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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

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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-

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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).