Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled c...

Article *in* Journal of Clinical Neuroscience · July 2017

DOI: 10.1016/j.jocn.2017.06.010

CITATIONS
6

READS
78

5 authors, including:

Nima Derakhshan
Shiraz University of Medical Sciences
67 PUBLICATIONS **187** CITATIONS
SEE PROFILE

Hosseinali Khalili
Shiraz University of Medical Sciences
49 PUBLICATIONS **320** CITATIONS
SEE PROFILE

Fariborz Ghaffarpasand
Shiraz University of Medical Sciences
130 PUBLICATIONS **1,566** CITATIONS
SEE PROFILE

Shahram Paydar
Shiraz University of Medical Sciences
146 PUBLICATIONS **568** CITATIONS
SEE PROFILE

Journal of Clinical Neuroscience xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical commentary

Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled clinical trial

Gholam Reza Farzanegan [a], Nima Derakhshan [a,b,*], Hosseinali Khalili [b], Fariborz Ghaffarpasand [b], Shahram Paydar [b]

[a] Trauma Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[b] Trauma Research Center, Shahid Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article history:
Received 6 January 2017
Accepted 8 June 2017
Available online xxxx

ABSTRACT

The aim of the current study was to investigate the effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury (TBI). The study was conducted as a randomized clinical trial during a 16-month period from May 2015 and August 2016 in a level I trauma center in Shiraz, Southern Iran. We included 65 patients with moderate (GCS: 9–13) to severe (GCS: 5–8) TBI who had brain contusions of less than 30 cc volume. We excluded those who required surgical intervention. Patients were randomly assigned to receive daily 20 mg atorvastatin for 10 days (n = 21) or placebo in the same dosage (n = 23). The brain contusion volumetry was performed on days 0, 3 and 7 utilizing spiral thin-cut brain CT-Scan (1-mm thickness). The outcome measured included modified Rankin scale (MRS), Glasgow Outcome Scale (GOS) and Disability rating Scale (DRS) which were all evaluated 3 months post-injury.

There was no significant difference between two study group regarding the baseline, 3rd day and 7th day of the contusion volume and the rate of contusion expansion. However, functional outcome scales of GOS, MRS and DRS at 3-months post-injury were significantly better in atorvastatin arm of the study compared to placebo (p values of 0.043, 0.039 and 0.030 respectively). Even though atorvastatin was not found to be more effective than placebo in reducing contusion expansion rate, it was associated with improved functional outcomes at 3-months following moderate to severe TBI.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and life-long disability worldwide. In the United States, about 50,000 deads are recorded as a consequence of TBI every year [1–3]. Despite recent advancements in pre-hospital care, surgical techniques and neuro-intensive care units, casualties still remained high [4,5] and novel therapeutic approaches should be considered [6,7]. TBI is categorized to primary which happens as an impact at the moment of traumatic event and secondary which are injuries that occur afterwards and further worsens the primary insult. Secondary injuries such as accumulation of intracellular potassium and calcium [8], neuroinflammation [9,10], free radical damage and excitotoxicity [11], oxidative stress and apoptosis [12] were known to increase the intensity of primary injury by ischemia, edema and progressive secondary hemorrhage. In the last two decades there has been a paradigm shift in the management of TBI with further emphasis on prevention and treatment of secondary injuries.

Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are a pharmacologic class of drugs which are well known for their effects on decreasing low-density lipoprotein (LDL) and beneficial effects in cardiovascular and cerebrovascular diseases. Their anti-inflammatory and anti-apoptotic properties have made them interesting drugs which may prove useful in attenuating secondary insults of TBI [13]. Atorvastatin has been associated with decreased cerebral edema [13], reduction in the volume of parenchymal hemorrhage [14], improved cerebral blood flow [15], increased synaptogenesis and angiogenesis [16], improved neurological outcome and further preservation of neuro-cognitive function [17–19] in animal models of TBI.

Safety of statins like atorvastatin, rosuvastatin and simvastatin with the dosage of 20 mg daily, in human subjects suffering trauma has been assessed in several previous clinical trials. [20–22] Pre-

* Corresponding author at: Trauma Research Center, Baqiyatallah University of Medical Sciences, Molla-Sadra Street, Tehran, Iran.
E-mail address: nima_med83@yahoo.com (N. Derakhshan).

http://dx.doi.org/10.1016/j.jocn.2017.06.010
0967-5868/

injury usage of atorvastatin in elderly victims of TBI was shown to be beneficial in terms of reduction in mortality rate and improved functional outcomes [23].

Thus we were encouraged to design a randomized clinical trial to evaluate the effect of atorvastatin on brain contusion volume and functional outcome in patients with moderate and severe TBI.

2. Materials and methods

2.1. Study population

This randomized clinical trial was conducted during a 16-month period from May 2015 to August 2016 in Shahid Rajaei hospital, a level I trauma center affiliated with Shiraz University of Medical Sciences. The study protocol was approved by the institutional review board (IRB) and medical ethics committee of Shiraz University of Medical Sciences (Reference number: CT-P-9375-7265). The study proposal was also registered with Iranian registry of clinical trials (www.irct.ir; IRCT2015050920353N2). All the patients' legally authorized representative provided their informed written consents before inclusion in the study. We included patients with moderate (GCS: 9–13) and severe (GCS: 5–8) TBI and those who had brain contusions of less than 30 cc volume in initial brain CT-Scan. All the included patients aged between 18 and 75 years, were referred less than 10 h of injury and had legally authorized representative. We excluded those patients with GCS of 3 and 4, brain CT-Scan Marshall grade IV or lesions who urged surgical evacuation, those with severe confounding injuries to internal organs, spinal cord injury (SCI), penetrating brain injuries, any known history of renal or hepatic diseases, Creatinine >2.5 mg/dl or patients on hemodialysis, total bilirubin over 1.5 times of normal value, past medical history of brain tumors, stroke, infections and previous craniotomy, pregnant women or those who intend to breastfeed after being discharged, international normalized ratio (INR) above 1.5 or history of coagulopathy or usage of anticoagulants (aspirin, clopidogrel, warfarin or low molecular weight heparin) within 7 days prior to admission, contusions in brain stem, an initial systolic BP below 90 mm Hg without respond to fluid resuscitation, contraindications of oral route for taking the medication and treatment with other investigational agents during hospitalization.

2.2. Randomization and intervention

All the patients were initially evaluated by a neurosurgery resident and the demographic, clinical and radiologic examinations were recorded in a data gathering form. Patients were randomly assigned to two study groups with a 1 to 1 ratio using a computerized random digit generator utilizing the admission number of the patients. Those assigned to first study group received 20 mg atorvastatin (Atorvastatin, 20 mg tablets, RAHA Pharmaceutical co., Isfahan, Iran) daily for 10 days while those assigned to second study group received placebo in the same dosage (n = 32). All the patients received the intervention within 10 h of injury. The placebo was prepared in Shiraz pharmacy school with resemblance to atorvastatin tablets in size and color.

2.3. Contusion volumetry

Non-contrasted spiral thin-cut (1-mm thickness) brain CT-Scans were obtained on admission, at 3rd and 7th days after injury. Volumetric measurements of contusions were carried out by manual outlining of the contusions in the source images sent to General electric advanced workstation 4.4, by a radiologist blinded to the patients' study group and the chronology of scans, using volume viewer 3, built-in software. For those who had multiple brain contusions, the sum of volumes was recorded. The patients, physicians, those giving the intervention and those recording the outcome were all blinded to the study groups. Only statisticians were aware of the study groups.

2.4. Outcome measures

The main outcome of the study was the contusion volume and the functional recovery. The volumetry was defined above and the variables are discussed in next section. All the patients were followed for 3 months and were visited in outpatient clinics in a monthly basis. The functional recovery was measured and recorded by a neurosurgery resident blinded to the study groups, using Glasgow outcome scale (GOS), modified Rankin scale (MRS) and Disability rating scale (DRS) at 3-month follow-up visit. The assessment was based on asking the patient and his or her guardians about arousability and awareness and the level of independence in feeding, grooming, toileting, ambulation and return of the patient to previous employability status.

2.5. Statistical analysis

In order to have 80% power to detect 5% difference between main outcome measures including the GOSE and contusion volume with α equal to 0.05 and β equal to 0.2, we required 30 patients in each study group. In order to compensate for non-evaluable patients and those being lost to follow-up, we included a total number of 64 patients (32 in each study group). All the statistical analyses were performed using statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 22.0. Data are reported as mean ± SD as appropriate. To evaluate the expansion of contusions we defined a variable as (volume 2 – Volume 1) × 100/Volume 1 which revealed the rate of expansion of contusion volume comparing the initial brain CT-scan and the one on the 3rd admission day and another variable as (Volume3 – volume1) × 100/Volume 1 to compare the rate of expansion of contusion volume between the first CT and the one on the 7th day of admission. In order to compare the parametric variables with normal distribution between two study groups, independent *t*-test was utilized. Kruskal-Wallis test was used to compare parametric data without normal distribution between two study groups. Changes in contusion volumes within study groups were compared using repeated measures. Non-parametric data were compared using chi-square test. A 2-sided p-value of less than 0.05 was considered statistically significant.

$$\textit{Variation } 1-2(\%) = \frac{100 \times (\text{Volume } 2 - \text{Volume } 1)}{\text{Volume } 1}$$

$$\textit{Variation } 1-3(\%) = \frac{100 \times (\text{Volume } 3 - \text{Volume } 1)}{\text{Volume } 1}$$

3. Results

Overall we recruited 65 patients for eligibility of whom 1 was excluded and 64 were randomized to two study groups (each containing 32). In those receiving atorvastatin, 10 were lost to follow-up and 1 discontinued medication due to side effects. In placebo group 6 were lost to follow-up and 3 discontinued interventions. Thus the final number of patients included in the final analysis was 44 (21 in atorvastatin and 23 in placebo group). The CONSORT flow diagram of the study is demonstrated in Fig. 1. There was no significant difference between two study groups regarding the baseline characteristics (Table 1).

Please cite this article in press as: Farzanegan GR et al. Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled clinical trial. J Clin Neurosci (2017), http://dx.doi.org/10.1016/j.jocn.2017.06.010

We found that there was no significant difference between two study group regarding the baseline, 3rd day and 7th day of the contusion volume (Table 2). Also, no difference was seen between the two study groups regarding the rate of expansion of contusions based on the two variations 1–2 and 1–3, previously defined. However, functional outcome scales of GOS, MRS and DRS were significantly better in atorvastatin arm of the study compared to placebo (p values of 0.043, 0.039 and 0.030 respectively). The comparison of functional outcome scales between the two groups is summarized in Table 3.

4. Discussion

Despite recent advancements in the management of patients with TBI, moderate and severe TBI is still associated with a considerable and devastating mortality and long term disability rate. In the current study, we investigated the efficacy of atorvastatin on contusion volume and functional outcome of patients with moderate to severe TBI. We concluded that atorvastatin is associated with improved functional outcome in patients with moderate and severe TBI who sustained cerebral contusion. Our study has failed to demonstrate any beneficial effect on expansion rate of cerebral contusions in these patients.

Atorvastatin was shown to modulate oxidative stress and glutamate excitotoxicity in Central nervous system (CNS) injuries [24]. In sub arachnoid hemorrhage (SAH) atorvastatin reduces cerebral vasospasm through its anti-apoptotic potential by attenuating up-regulation of caspases [25]. Atorvastatin was also associated with improved behavior recovery in animal models of subdural hematoma, implicating its beneficial role in TBI. This anti-neuroinflammatory potential was attributed to decreased TNF-α and IL-6 level as well as vascular endothelial growth factor (VEGF)

Table 1
The baseline characteristics of 44 patients with moderate and severe traumatic brain injury receiving atorvastatin or placebo.

	Atorvastatin (n = 21)	Placebo (n = 23)	p-value
Age (years)	37.29 ± 20.52	30.48 ± 14.33	0.206
Gender			
Men (%)	20 (95.2%)	20 (87.0%)	
Women (%)	1 (4.8%)	3 (13.0%)	
Initial GCS	9.29 ± 2.51	8.43 ± 2.72	0.29
Best Motor Response	5.14 ± 0.85	4.78 ± 1.08	0.23
Pupil			0.705
Reactive (%)	18 (85.6%)	20 (87.0%)	
Non-reactive (%)	2 (9.6%)	1 (4.3%)	
Anisocoria (%)	1 (4.8%)	2 (8.7%)	
Marshall Classification			0.196
II (%)	20 (95.2%)	19 (82.6%)	
III (%)	1 (4.8%)	4 (17.4%)	
Rotterdam CT Score			0.992
1 (%)	2 (9.6%)	0 (0.0%)	
2 (%)	8 (38.0%)	11 (47.8%)	
3 (%)	9 (42.8%)	12 (52.2%)	
4 (%)	2 (9.6%)	0 (0.0%)	

Table 2
The contusion volumetry of 44 patients with moderate and severe traumatic brain injury being treated with atorvastatin or placebo.

	Atorvastatin (n = 21)	Placebo (n = 23)	p-value
Contusion Volume			
On admission (cm^3)	6.06 ± 2.98	6.08 ± 3.54	0.98
At 3rd day (cm^3)	6.24 ± 2.92	6.59 ± 3.84	0.73
At 7th day (cm^3)	6.34 ± 3.03	6.57 ± 3.73	0.82
Contusion expansion ratio			
Ratio 1–2 (%)	4.82 ± 6.52	9.22 ± 9.46	
Ratio 1–3 (%)	5.23 ± 7.54	10.20 ± 10.94	

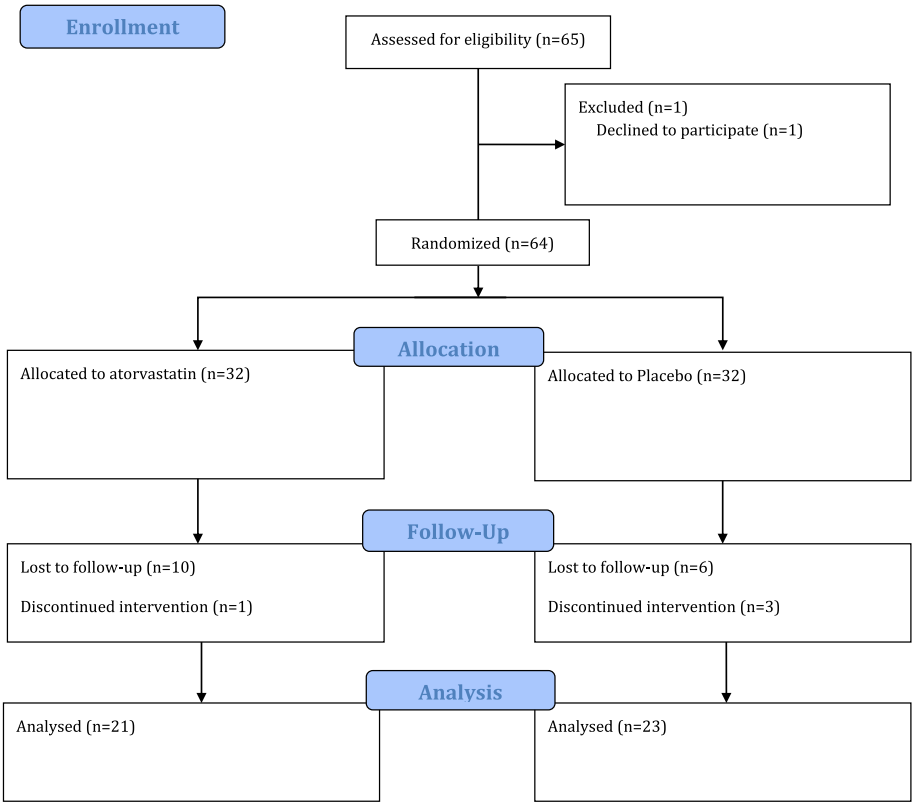

Fig. 1. CONSORT flow diagram of the study.

Please cite this article in press as: Farzanegan GR et al. Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled clinical trial. J Clin Neurosci (2017), http://dx.doi.org/10.1016/j.jocn.2017.06.010

Table 3
The functional outcome of 44 patients with moderate and severe traumatic brain injury being treated with atorvastatin vs. placebo.

	Atorvastatin (n = 21)	Placebo (n = 23)	p-value
3-Month GOS	4.57 ± 0.74	4.09 ± 0.79	0.043
Good Recovery (%)	15 (71.4%)	8 (34.8%)	
Moderate disability (%)	3 (14.3%)	9 (39.1%)	
Severe disability (%)	3 (14.3%)	6 (26.1%)	
Persistent vegetative state (%)	0 (0.0%)	0 (0.0%)	
Death (%)	0 (0.0%)	0 (0.0%)	
3-Month MRS	1.57 ± 1.24	2.39 ± 1.30	0.039
No Symptoms (%)	3 (14.3%)	1 (4.3%)	
No significant disability (%)	10 (47.7%)	7 (30.4%)	
Slight disability (%)	3 (14.3%)	3 (13.0%)	
Moderate disability (%)	4 (19%)	6 (26.1%)	
Moderately severe disability (%)	0 (0.0%)	6 (26.1%)	
Severe disability (%)	1 (4.7%)	0 (0.0%)	
Dead (%)	0 (0.0%)	0 (0.0%)	
3-Month DRS	2.86 ± 4.83	6.91 ± 6.84	0.030
Normal (%)	9 (42.8%)	1 (4.3%)	
Mild (%)	7 (33.3%)	7 (30.4%)	
Partial (%)	0 (0.0%)	4 (17.4%)	
Moderate (%)	1 (4.7%)	1 (4.3%)	
Moderately Severe (%)	4 (19%)	4 (17.4%)	
Severe (%)	0 (0.0%)	2 (8.7%)	
Extremely Severe (%)	1 (4.7%)	4 (17.4%)	
Vegetative State (%)	0 (0.0%)	0 (0.0%)	
Extreme vegetative state (%)	0 (0.0%)	0 (0.0%)	

DRS: Disability Rating Scale; GOS: Glasgow Outcome Scale; MRS: Modified Rankin Scale.

gene expression [26]. Two recent studies by Mountney et al. [27,28] evaluated simvastatin treatment in a rat model of severe TBI and concluded that it was associated with improved cognitive outcomes, especially when administered through intravenous route.

A recent study by Neilson et al. [29] demonstrated that prior statin usage was not associated with improved functional outcome in an asian population with severe TBI. This might be due to holding the medication in hospital course which was unclear in the mentioned study and also differences in races between pharmacokinetics of statins and different members of statin family being used by the patients. A study by Sánchez-Aguilar et al. [30] concluded that rosuvastatin was associated with reduction of tumor necrosis factor-α (TNF-α) and disability scores, despite not having effect on other inflammatory cytokines such as IL-1β, IL-6, and IL-10. This study supports the fact that statins may prove beneficial in alleviating outcome of severe TBI in human and opened a window to investigate other members of statin family for such an effect.

The last two studies were among the only clinical data available in the literature on the role of statins in moderate to severe TBI. Here in, we found atorvastatin at the dosage of 20 mg daily for 10 days to be beneficial in improving the 3-months functional outcome of moderate and severe TBI patients sustaining cerebral contusions. However, atorvastatin-treated patients were not different from their placebo-treated counterparts, according to rate of contusion expansion and length of hospital stay.

We faced some limitations in the current study. First, the calculated sample size was 30 for each group and we included 32 in order to compensate for non-evaluable patients. But a significant number of patients were lost to follow-up in both study groups resulting in reduction of the population size to less than optimal. Despite this fact, the final results demonstrated an 80% power which is acceptable. Whether or not inclusion of the lost to follow-up individuals would have resulted in neutral results for the outcome measures, is yet to be cleared with further clinical trials with larger population size. This fact should be taken into consideration that restricts inclusion and exclusion criteria resulted in limited number of patients being eligible to be included in the study. The other limitation was that MRI is the method of choice for volumetric analysis of brain contusions. However, as most of the patients are intubated and our hospital is source limiting, performing MRI was not applicable. Volumetric assessment of brain lesions with CT scan was shown to have an acceptable accuracy and reliability compared to MRI [31] and its application was also investigated in volumetric assessment of brain contusions in patients with moderate and severe TBI [32].

Taking all these together, this is among the only available clinico-radiologic data in the literature regarding the role of atorvastatin in management of patients with moderate to severe TBI which should be followed by larger multi-center clinical trials.

Clinical trial registry

This trial is registered in Iranian Registry of Clinical Trials (www.irct.ir; IRCT 2015050920353N2).

Conflict of interest

No conflict of interest.

Acknowledgements

This study is result of the thesis of Dr. Nima Derakhshan for partial fulfillment of the requirements for military service as a member of Iran's National Elite Foundation (INEF) which was conducted through a cooperation between Trauma Research Center of Baqiyatallah University of medical sciences (Tehran, Iran) and Shahid Rajaee Trauma research center, affiliated with Shiraz University of medical sciences (Shiraz, Iran). We sincerely appreciate the collaboration of intensive care unit and radiology unit personnel of Shahid Rajaei Hospital. We would also like to acknowledge the participation of the patients and their families in the current research.

References

[1] Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil 2006;21(6):544–8.
[2] Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. J Head Trauma Rehabil 2010;25(2):72–80.
[3] Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil 2008;23(2):123–31.
[4] Peymani P, Heydari ST, Hoseinzadeh A, Sarikhani Y, Hedjazi A, Zarenezhad M, et al. Epidemiological characteristics of fatal pedestrian accidents in Fars Province of Iran: a community-based survey. Chin J Traumatol 2012;15(5):279–83.
[5] Heydari ST, Hoseinzadeh A, Ghaffarpasand F, Hedjazi A, Zarenezhad M, Moafian G, et al. Epidemiological characteristics of fatal traffic accidents in Fars province, Iran: a community-based survey. Public Health 2013;127(8):704–9.
[6] Khalili H, Sadraei N, Niakan A, Ghaffarpasand F, Sadraei A. Role of intracranial pressure monitoring in management of patients with severe traumatic brain injury: results of a large level I trauma center in Southern Iran. World Neurosurg 2016;94:120–5.
[7] Khalili H, Niakan A, Ghaffarpasand F. Effects of cerebrolysin on functional recovery in patients with severe disability after traumatic brain injury: a historical cohort study. Clin Neurol Neurosurg 2016;152:34–8.
[8] Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. Dis Model Mech 2013;6(6):1307–15.
[9] Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav Immun 2012;26(8):1191–201.
[10] Nwachuku EL, Puccio AM, Adeboye A, Chang YF, Kim J, Okonkwo DO. Time course of cerebrospinal fluid inflammatory biomarkers and relationship to 6-month neurologic outcome in adult severe traumatic brain injury. Clin Neurol Neurosurg 2016;149:1–5.
[11] Greve MW, Zink BJ. Pathophysiology of traumatic brain injury. Mt Sinai J Med 2009;76(2):97–104.
[12] Ozay R, Turkoglu E, Gurer B, Dolgun H, Evirgen O, Erguder BI, et al. Does decorin protect neuronal tissue via its antioxidant and antiinflammatory activity from traumatic brain injury: an experimental study. World Neurosurg 2016.

[13] Turkoglu OF, Eroglu H, Okutan O, Gurcan O, Bodur E, Sargon MF, et al. Atorvastatin efficiency after traumatic brain injury in rats. Surg Neurol 2009;72(2):146–52. discussion 52.
[14] Lu D, Mahmood A, Qu C, Goussev A, Lu M, Chopp M. Atorvastatin reduction of intracranial hematoma volume in rats subjected to controlled cortical impact. J Neurosurg 2004;101(5):822–5.
[15] Wang H, Lynch JR, Song P, Yang HJ, Yates RB, Mace B, et al. Simvastatin and atorvastatin improve behavioral outcome, reduce hippocampal degeneration, and improve cerebral blood flow after experimental traumatic brain injury. Exp Neurol 2007;206(1):59–69.
[16] Lu D, Goussev A, Chen J, Pannu P, Li Y, Mahmood A, et al. Atorvastatin reduces neurological deficit and increases synaptogenesis, angiogenesis, and neuronal survival in rats subjected to traumatic brain injury. J Neurotrauma 2004;21 (1):21–32.
[17] Qu C, Lu D, Goussev A, Schallert T, Mahmood A, Chopp M. Effect of atorvastatin on spatial memory, neuronal survival, and vascular density in female rats after traumatic brain injury. J Neurosurg 2005;103(4):695–701.
[18] Lu D, Mahmood A, Goussev A, Schallert T, Qu C, Zhang ZG, et al. Atorvastatin reduction of intravascular thrombosis, increase in cerebral microvascular patency and integrity, and enhancement of spatial learning in rats subjected to traumatic brain injury. J Neurosurg 2004;101(5):813–21.
[19] Peng W, Yang J, Yang B, Wang L, Xiong XG, Liang Q. Impact of statins on cognitive deficits in adult male rodents after traumatic brain injury: a systematic review. Biomed Res Int 2014;2014:261409.
[20] Akcay M, Akcay G, Kiziltunc A, Oztürk G, Aydinli B. The effect of short-term treatment with atorvastatin on E-selectin levels in severely burned patients. Int J Clin Pharmacol Res 2004;25(2):65–9.
[21] Tapia-Perez JH, Sanchez-Aguilar M, Torres-Corzo JG, Gordillo-Moscoso A, Martinez-Perez P, Madeville P, et al. Effect of rosuvastatin on amnesia and disorientation after traumatic brain injury (NCT00329758). J Neurotrauma 2008;25(8):1011–7.
[22] Patil S, Holt G, Raby N, McLellan AR, Smith K, O'Kane S, et al. Prospective, double blind, randomized, controlled trial of simvastatin in human fracture healing. J Orthop Res 2009;27(3):281–5.
[23] Schneider EB, Efron DT, MacKenzie EJ, Rivara FP, Nathens AB, Jurkovich GJ. Premorbid statin use is associated with improved survival and functional outcomes in older head-injured individuals. J Trauma 2011;71(4):815–9.
[24] Vandresen-Filho S, Martins WC, Bertoldo DB, Mancini G, Herculano BA, de Bem AF, et al. Atorvastatin prevents cell damage via modulation of oxidative stress, glutamate uptake and glutamine synthetase activity in hippocampal slices subjected to oxygen/glucose deprivation. Neurochem Int 2013;62(7):948–55.
[25] Cheng G, Wei L, Zhi-Dan S, Shi-Guang Z, Xiang-Zhen L. Atorvastatin ameliorates cerebral vasospasm and early brain injury after subarachnoid hemorrhage and inhibits caspase-dependent apoptosis pathway. BMC Neurosci 2009;10:7.
[26] Li T, Wang D, Tian Y, Yu H, Wang Y, Quan W, et al. Effects of atorvastatin on the inflammation regulation and elimination of subdural hematoma in rats. J Neurol Sci 2014;341(1–2):88–96.
[27] Mountney A, Bramlett HM, Dixon CE, Mondello S, Dietrich WD, Wang KK, et al. simvastatin treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma 2016;33(6):567–80.
[28] Mountney A, Boutte AM, Gilsdorf J, Lu XC, Tortella FC, Shear DA. Intravenous administration of simvastatin improves cognitive outcome following severe traumatic brain injury in rats. J Neurotrauma 2016;33(16):1492–500.
[29] Neilson SJ, See AA, King NK. Effect of prior statin use on outcome after severe traumatic brain injury in a South-East Asian population. Brain Inj 2016;30 (8):993–8.
[30] Sanchez-Aguilar M, Tapia-Perez JH, Sanchez-Rodriguez JJ, Vinas-Rios JM, Martinez-Perez P, de la Cruz-Mendoza E, et al. Effect of rosuvastatin on cytokines after traumatic head injury. J Neurosurg 2013;118(3):669–75.
[31] Volbers B, Staykov D, Wagner I, Dorfler A, Saake M, Schwab S, et al. Semi-automatic volumetric assessment of perihemorrhagic edema with computed tomography. Eur J Neurol 2011;18(11):1323–8.
[32] Khalili H, Derakhshan N, Niakan A, Ghaffarpasand F, Salehi M, Eshraghian H, et al. Effects of oral glibenclamide on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injuries: a randomized double-blind placebo-controlled clinical trial. World Neurosurg 2017;101:130–6.

Please cite this article in press as: Farzanegan GR et al. Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled clinical trial. J Clin Neurosci (2017), http://dx.doi.org/10.1016/j.jocn.2017.06.010