EGYPTIAN JOURNAL OF ANAESTHESIA
2023, VOL. 39, NO. 1, 715–721
https://doi.org/10.1080/11101849.2023.2246232

The anti-inflammatory effects of atorvastatin upon the outcome of traumatic brain injury patients: A randomized-controlled double-blind clinical trial

Emad Zarief Kamel[a], Nagwa M Ibrahem[a], Hazem Abu Zeid Yousef[b], Mohammed Gaber Farghly[a], Shady Safwat Hassan[c], Khaled Tolba Younes[a], Yasser Ashraf Gamal[d], Mina Maher Raouf[e] and Omar Makram Soliman[a]

[a]Anesthesia and intensive care department, Faculty of Medicine, Assiut University, Assiut, Egypt; [b]Diagnostic Radiology department, Faculty of Medicine, Assiut University, Assiut, Egypt; [c]Department of Neurology, Medical Faculty, Assiut University Hospital, Assiut, Egypt; [d]Faculty of Medicine, Assiut University, Assiut, Egypt; [e]Anesthesia and intensive care department, Faculty of medicine, Minia university, Minia, Egypt

ABSTRACT

Background: Traumatic brain injury (TBI) is a quite common health problem. A lot of delayed complications are related to inflammatory responses that occurred within the brain itself. Atorvastatin is related to lipid lowering drugs carrying some anti-inflammatory properties and upon this fact this study hypothesis was built.

Methods: Twenty adult patients with TBI, Glasgow coma scale (GCS) 9–11. Patients were equally and randomly allocated into two groups (**group C** as control group and **group S** received atorvastatin 40 mg once daily for 48 h). After 48 h, participants have undergone magnetic resonance imaging brain spectroscopy examination (MRS). The spectral peaks of N-Acetyl aspartate (NAA), Choline, and Creatinine (Cr) were assessed in brain tissue. The primary outcome was presented as ratios of NAA/Cr), Cho/Cr, and NAA/Cho. Other outcomes included GCS and ICU stay.

Results: There were insignificant variations between groups were found in the MRS results for metabolite alterations (NAA, Cr, and Cho). Contrasted with the control group, the statin group's Cho/Cr ratio was significantly lower ($P = 0.005$), and NAA/Cho was significantly greater in the statin group than control group ($P = 0.022$). Statin group showed higher GCS the 1st day ($P = 0.01$), and lesser ICU stay ($P = 0.04$)

Conclusion: Atorvastatin can be used safely in mild-to-moderate TBI patients with a favourable outcome in the form of decreased Cho/Cr ratio and increased NAA/Cho ratio, higher GCS, and decreased ICU length of stay.

ARTICLE HISTORY
Received 19 July 2023
Revised 1 August 2023
Accepted 6 August 2023

KEYWORDS
Traumatic brain injury; atorvastatin; brain protection

1. Introduction

Traumatic brain injury (TBI) is a very common financial health problem. After the ending of the acute care period, a large number of TBI patients are left with cognitive, motor, or emotional dysfunction from the injury [1]. Management of TBI is usually supportive, aiming to treat reduced intracranial hypertension and cerebral edema by using temporizing measures, by giving of hyperventilation, osmotic agents, and sometimes ventricular drainage [2]

Low-density lipoprotein and cholesterol levels usually decrease by taking statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors. Statins have neuroprotective good results on ischemic stroke through its lipid-lowering medications [3]. Statins contain endothelial and vasoactive endothelial effects, and anti-inflammatory, antioxidant, anti-excitotoxicity, and anti-thrombotic activities. They also have a positive influence on different pathways of acute and secondary brain injury. Also, statins are widely available, approved by FDA, have low side effects, and are safe in populations with properly severe illnesses, statin medication would be feasible to be used in patients with TBI [3–5].

To evaluate the degree of TBI, brain micro dialysis, positron emission tomography, arterio-venous difference, assessment of metabolites and/or magnetic resonance spectroscopy (MRS) can be utilized. MRS is considered a non-invasive tool with no use of radiation allowing measurement of some brain metabolites not detectable by other modalities in different brain regions both in the extra and intracellular regions [6,7]. Because of this, MRS in TBI may be employed to determine which patients will benefit from certain neuropsychiatric and cognitive rehabilitation.

This work is aimed to assess the difference between using and not using atorvastatin for the first 48 h after

CONTACT Mohammed Gaber Farghly mohammed.gaber60@yahoo.com Anesthesia and intensive care department, Faculty of Medicine, Assiut University, Assiut, Egypt

traumatic brain injury (TBI). Neurochemical outcomes are measured by using MRI brain spectroscopy as a primary outcome. Secondary outcomes included inflammatory mediators, ICU stay, and conscious level changes.

2. Patients and methods

It is a prospective, double-blind, randomized clinical study conducted from March 2021 to April 2022 in Trauma ICU and General ICU of Assiut University Hospitals. It was carried on adult patients with TBI after taking approval from the Local Research Ethics Committee, Faculty of Medicine, Assiut University, Assuit, Egypt, under (IRB-17200583) and after registration on clinicaltrials.gov (NCT04718155).

It involved 20 adults with TBI, Glasgow coma scale 9–11. Patients with pre-trauma lipid lowering therapy during the last 3 months, pre-trauma immunosuppressive, anti-inflammatory, antipsychotic medications, or uncontrolled systemic disease(s) e.g., uncontrolled cardiac problems, diabetes mellitus, severe hepatic or renal impairment were excluded from the study.

Patients were equally and randomly allocated into two groups through a web-based randomizer (**group** : control group and **group S**: statin group) after obtaining written informed consent from the patient's legal guardians. The grouping was hidden from the patients, their family members, and the doctor who collected the data.

2.1. Grouping

Group S received atorvastatin 40 mg once daily for 48 h and Group C was the control one and received conventional therapy only.

The participants were admitted to the trauma intensive care unit and received conventional institutional treatment. Patients who developed seizures on admission or with moderated TBI have received levetiracetam 500 mg/12 hr. Arterial oxygen saturation was kept >95% with simple oxygen mask (6 L/min) if needed and mean arterial blood >70 mm Hg to obtain suspected cerebral perfusion pressure 60–70 mm Hg. Analgesia was attained by intravenous paracetamol 1 g/6 hr. Head elevation was kept during the whole period of ICU admission (30°). Ondansetron antiemetic was administered in the dose of 4 mg/12 hr. Blood sugar was measured regularly every 6 h and kept between 110 and 180 mg/dl. After 48 h, all patients have undergone magnetic resonance imaging brain spectroscopy examination.

2.2. Anesthesia for preparation for MRS

Patients' preparation was done by 6 h of fasting regarding semisolids and 2 h regarding clear fluids. Fentanyl 1 µg/kg then propofol 2 mg/kg were employed to induce general anesthesia. Participants were subjected to full basic monitoring including five leads ECG, oxygen saturation SPO2, noninvasive blood pressure, and end-tidal CO2. Cis-atracurium 0.3 mg/kg was administered to facilitate endotracheal intubation and 0.15 mg/kg of cis-atracurium on demand. Propofol IV 3–10 mg/kg/h was employed to maintain anesthesia. Atropine 0.01 mg/kg and neostigmine 0.05 mg/kg were given to reverse the effects of muscular relaxation.

2.3. MRI brain spectroscopy technique

Imaging and spectroscopy were carried out utilizing a 1.5 Tesla superconducting magnet Philips Achieva (Best, The Netherlands) system utilizing standard clinical head phased array coils. Axial DWI, axial FLAIR, axial FFE/GRE, and axial turbo spin echo T1 were utilized through the standard imaging technique after a multiplanar scout image was taken. A frontal or parietal lobe's posterior portion, which primarily contains white matter pathways but also contains some deep grey matter, was employed to gather proton spectra (basal ganglia). To prevent the hitting of any T1 or T2 abnormalities, the voxel was carefully placed. The spectroscopy hardware and software that were readily available on the market used to optimize the MRS procedures. The point-resolved spectroscopy pulse sequence (PRESS) was employed to conduct the single volume MRS with TR 2000 ms and TE 30 (1.5T) or TE 144 ms. The VOI for each participant was 15 × 15x15mm. Post-processing of spectra, the vendor application was employed to examine the spectral data [8–12].

2.4. Data collection

The spectral peaks of N-Acetyl aspartate (NAA), Choline (Cho), and Creatine (Cr) were integrated after being fitted to Gaussian line shapes. The outcomes were presented in the following metabolite ratios (primary outcome): N-acetyl aspartate/creatine (NAA/Cr), choline/creatine (Cho/Cr), NAA/Cho.

2.5. Other outcomes

The other outcomes included patients' demographic characters, C-reactive protein (CRP), C-reactive protein/albumin ratio (CAB), Glasgow coma scale, Richmond agitation and sedation scale (RASS) and ICU stay.

2.6. Statistical analysis

Sample size calculation via utilizing G power sample size calculator. It was assumed that if our intervention can make a 20% change in the primary outcome (brain

metabolite) with an 80% power and alpha error of 0.05, accordingly, sample size was calculated to be 20 patients. Kolmogorov–Smirnov test was employed to determine the data's initial normality. Discrete variables are provided as frequencies and percentages or ratios, whereas all continuous variables are expressed as mean ± standard deviation. The categorical data were contrasted utilizing chi-square $\chi 2$ test. Analysis of continuous variables in the same group performed with Student's t-test. Comparisons between times in the same group executed utilizing paired *t*-test. When comparing nonparametric data, the Mann–Whitney test and the Wilcoxon test were utilized. It was deemed statistically significant if the *P*-value was <0.05. The statistical analysis was performed via IBM SPSS software version 23.0 of Windows statistics.

3. Results

Twenty-eight patients were enrolled in the study; however, only 20 patients were included, and 8 patients were excluded, 7 were not fulfilling the inclusion criteria, and one patient's relatives declined to be included in the study. The included patients were randomly allocated to the two research groups at random (Figure 1).

Patients in the study groups were comparable regarding demographic and clinical data with insignificant variation between groups as noted in (Table 1).

Insignificant variations between groups were found in the MRS results for metabolite alterations (NAA, Cr, and Cho); however, contrasted with the control group, the statin group's Cho/Cr ratio was significantly lower. Regarding the NAA/Cho ratio, it was significantly greater in the statin group than control group. The NAA/Cr ratio did not significantly differ between the groups (Table 2).

The conscious level was assessed by GCS and RASS, and there was significantly decreased RASS in the statin group in contrast to the control group during the 1st and 2nd days as shown in Table 3. Regarding the GCS, 1st day GCS was significantly greater in the statin group in comparison to the control group.

Inflammatory and laboratory markers as demonstrated on CRP, albumin and CAR showed insignificant differences between both studied groups as shown in Table 4.

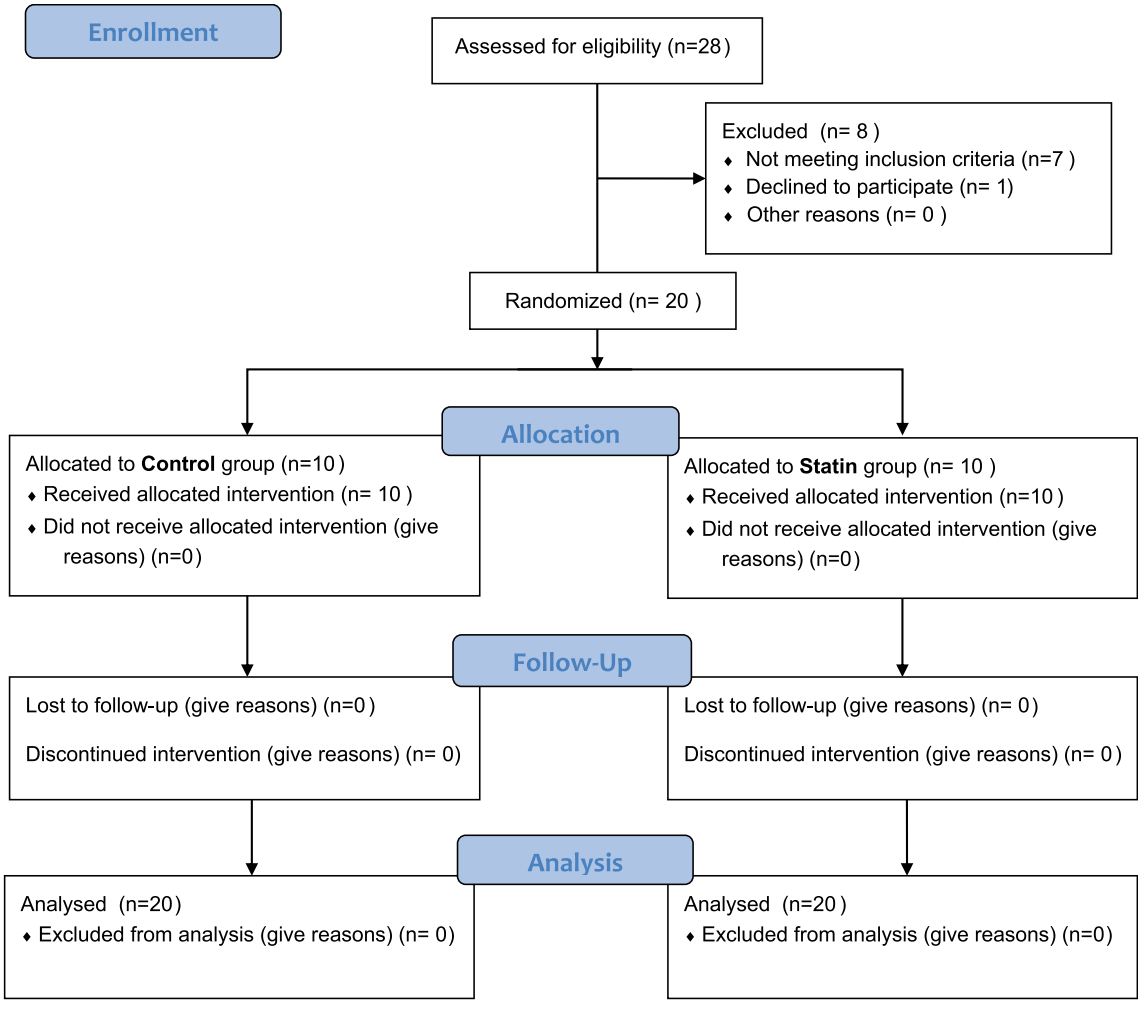

Figure 1. Consort 2010 Flow Diagram

Table 1. Demographic and clinical data of the studied groups.

Variables	Group C $n = 10$	Group S $n = 10$	*P*-value
Gender male/female	10/0	7/3	.62
Weight Kg	86 ± 12.9	77.4 ± 14	.15
Height cm	169.6 ± 6.7	168 ± 6	.65
BMI	26 ± 3.7	23.5	.17
GIT complications	4 (40%)	2(20%)	.62
ICU stay (days)	16.3 ± 7.5	10 ± 5.2	.04
CT brain findings			
• Contusion	8 (80%)	8 (80%)	.79
• Edema	6 (60%)	8 (80%)	
• Subarachnoid hemorrhage	6 (60%)	3 (30%)	
• Intraventricular hemorrhage	1 (10%)	1 (10%)	

Data are expressed as ratio, mean± standard deviation, and or number (percentage). $P < 0.05$ is considered statistically significant.

Table 2. Magnetic resonance spectroscopy (MRS) findings in the study groups.

Variables	Group C $n = 10$	Group S $n = 10$	*P*-value
Metabolites			
Increased NAA	1 (10%)	-	1
Decreased Cho	3 (30%)	6 (60%)	.3
Increased Cho	1(10%)	-	
Decreased Cr	7 (70%)	6 (60%)	.58
Increased Cr	-	1 (10%)	
Cho/Cr	1.75 ± .57	1.02 ± .37	.005
NAA/Cr	1.62 ± .09	1.65 ± .08	.836
NAA/Cho	.83 ± .29	1.33 ± .52	.022

Data are expressed as number (percentage) or mean ± standard deviation. N-Acetyl aspartate (NAA), Choline (Cho) creatine (Cr). $P < 0.05$ is considered statistically significant.

Table 3. Conscious level of the studied groups.

Variables	Group C $n = 10$	Group S $n = 10$	P-value
GCS 0	12.5 [1]	12.5 [1]	-
GCS 1	1.5 [4]	13 [2]	.01
GCS 2	1.5 [5]	14 [1]	.11
RASS 0	1 (0)	−1 (0)	.14
RASS 1	1 (0)	−1 (0)	.02
RASS 2	1 [2]	−1 [1]	.039

Data are expressed median (interquartile range). GCS Glasgow coma scale, RAAS Richmond agitation sedation scale. (0) on admission [1], 1st day of ICU stay [2], 2nd day of ICU stay. $P < 0.05$ is considered statistically significant.

Table 4. Inflammatory

Variables	Group C $n = 10$	Group S $n = 10$	*P*-value
CRP 0 mg/L	23.80 ± 8.23	34 ± 1.7	.2
CRP 2 mg/l	27.40 ± 8.47	23.78 ± 14.6	.51
Albumin 0 g/L	31.50 ± .980	3.30 ± 1.476	.59
Albumin 2 g/L	29.50 ± .792	3.00 ± 1.5	.81
CAB 0	.7740 ± .09908	1.4750 ± .25	.007
CAB 2	1.035 ± .22*	1.1 ± .30*	.85

Data are presented as mean ± standard deviation. C-reactive protein (CRP), C-reactive protein/albumin ratio (CAB). (0) on admission [2] 2nd day in the ICU. *Significant change from the base line.

Hemodynamics including MAP and HR showed insignificant variation between groups during the whole study period as demonstrated in Table 5.

4. Discussion

This study revealed that the early use of such a dose of atorvastatin in patients with moderate TBI has significantly decreased Cho/Cr ratio and increased NAA/Cho ratio, otherwise, no other changes were reflected upon brain MRS metabolites were noted.

The Cho/Cr ratio was significantly increased in the control group relative to the statin group, suggesting the effect of the therapy. An increase in Cho in patients after TBI and increased choline/creatine ratio in normal appearing white matter are addressed in multiple

Table 5. Hemodynamics

Variables	Group C $n = 10$	Group S $n = 10$	*P*-value
MBP 0 mm Hg	69 ± 8.367	69.8 ± 8.4	.83
MBP 1 mm Hg	73.60 ± 9.240	69.4 ± 7.98	.29
MBP 2 mm Hg	73.50 ± 1.124	69.5 ± 5.5	.28
HR 0 beat/m	81.20 ± 17.498	73.7 ± 5.9	.21
HR 1 beat/m	78 ± 11.416	73.7 ± 5.5	.28
HR 2 beat/m	79.80 ± 11.989	75.2 ± 7.2	.31

previous studies "Garnet et al. 2000", "Wild et al. 1999", "Stovell et al. 2017" [13–15]. Other alterations in brain metabolites following TBI and that were described in previous studies were not found to be of significant difference in the current study, and we assume that it could be due to the relatively small sample size.

Our findings are too close with Garnett et al. 2000 [14], who found an increased choline/creatine ratio in proportion to the severity of injury in normal-appearing white matter during MRS studies of 26 patients performed early point following injury (mean 12 days) and at a later time point (mean 6.2 months). Also, our results are in line with the study done by Friedman *et al*. 1999 who had studied MRS of 14 patients with TBI about one-month post trauma and found early increased choline/creatine ratio in gray matter was related to the severity of head trauma [16]. Wild et al. found no correlation when comparing nine MRS 2 weeks post-trauma of moderate head trauma patients to six healthy volunteers, this could be due to changes in creatine blunting the effect of any relative change [15]. Marino and coworkers detected an elevation of choline/total metabolites in 10 patients and their findings were demonstrated within 48–72 h of moderately severe TBI, but this also did not correlate with presentation GCS or outcome up to 3 months [8].

We have found that NAA/Cho ratio has significantly increased in the statin group and this is in line with the study of Garnett et al. 2000 who found an early reduction in the NAA/Cho ratio that was significantly correlated with the severity of TBI [14]. In contrast to our findings, Condon B et al. 1998 studied MRS on four patients with TBI and demonstrated a reduction in NAA/choline ratio compared to healthy controls during 1ST 24-h post-trauma [9].

Another study of 10 patients with moderately severe TBI studied MRS 48–72 h after injury and found a reduction in NAA in MRS compared to healthy volunteers, which was correlated with injury severity (GCS at presentation) Marino S,2006 et al. [8]

As regards inflammatory markers (CRP, albumin, CAR) our results showed insignificant differences between both groups. This is in agreement with Aguilar et al. 2013 who reported statistically insignificant anti-inflammatory markers during the 72 h of administration of 20 mg of rosuvastatin in 19 patients with moderate-to-severe TBI compared to 17 who received a placebo [10]. In contrast to our study, Naqib et al. 2016 reported a significant decrease in CRP level 48 h after administration of Simvastatin in TBI patients. We assume that our results are different from the Naqib study due to the sample size we have included small, additionally, the different dose and nature of statin used [11]; however, they did not report a significant difference concerning the Interleukin 6 levels [11]. Moreover, Farhad Soltani et al. 2020 found that oral 40 mg atorvastatin in 30 patients with moderate TBI significantly reduced the rate of inflammatory factors (CRP and ESR) on the 14th day of ICU admission compared to placebo which is not in line with the findings of the present study [12]. This discrepancy can be attributed to the short period of our study (48 h) and sample size as well.

In the present study, a significant difference was observed concerning the length of ICU stay between the two groups. This result was in agreement with Soltani et al. 2020 noted that the length of ICU stay was significantly lower in the atorvastatin group [12]. On the other hand, Naqib trial investigating the effect of Simvastatin in TBI patients revealed no significant reduction in the length of intensive care unit stays in patients who were given statins [11].

We reported that post-TBI delirium-free status measured by RAAS was significantly higher in patients receiving atorvastatin in comparison to the control group. That results agree with Seyed Mojtaba et al. in 2019 who reported that the consumption of 40 mg/day of atorvastatin in 40 general ICU patients significantly lowers the mean RASS score and increases delirium-free days at both morning and afternoon time points compared to the control group [17]. Page VJ et al. and Morandi A et al. in their cohort studies conducted in 2014 found also that statin therapy was accompanied by less delirium in ICU patients [18,19]. On the other hand, an observational cohort study revealed no significant reduction of delirium in patients who were given statins before coronary revascularization, Mariscalco G,2012 et al. [20]. A meta-analysis that reviewed the results of six studies with high heterogeneity (two studies in ICU patients and four studies in cardiac surgery patients) indicated that statins had no effects on delirium status in critically ill and cardiac surgery patients. It was suggested that more studies are required to clarify the relationship between statin

therapy, particularly concerning the type of statin and dosage, and delirium status, its mechanisms and outcomes in ICU patients, Vallabhajosyula S, 2017 et al. [21]

Multiple studies mentioned that statins may improve delirium through effects on N-methyl-d-aspartate (NMDA)-mediated glutamate excitotoxicity [22,23] or endothelial function [24,25], which might have beneficial effects on neuronal function. In addition, it has been reported that in response to the statin therapy, cerebral blood flow was increased in the ischemic penumbra, and the behavioral deficits were improved in the brain injury [26,27].

Another study of 10 patients with moderately severe TBI studied MRS 48–72 h after injury and found a reduction in NAA in MRS compared to healthy volunteers, which was correlated with injury severity (GCS at presentation) Marino S,2006 et al. [8]

Limitations of this study include its small sample size, short duration of therapy, and not considering other inflammatory markers.

5. Conclusion

Atorvastatin can be used safely in patients with TBI for 48 h post-traumatic and resulting in a significantly decreased Cho/Cr ratio and increased NAA/Cho ratio, decreased ICU length of stay and reduced delirium.

MRS is a good noninvasive technique as a quantitative measurement tool for brain metabolites in patients with TBI.

Disclosure statement

The authors have no conflict of interest to report.

Author contribution

Emad Zarief, Nagwa Mostafa, and Omar Makram had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Shady Safwat and Hazem Yousef designed the study protocol. Mohamed Gaber, Khaled Tolba, Mina Maher, and Yasser Ashraf managed the literature searches, and summaries of the previous related work, and wrote the first draft of manuscript.

References

[1] Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006;21(5):375–378. doi: 10.1097/00001199-200609000-00001

[2] Bulger EM, Nathens AB, Rivara FP, et al. Management of severe head injury: institutional variations in care and effect on outcome. Crit Care Med. 2002;30 (8):1870–1876. doi: 10.1097/00003246-200208000-00033

[3] Gao F, Linhartova L, Johnston AM, et al. Statins and sepsis. Br J Anaesth. 2008;100(3):288–298. doi: 10.1093/bja/aem406

[4] Guasti L, Marino F, Cosentino M, et al. Prolonged statin-associated reduction in neutrophil reactive oxygen species and angiotensin II type 1 receptor expression: 1-year follow-up. Eur Heart J. 2008;29 (9):1118–1126. doi: 10.1093/eurheartj/ehn138

[5] Fischetti F, Carretta R, Borotto G, et al. Fluvastatin treatment inhibits leucocyte adhesion and extravasation in models of complement-mediated acute inflammation. Clin Exp Immunol. 2004;135 (2):186–193. doi: 10.1111/j.1365-2249.2003.02358.x

[6] Carpenter KL, Czosnyka M, Jalloh I, et al. Systemic, local, and imaging biomarkers of brain injury: more needed, and better use of those already established? Front Neurol. 2015;6:26. DOI:10.3389/fneur.2015.00026

[7] De Graaf RA. In vivo NMR spectroscopy: principles and techniques. John Wiley & Sons: 2019. doi:10.1002/9781119382461

[8] Marino S, Zei E, Battaglini M, et al. Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. J Neurol Neurosurg Psychiatry. 2007;78(5):501–507. doi: 10.1136/jnnp.2006.099796

[9] Condon B, Oluoch-Olunya D, Hadley D, et al. Early 1H magnetic resonance spectroscopy of acute head injury: four cases. J Neurotrauma. 1998;15(8):563–571. doi: 10.1089/neu.1998.15.563

[10] Sánchez-Aguilar M, Tapia-Pérez JH, Sánchez-Rodríguez JJ, et al. Effect of rosuvastatin on cytokines after traumatic head injury. J Neurosurg. 2013;118 (3):669–675. doi: 10.3171/2012.12.JNS121084

[11] Naghibi T, Madani S, Mazloomzadeh S, et al. Simvastatin's effects on survival and outcome in traumatic brain injury patients: a comparative study. Turk J Med Sci. 2016;46(1):1–5. doi: 10.3906/sag-1404-125

[12] Soltani F, Nassajian N, Tabatabaee K, et al. The effect of low-dose atorvastatin on inflammatory factors in patients with traumatic brain injury: a randomized clinical trial. Arch Neurosci. 2020;7(4). doi: 10.5812/ans.106867

[13] Stovell MG, Yan J-L, Sleigh A, et al. Assessing metabolism and injury in acute human traumatic brain injury with magnetic resonance spectroscopy: current and future applications. Front Neurol. 2017;8:426. DOI:10.3389/fneur.2017.00426

[14] Garnett MR, Blamire AM, Corkill RG, et al. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. Brain. 2000;123(10):2046–2054. doi: 10.1093/brain/123.10.2046

[15] Wild J, Macmillan C, Wardlaw J, et al. 1H spectroscopic imaging of acute head injury—evidence of diffuse axonal injury. Magn Resonance Mate Phys, Biol Med. 1999;8(2):109–115. doi: 10.1007/BF02590527

[16] Friedman S, Brooks W, Jung R, et al. Quantitative proton MRS predicts outcome after traumatic brain injury. Neurology. 1999;52(7):1384–. doi: 10.1212/WNL.52.7.1384

[17] Sohrevardi SM, Nasab FS, Mirjalili MR, et al. Effect of atorvastatin on delirium status of patients in the intensive care unit: a randomized controlled trial. Arch Med Sci. 2021;17(5):1423. doi: 10.5114/aoms.2019.89330

[18] Page VJ, Davis D, Zhao XB, et al. Statin use and risk of delirium in the critically ill. Am J Respir Crit Care Med.

2014;189(6):666–673. doi: 10.1164/rccm.201306-1150OC

[19] Morandi A, Hughes CG, Thompson JL, et al. Statins and delirium during critical illness: a multicenter, prospective cohort study. Crit Care Med. 2014;42(8):1899. doi: 10.1097/CCM.0000000000000398

[20] Mariscalco G, Cottini M, Zanobini M, et al. Preoperative statin therapy is not associated with a decrease in the incidence of delirium after cardiac operations. Ann Thorac Surg. 2012;93(5):1439–1447. doi: 10.1016/j.athoracsur.2012.02.012

[21] Vallabhajosyula S, Kanmanthareddy A, Erwin PJ, et al. Role of statins in delirium prevention in critical ill and cardiac surgery patients: a systematic review and meta-analysis. J Crit Care. 2017;37:189–196. doi: 10.1016/j.jcrc.2016.09.025

[22] Semmler A, Okulla T, Sastre M, et al. Systemic inflammation induces apoptosis with variable vulnerability of different brain regions. J Chem Neuroanat. 2005;30(2–3):144–157. doi: 10.1016/j.jchemneu.2005.07.003

[23] Zacco A, Togo J, Spence K, et al. 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors protect cortical neurons from excitotoxicity. J Neurosci. 2003;23(35):11104–11111. doi: 10.1523/JNEUROSCI.23-35-11104.2003

[24] Pleiner J, Schaller G, Mittermayer F, et al. Simvastatin prevents vascular hyporeactivity during inflammation. Circulation. 2004;110(21):3349–3354. doi: 10.1161/01.CIR.0000147774.90396.ED

[25] McGown C, Brown N, Hellewell P, et al. Beneficial microvascular and anti-inflammatory effects of pravastatin during sepsis involve nitric oxide synthase III. Br J Anaesth. 2010;104(2):183–190. doi: 10.1093/bja/aep361

[26] Sironi L, Cimino M, Guerrini U, et al. Treatment with statins after induction of focal ischemia in rats reduces the extent of brain damage. ATVB. 2003;23(2):322–327. doi: 10.1161/01.ATV.0000044458.23905.3B

[27] Stêpieñ K, Tomaszewski M, Czuczwar Sa J. Neuroprotective properties of statins. Pharmacol Rep. 2005;57(5):561–569.