obtained by venipuncture and the cells were removed by centrifugation. Serum aliquots were stored at –70 °C until they were analyzed. The level of IL-6 was measured by an ultrasensitive ELISA method and CRP was measured via a high-sensitivity latex-enhanced immunonephelometric assay. The minimum and upper reference limit reported by the package insert for CRP was 0.2 and 5 mg/L.

2.6. Outcome

The primary outcome was ICU mortality. Secondary outcomes included the GCS level at discharge, the ICU length of stay, and the duration of mechanical ventilation.

2.7. Statistical analysis

SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Continuous variables in 2 groups were compared using independent sample t-test when data were normally distributed. The Mann–Whitney U test was used when numerical data were not normally distributed. Between-group comparisons of proportions were performed by using the chi-square test or the Fisher exact test, as appropriate. Results were expressed as mean ± standard deviation (SD) and number (percentage), as appropriate. Significance was defined as a P-value of less than 0.05.

3. Results

3.1. Patient characteristics

Forty-four patients were enrolled in this prospective, randomized study. One patient was not included due to his drug history. Of the 43 patients, 22 received simvastatin and 21 received a placebo. As shown in Table 1, patient characteristics were comparable in terms of age, sex, ISS score, APACHE II score, GCS score, and CRP and IL-6 levels upon admission ($P > 0.05$).

3.2. Biomarker analysis

The CRP concentration 48 h after trauma was statistically significantly different between the 2 groups. Values in the statin group were significantly lower than in the placebo group ($P = 0.042$). Analyzing the CRP concentration changes according to treatment arm shows that patients treated with simvastatin had a significant reduction in CRP level after 48 h of therapy ($P < 0.001$). CRP level after

Table 1. Baseline characteristics of patients on statin therapy and placebo therapy.

	Statin group (n = 22)	Placebo group (n = 21)
Age in years (mean ± SD)	38.3 ± 16.5	37.4 ± 17.5
Male sex, no. (%)	19 (86.4)	20 (95.2)
ISS, mean ± SD	26.7 ± 10.2	25.5 ± 8.7
APACHE II, mean ± SD	14.2 ± 6.6	14.8 ± 6.8
GCS, mean ± SD	6.6 ± 2.5	7.6 ± 2.9
CRP level mg/L, mean ± SD	77 ± 12.3	89 ± 45.3
IL-6 level pg/mL, mean ± SD	159.9 ± 65.7	145.1 ± 57.38

There was no statistically significant difference between groups (P > 0.05).
SD: Standard deviation, ISS: Injury Severity Score, APACHE II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow Coma Scale, CRP: C-reactive protein, IL-6: interleukin-6.

48 h of trauma was increased in the placebo group, but this change was not statistically significant (P = 0.192).

The IL-6 level 48 h after trauma in the simvastatin group was lower than that of the control group; however, there was no statistically significant difference between the 2 groups according to the IL-6 level 48 h after trauma (P = 0.55). Analyzing the IL-6 concentration changes in the simvastatin group shows that patients treated with simvastatin had a significant reduction in IL-6 level after 48 h of therapy (P < 0.001), but this significant reduction was not observed in the placebo group (P = 0.067).

3.3. Outcome

The overall ICU mortality rate, the duration of mechanical ventilation, and the length of ICU stay were similar between the groups (Table 2).

When the GCS score at discharge was compared with GCS at admission, there was an increase in both groups; however, the GCS score at discharge was significantly higher in the simvastatin group (Table 2).

4. Discussion

In animal studies the beneficial effect of statin treatment after TBI has been shown in several studies. Wang et al. showed that in adult rats following experimental TBI simvastatin could attenuate the activation of cerebral vascular endothelial inflammatory response and decrease the loss of neurological function and brain tissue (12). In another animal study, the positive effect of simvastatin combined with an antioxidant was demonstrated as neuroprotective in experimental TBI (13).

The beneficial effect of statin treatment after TBI is probably true in humans as well as in animals (14). Our study presents preliminary data that are in agreement with this theory. In this study, TBI patients treated with simvastatin showed higher GCS scores at discharge compared with the control group. The reason for this

Table 2. Outcome of the included patients.

Outcome	Statin group (n = 22)	Placebo group (n = 21)	P-value
ICU mortality, no. (%)	1 (4.5)	5 (23.8)	0.95
GCS at discharge, mean ± SD	13.2 ± 2.7	10.8 ± 4.9	0.004*
Duration of mechanical ventilation, days, mean ± SD	4.5 ± 2.3	5.7 ± 3.4	0.15
Length of ICU stay, days, mean ± SD	7.1 ± 3.2	6.8 ± 4.1	0.135

*Statistically significant difference between groups (P < 0.05).
SD: Standard deviation, GCS: Glasgow Coma Scale, ICU: intensive care unit.

finding can be related to the antiinflammatory effect of statins on secondary injury mechanisms after TBI. Antiinflammatory and neuroprotective effects of statins have been proven by several preclinical studies. Béziaud et al. demonstrated in a randomized study that simvastatin reduced cerebral edema in rats with TBI by preserving damage to tight junctions and neutrophil infiltration into the parenchyma, which results in preserving the blood–brain barrier integrity (15). The neuroprotective effects of statins have been shown in many preclinical models as well as in animal studies with TBI (16). The favorable effect of statins in brain injury has been recently investigated in a few clinical studies. In a double-blind randomized clinical trial involving 36 TBI patients, the authors showed that statins may induce an antiinflammatory effect, and may promote recovery after TBI and reduce disability scores compared with a placebo group (14). In addition, Tapia-Pérez et al. assessed the continued use of statins after acute intracranial hemorrhage and showed that it could be associated with early neurological improvement (17). The results of these studies could explain the reason for the better GCS score at discharge in the simvastatin group in the present study.

Several investigations have shown the favorable effects of statin therapy on mortality in critically ill patients. Reduction of hospital mortality with statin therapy during ICU stay was shown by a cohort study in a tertiary ICU (6).

In another cohort study, Christensen et al. reported that preadmission statin use was associated with reduced risk of death following intensive care (18).These findings are inconsistent with present study, in which there was no significant difference in the mortality between the 2 groups. This disagreement with the findings of our study may be explained by differences in study design, patient population, statin types, and statin doses.

IL-6 and CRP levels were also measured as inflammatory biomarkers at ICU admission and 48 h after TBI. In a double-blind placebo-controlled randomized clinical trial, Novack et al. reported that statin therapy may be associated with a reduction in the levels of inflammatory cytokines in patients with acute bacterial infections (19). A similar finding was noted in the present study, in which IL-6 levels decreased significantly at 48 h after TBI in the statin group compared to the placebo group. Another inflammation biomarker that has shown the antiinflammatory effect of simvastatin in TBI patients was CRP level changes. In this study, the CRP concentration 48 h after trauma in the statin group was significantly lower than that in the placebo group. These findings show the favorable effect of statins in TBI patients. Based on previous findings, circulating cytokines released as a result of an inflammatory response can cross the blood–brain barrier and activate quiescent microglia or cause an exaggerated inflammatory response in primed microglia. Therefore, statins might have changed the pathophysiologic response of the CNS to the inflammation in patients suffering TBI (20).

In this study, patients in the intervention and control groups did not have significantly different lengths of ICU stay or durations of mechanical ventilation. A similar finding was noted by Makris et al. in a randomized controlled trial in which they suggested that oral pravastatin in the treatment of ICU patients has no significant effect on the length of ICU stay or the duration of mechanical ventilation (21).

These findings suggest that statins may be useful as an adjunctive therapy in critically ill patients. In this respect, our results support the findings of previous studies suggesting that statins may favorably affect the course of critically ill patients.

The main limitation of this study was that it was carried out in a single institute and only on patients of the same race. Furthermore, the sample size was small. It is recommended that other researchers should carry out larger trials.

In conclusion, a significant difference in the GCS score between the 2 groups was observed, which suggests that this is the most significant marker of morbidity in patients with brain injury; however, there was no significant difference in the length of ICU stay, duration of mechanical ventilation, or mortality in patients. In addition, the inflammatory biomarkers in the intervention group had a significant reduction in comparison with the control group, which could reduce secondary damage following inflammation. Based on these findings, it could be suggested that statins may be useful as an adjunctive therapy in patients with head trauma. For more confirmation, the authors suggest additional clinical trials with larger sample sizes.

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