Enoxaparin in the treatment of severe traumatic brain injury: A randomized clinical trial

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Abstract

**Background:** Enoxaparin was shown to have a neuroprotective effect in animal models as well as a human study following traumatic brain injury. This study was conducted to assess the effect of enoxaparin on the clinical outcome of severe traumatic brain injury (TBI) and its safety.

**Methods:** This study is a randomized double-blinded placebo-controlled trial. The inclusion criteria were age 16–70, a closed head injury, a postresuscitation Glasgow Coma Scale (GCS) between 5 and 8, and a latency time between the injury and entering the study of less than 5 h. The patients were randomized into enoxaparin and placebo groups. In the enoxaparin group, 0.5 mg/kg enoxaparin was injected subcutaneously every 6 h in six total doses. The two groups were compared for the occurrence of intracranial hematoma (ICH) and for clinical neurological outcome, assessed by the Glasgow Outcome Scale.

**Results:** Twenty-seven patients were assigned to the placebo group and 26 to the enoxaparin group. The two groups were similar regarding baseline characteristics, including age, sex, postresuscitation GCS, and best motor response. The occurrence of new ICH or an ICH size increase was insignificantly more frequent in the enoxaparin group than the placebo group (26.9% vs. 7.4%, \( P = 0.076 \)). The favorable outcome rate in the enoxaparin group was significantly higher than in the placebo group (57.7% vs. 25.9%, \( P = 0.019 \)).

**Conclusions:** This study showed that the early administration of enoxaparin could lead to favorable outcomes in severe TBI patients without significantly increasing cerebral hemorrhagic complications.

**Key Words:** Enoxaparin, intracranial hematoma, outcome, traumatic brain injury

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INTRODUCTION

Traffic accidents are a common cause of morbidity and mortality in Iran. Traumatic brain injury (TBI) is the most common fatal consequence of traffic accidents and the most common cause of death and disability following motor vehicle accidents. The primary insult can result in severe brain damage at the time of impact. However, a significant portion of neurological impairments are due to secondary insults, including hypoxia, hypotension, brain edema, intracranial hypertension, cerebral hyperperfusion, seizure, and coagulopathy. Following TBI, circulating leukocytes and particularly polymorphonuclear cells are believed to interact with cerebrovascular endothelial cells to migrate out of circulation. The recruited leukocytes promote the inflammatory process in the interstitial area, leading to blood–brain barrier permeability and impairments that induce secondary insults as brain swelling. In addition to their anticoagulant behaviors, heparinoid derivatives, such as enoxaparin, have anti-inflammatory effects by blunting endothelial activation and restoring endothelial cells. Studies in animal models have shown that the heparinoid derivatives reduce cerebral edema and brain damage following TBI through their anti-inflammatory effects.

Recent studies have reported that heparin and low molecular weight heparin (enoxaparin) are safe for the prevention of deep vein thrombosis (DVT) in TBI and can be used even in the early phase in patients with traumatic intracranial hematoma (ICH) without increasing the risk of hemorrhage. A recent human study revealed that the early initiation of DVT prophylaxis can improve radiological and neurological outcomes in patients with severe TBI. We conducted a double-blind randomized study to evaluate the effect of a high dose of enoxaparin on the occurrence of intracranial hemorrhage and neurological outcome in severe TBI.

MATERIALS AND METHODS

This study was a pilot trial to compare the effects of subcutaneous enoxaparin versus placebo in severe TBI. The study design was a randomized double-blinded placebo-controlled clinical trial. The study was approved by the ethics committee of Mashhad Medical Faculty. As the patients had severe TBI, informed consent was obtained from their nearest relatives.

Patients with the following criteria were enrolled in the study: age between 16 and 70, closed head injury, postresuscitation Glasgow Coma Scale (GCS) between 5 and 8, and latency time between injury and entering the study of less than 5 h. Patients with the following criteria were excluded from the study: ICH greater than 5 mm in diameter, major extracranial injury, history of coagulopathy, history of anticoagulant or anti-aggregant drugs, abnormal coagulation profile on admission, pregnancy, and admission creatinine of more than 2 mg/dL. Any petechial hemorrhage with a diameter of less than 5 mm, extra-axial hematoma with a diameter of less than 2 mm, small subarachnoid hemorrhage (SAH) in only one cistern or one sulcus, or small intraventricular hemorrhage (IVH) in one ventricle were accepted.

In a randomized balanced fashion, one patient received enoxaparin and one received placebo. The dosage of enoxaparin was 0.5 mg/kg in each subcutaneous injection; the placebo was 2 mL sterile water in each subcutaneous injection. The patients were subjected to six doses every 6 h, and the first dose was administered within 5 h of trauma. The patient, investigators, and evaluators were blinded to the treatment, with the exception of the nurse responsible for randomization and injection.

On admission, the basic characteristics, including age, sex, mechanism of trauma, vital signs, postresuscitation GCS, best motor response (BMR), and associated extracranial injury, were recorded.

On admission, the complete blood count, coagulation profile (prothrombin time, partial thromboplastin time, and international normalized ratio), and brain CT scan were carried out. Then, every 6 h, the above lab tests and CT scan were repeated for 2 days and evaluated before each treatment injection. The laboratory tests were assessed every other day for the next 12 days. The CT scans were repeated at day 4 and before discharge. The CT scan could be repeated as needed in case of neurological changes. On admission and every other day, blood sugar, blood urea nitrogen, and creatinine were measured for 2 weeks. The patient’s CT scans were evaluated according to the Marshall Classification. All hematomas, including contusion, petechial hemorrhage, extra-axial hematoma, SAH, or IVH, were considered as ICH. The hematomas were assessed for an increase in size and number. If the ICH size increased to more than 5 mm, the treatment was stopped. The injections were also stopped if the coagulation profile became abnormal during treatment.

The patients were treated and monitored based on the routine guidelines for severe TBI at the neurosurgical ICU. Because of bleeding risk, intracranial pressure monitoring was not carried out. All patients received DVT prophylaxis starting 48 h after admission.

At discharge, the patient’s outcome was assessed according to the Glasgow Outcome Scale, that is, good recovery, moderate disability, severe disability, vegetative state, and death. Additionally, the clinical outcome was divided into two groups: favorable outcome, including good recovery and moderate disability; and poor outcome, including severe disability, vegetative state, and death.
The primary end point was the radiological appearance of a new ICH or an increase in the size of the previous ICH. Any ICH change was considered major if it led to neurosurgical intervention or neurological deterioration. The secondary end point was the clinical outcome of the patient at discharge, favorable outcome versus poor outcome, or death.

The statistical analysis was performed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test, two-tailed Fisher’s exact test, and t-test were used to compare differences between two groups for categorical and continuous variables accordingly. The Mann–Whitney U test was used to compare medians. P < 0.05 was considered to indicate significance.

RESULTS

Basic characteristic
Fifty-four patients were enrolled in the study and randomized. One patient was excluded because he had an ICH larger than 5 mm on admission. Of the remaining 53 patients, 27 were assigned into the placebo group and 26 to the enoxaparin group. The patient characteristics are shown in Table 1. The mean age of the patients was 26.5 with a range of 17–66. Males were predominant. The mechanism of trauma was motor vehicle accident in all patients. The median postresuscitation GCS was 7 with a BMR median of 5. The two groups were similar for baseline characteristics, with the exception of a higher rate of abnormal pupils and poor GCS (GCS 5–6) in the placebo group, which was not significant.

Primary end point
In the enoxaparin group, seven patients (26.9%) showed new ICH or increasing ICH size compared with two patients (7.4%) in the placebo group [Table 2]. The rate of ICH development was more than twofold of the enoxaparin group; however, this difference did not reach statistical significance (P = 0.076). In the enoxaparin group, three patients developed new small extra-axial hematoma, two patients developed new small contusions, and another two showed an expansion of existing contusions. In the placebo group, small petechial hemorrhage and small IVH were found in the follow-up CT scan of two patients. None was major, and no patients required neurosurgical intervention.

According to Marshall CT grade,[22] four patients (14.8%) showed worsening grade (two patients in each group), which is compatible with increasing edema. Follow-up CT scan showed brain injury sequelae in seven patients (30.4%) in the placebo group compared with two patients (8.3%) in the enoxaparin group.

Secondary end point
On discharge, death occurred in two patients (7.7%) in the enoxaparin group versus four patients (14.8%) in the placebo group; vegetative state occurred in two patients (7.7%) in the enoxaparin group versus nine (33.3%) in the placebo group; severe disability occurred in 26.9% in the enoxaparin group versus 25.9% in the placebo group; moderate disability occurred in 7.7% of the enoxaparin group versus 18.5% in the placebo group; and good recovery occurred in 50% of the enoxaparin group versus 7.4% in the placebo group [Table 3]. As shown in Figure 1, there was a significant tendency toward a better outcome in the enoxaparin group compared with the placebo group (P = 0.006). The favorable outcome rate was significantly higher in the enoxaparin group than in the placebo group (57.7% vs. 25.9%, P = 0.019). Death occurred twice in the placebo group; however, the difference was not significant. The two groups were similar regarding ICU stay and hospital stay. Coagulation abnormalities occurred in 29.6% of the placebo group and

Table 1: Basic patient characteristics

| Basic characteristic                     | Total 53 (100%) | Enoxaparin group 26 (100%) | Placebo group 27 (100%) | P     |
|------------------------------------------|-----------------|----------------------------|-------------------------|-------|
| Age (years)                              | 26.5±11.3       | 27.2±13.2                  | 25.9±0.9                | 0.669 |
| Male                                     | 43 (81.1)       | 22 (84.6)                  | 22 (81.5)               | 1.000 |
| Motor vehicle accident                   | 53 (100)        | 26 (100)                   | 27 (100)                |       |
| Abnormal pupil                           | (13)            | (3)                        | (11.5)                  | 0.054 |
| Postresuscitation                         | 7               | 7                          | 7                       | 0.378 |
| GCS                                       |                 |                            |                         |       |
| BMR                                       | 5               | 5                          | 5                       | 0.064 |
| GCS 5–6                                   | 15 (28.3)       | 4 (15.4)                   | 11 (37)                 | 0.119 |
| Hypotension                               | 3 (5.7)         | 0 (0.0)                    | 3 (11.1)                | 0.236 |
| Hypoxia                                   | 3 (5.7)         | 0 (0.0)                    | 2 (7.4)                 | 0.491 |
| History of opium abuse                    | 23 (43.4)       | 11 (42.3)                  | 12 (44.4)               | 0.875 |
| Intracranial hematoma                     | 20 (37.7)       | 11 (42.3)                  | 9 (33.3)                | 0.500 |
| Marshall CT grade >1                      | 13 (24.5)       | 6 (23.1)                   | 7 (25.9)                | 0.810 |

Table 2: CT changes during hospitalization (primary outcome)

| CT changes during hospitalization (primary outcome) | Total 53 (100%) | Enoxaparin group 26 (100%) | Placebo group 27 (100%) | P     |
|---------------------------------------------------|-----------------|----------------------------|-------------------------|-------|
| New contusion                                     | 4 (7.5)         | 2 (7.7)                    | 2 (7.4)                 | 1.000 |
| Contusion expansion                               | 2 (3.8)         | 2 (7.7)                    | 0 (0.0)                 | 0.236 |
| New extra-axial hematoma                          | 3 (5.7)         | 3 (11.5)                   | 0 (0.0)                 | 0.111 |
| Any ICH change                                    | 9 (17.0)        | 7 (26.9)                   | 2 (7.4)                 | 0.076 |
| CT grade increase                                 | 4 (7.5)         | 2 (7.7)                    | 2 (7.4)                 | 1.000 |
| Follow-up CT sequels*                             | 9 (19.1)        | 2 (8.3%)                   | 7 (30.4%)               | 0.054 |

*Shown among survivors; ICH=Intracranial hematoma
a clinical trial could answer many questions regarding the neuroprotective effects of heparin derivatives and their safety.

Animal studies showed that enoxaparin reduced brain edema and secondary brain injury following TBI due to its anti-inflammatory effects. The anti-inflammatory effects of enoxaparin occurred in various ways. Enoxaparin could blunt oxidative lipid and protein damage, COX2 overexpression, and reactive astrocytosis in the hypothalamus of rats following TBI. Enoxaparin consequently reduced hypothalamic damage. Enoxaparin has also been shown to reduce the cerebrovascular interaction between circulating leukocytes and endothelial cells. By reducing brain edema involving the parietal cortex and hippocampus, enoxaparin improved the functional outcome in rats in the context of experimental TBI and cerebral ischemia. In addition to reducing the brain edema and improving the neurological outcome following TBI, enoxaparin did not increase the cerebral contusion size even with a dose as high as 1 mg/kg every 6 h. Enoxaparin was also hypothesized to prevent thrombosis in cerebral microcirculation and to reduce related damage in another study. This study did not find any evidence for reducing brain edema in a serial brain CT scan. In other words, the Marshall grading did not differ between the enoxaparin and placebo groups. However, the follow-up and late CT scans showed the less abnormalities, including brain atrophy and hypodensities, in the enoxaparin group compared with the placebo group, which may be consistent with reduced brain damage due to secondary brain injury. The better outcome in the enoxaparin group in this study supported the neuroprotective effects of enoxaparin shown in the other studies.

Several studies reported the safety of enoxaparin for preventing DVT and pulmonary embolism in severe TBI. Chemical DVT prophylaxis could be started in the early phase of severe TBI without increasing the occurrence of ICH or increasing their size. According to these studies, we started enoxaparin within 6 h of trauma. The next issue was the dose of enoxaparin. All human studies reported a prophylaxis dose of enoxaparin. However, the animal studies administered different doses from as low as 0.5 mg/kg in the initial dose followed by 0.5 mg/kg every 6 h to as high as 0.5 mg/kg in the initial dose and 2 mg/kg every 6 h. We chose the lowest dose in the animal studies, which was equal to the treatment dose for DVT. We used four doses of 0.5 mg/kg/day instead of two doses of 1 mg/kg/day to reduce the risk of potential hemorrhage in earlier treatment. Similar to studies with a prophylaxis dose, our results confirmed that a higher dose does not significantly increase the risk of hemorrhage. In addition, this study showed that the initiation of a high dose of enoxaparin in the very early
CONCLUSION

This study revealed that the treatment dose of enoxaparin is safe in the early phase of severe nonhemorrhagic TBI and that it did not significantly increase major cerebral hemorrhagic complications. Enoxaparin could also increase favorable outcomes in these patients. Double-blind randomized multicenter studies with larger cases could better evaluate the safety and effect of enoxaparin in severe TBI.

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Conflicts of interest
There are no conflicts of interest.

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