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The effect of head trauma on fracture healing: biomechanical testing and finite element analysis

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Objectives: We aimed to evaluate the effect of head trauma on fracture healing with biomechanical testing, to compare the results obtained from a femur model created by finite element analysis with experimental data, and to develop a finite element model that can be employed in femoral fractures.

Methods: Twenty-two Wistar albino rats were randomized into two groups. The control group was subjected to femoral fracture followed by intramedullary fixation, whereas the head trauma group was subjected to femoral fracture followed by intramedullary fixation along with closed blunt head trauma. Bone sections obtained with computed tomography from rat femurs were transferred into a computer and a 3D mathematical model of femur was created. At the end of week 4, femurs were examined by biomechanical testing and finite element analysis.

Results: The mean maximum fracture load was significantly higher in the head trauma group than in control group ($p<0.05$). Maximum strain values were also significantly high in the head trauma group ($p<0.05$). There was no significant difference between the groups with regard to maximum deformation ($p>0.05$). The head trauma group had significantly higher mean bending rigidity than the control group ($p<0.05$). The head trauma group showed no significant difference from the control group in terms of strain energy and elasticity module ($p>0.05$). There was no significant difference between experimental biomechanical test and finite element analysis ($p>0.05$).

Conclusion: Noninvasive methods such as finite element analysis are useful in examination of the mechanical structure of bones. Experimental biomechanical test and finite element analysis methods suggest that head trauma contributes to fracture healing.

Key words: Biomechanics; femur; finite element analysis; fracture healing; head trauma; 4-point bend test; rat.

Fracture healing is a repairing process characterized by regeneration of the fractured bone as a healthy original bone tissue with complete biomechanical integrity. The components of the bone tissue are regulated by local and systemic factors.[1,2] The effects of these factors over fracture healing have been identified by experimental and clinical studies.[3-5]

Previous clinical studies showed that callus size is larger and healing time is shorter in patients with a head trauma compared with the normal fracture

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cases.[6-10] Perkins and Skirving treated femoral fractures by intramedullary pinning in patients with and without head trauma, and observed larger callus sizes and shorter healing times in patients with head trauma than the ones with normal fractures.[8] Spencer reported a better radiological healing response of fractures in head trauma patients than in those without head trauma.[9] Newman et al.[11] found that fracture healing time in head trauma patients was approximately half the time required for the healing of the same fracture in patients without head trauma. Renfree et al.[12] showed that, osteoblast proliferation and alkaline phosphatase production are stimulated in the serum after head trauma. Additionally, many studies including cell models have been performed to reveal the pathophysiological mechanisms underlying the osteogenic effect of traumatic head injury.[10,13,14] However, while activation of serum osteoblasts has been shown in cerebral or spinal injuries, the stimulation of the osteogenesis in head trauma patients is not clearly known.

Mechanical behaviors of biological systems can be understood more accurately and sensitively with modelling complex structures by finite element analysis, which is a numerical computer method. These models allow investigators to repeat the tests at choice, calculate the variations in predicted mechanical responses by modifying the model, and have control over the experimental design.[15] On the other hand, comparison of parameters measured by biomechanical tests and values calculated by finite element analysis is required for the accuracy of the created model.

In this study, we aimed to evaluate the effect of head trauma on fracture healing by an experimental biomechanical study. We also aimed to compare the acquired results and experimental data by using a finite element model of the femur, and to develop a finite element model that can be used in femur fractures.

Materials and methods

In this study, 22 male Wistar albino rats weighing 220-240 g and of 2.5-3 months of age were used. Rats were kept at 21 C° in a 12-hour light/12-hour dark cycle. Throughout the course of the study, the rats were fed with standard rat diet and their water was provided ad libidum. The approval of the Ege University Faculty of Medicine Ethics Committee of Animal Experiments was obtained prior to the study and the study was conducted in accordance with the internationally accepted guidelines.

Rats were randomized into 2 groups. Group 1 (n=10), control group, was subjected to femoral fracture and intramedullary fixation, whereas Group 2 (n=12) was subjected to femoral fracture, intramedullary fixation, and closed blunt head trauma. All of the rats received single-dose 50 mg/kg cefazolin sodium (Sefazol®, Mustafa Nevzat İlaç Sanayi, İstanbul, Turkey) 2 hours before the operation for prophylactic purposes and this therapy was continued for 3 days postoperatively. General anesthesia was obtained by intramuscular injection of 10 mg/kg ketamine hydrochloride (Ketalar®, Eczacıbaşı İlaç Sanayi ve Ticaret A.Ş. İstanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Rompun®, Bayer Türk Kimya Sanayi, İstanbul, Turkey).

Operative technique

Following the achievement of anesthesia, right thighs of the rats were shaved, treated with povidone-iodine, and covered with sterile drapes. Corpus femoris (shaft of femur) was reached by opening an incision 2 cm lateral to the right femur and advancing further by across the vastus lateralis and hamstring muscle bundles. Throughout the incision, soft tissues were retracted, periosteum was cut, and a transverse fracture was induced by a costotome, while paying attention to not cause a fragmented fracture. Intramedullary fixation was performed on the fracture by a 1.3 mm catheter (18G) from trochanter major to distal aspect with an electric drill. The tip of the needle on the trochanter side was bended and left under the skin. After achieving osteosynthesis, subcutaneous tissues were closed with absorbable suture material, while skin was closed with nonabsorbable suture. The incision area was recleaned with povidone iodine and rats were put into their cages.

Head trauma model

In our system which was prepared according to the head trauma model described by Marmarou et al.,[16,17] heads of the rats were placed onto a foam block in order to prevent a rebound effect that might occur following the trauma (Fig. 1). A nickel plate was fixated on top of the heads of the rats. The metal rod, hung 1 m high, was positioned and adjusted as to fall onto the center of the metal plate. The cylindrical rod, weighing 450 g, was released to a free-fall from a height of 1 m in order to induce closed head trauma on the rats of Group 2.

Light microscopy

Two randomly picked rats were sacrificed for documentation of brain injury and histological analysis at the second day following head trauma. The acquired tissue specimens were fixated with formaldehyde for 10 days. After postfixation, 5 mm-thick parallel sections were sampled anteroposteriorly. The sections dyed with hematoxylin-eosin (H-E) were analyzed under light microscopy at x10, x20, and x40 magnification levels.

In both groups, rats were sacrificed at 28 days (week 4) postoperatively by delivering a high-dose thiopenthal (Pentothal, Abbott SpA, Aprilia LT, Italy) injection. Right femurs of the sacrificed rats were dissected from the soft tissues with their intramedullary fixation devices.

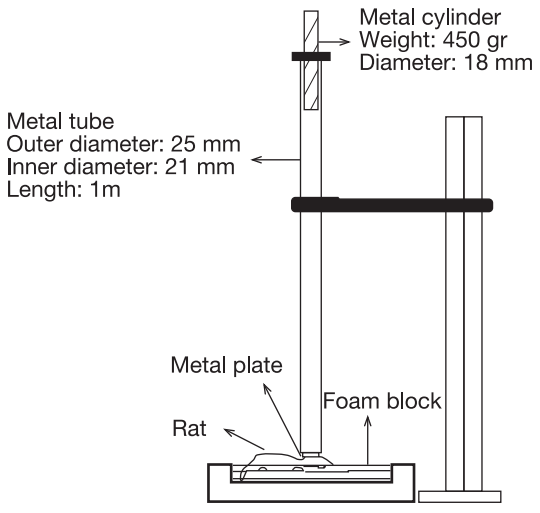

Fig. 1. Diagram of the head trauma induction system.

Experimental biomechanics

Femurs were stored at -20 °C until the biomechanical test. Prior to the experiment, we waited until they reached the room temperature in a moist environment. Four-point bend test was performed at room temperature by an Autograph AG-IS 5kN (Shimadzu Co. Kyoto, Japan) device in the Biomechanical Laboratory of Mechanical Engineering Faculty at Ege University. The initial velocity of the test was adjusted to 1 Newton (N) which was homogeneously increased until fracturing the femurs. The data were analyzed with a computer by using Trapezium-2 program which were later used for obtaining load (P)-deformation (δ) curves. The last load value which induced the fracture was identified as the maximum fracture load (P_{max}), whereas the deformation arising at the moment of fracture was recorded as maximum deformation (δ_{max}).

Maximum strain (S_{max}; Megapascal, MPa) denotes the stress suffered by the bone just before fracture. By using maximum fracture load, maximum straining (σ_{max}; bending strain) was calculated. Area moment of inertia (I; mm^4) was measured by considering the cross-section of the femurs as an ellipse. The components of this measurement such as anteroposterior and lateral axis sizes of the bones as well as mean cortex thicknesses, were calculated by transferring the images of 1 mm thick cross-sections obtained by computed tomography at femoral levels receiving the load. The acquired data were used for finding the bending rigidity (EI; Nmm^2) value and elasticity module (E; N/mm^2). In the section where maximum bending moment is applied, total energy absorbed by the femur from the beginning of the test to the moment of fracture equals to the area below the load-deformation curve. Thus, strain energy (U; Joule) was calculated accordingly.[2,18]

Finite element analysis

Computed tomography images at 0.6 mm interslice gap were obtained from one of the femurs of the rats in the Group 2. Elements of the model whose surface mesh was generated with MIMICs program, were

transferred to the ANSYS 11.0 program (ANSYS Inc. Houston, PA, USA). Solid 92 10-node tetrahedral solid element was employed for the analysis (Fig. 2). In the femur model, 177362 nodes and 123830 elements were used. During the modelling process of finite element method, the bone was recognized as having a linear, elastic, and isotropic structure. We used data calculated separately from the results acquired from experimental biomechanical studies on femur. Poisson ratio of the bone used in the analysis was taken as 0.3.[19] Load values used in the finite element analysis were taken from the maximum (fracture) loads in 4-point bend test, and they were picked as to apply to the same points as with the bones (Fig. 3). The applied loads were equally divided into 14 nodes across the z axis at both tips of the midline point which formed an evenly distributed load.

Total equivalent strain (Von Mises) values acquired by finite element analysis for both of the groups were compared, while amount of deformation towards y axis as a result of applying vertical load on both surface areas of the bone, and σ_z strains (maximum strain) on the longitudinal axis, were compared with the experimentally obtained deformation and strain values (Fig. 4).

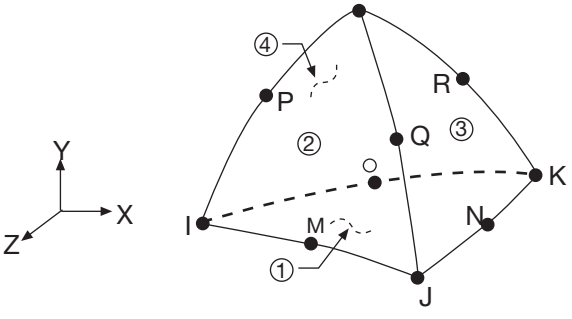

Fig. 2. Ten-node tetrahedral solid element.

Statistical analysis

SPSS (Statistical Package for Social Sciences) program for Windows 16.0 was used for statistical analyses. The study groups were compared with Mann-Whitney U-test. The results were evaluated within 95% confidence interval and $p<0.05$ was recognized as the level of statistical significance.

Results

The rats in the head trauma group demonstrated neurological injury signs in the form of flexion of forefeet in addition to spastic extension of the hindlegs and tail during head trauma. Histological analysis results about the efficacy of the applied method and head trauma model were consistent with the results outlined in the literature. Ventricular dilatation, periventricular edema, perivascular neuronal hyperplasia, swollen red neurons, and vascular congestion were remarkable in the brain tissue (Fig. 5).[16,17,20]

Biomechanical test results of the rats are listed in Table 1. When compared with the control group, mean maximum fracture load was significantly higher in the head trauma group ($p<0.05$). Since P_{max} can vary depending on the physical differences between the rats, we preferred to evaluate the maximum strain values for a more objective assessment and found higher S_{max} values in the head trauma group

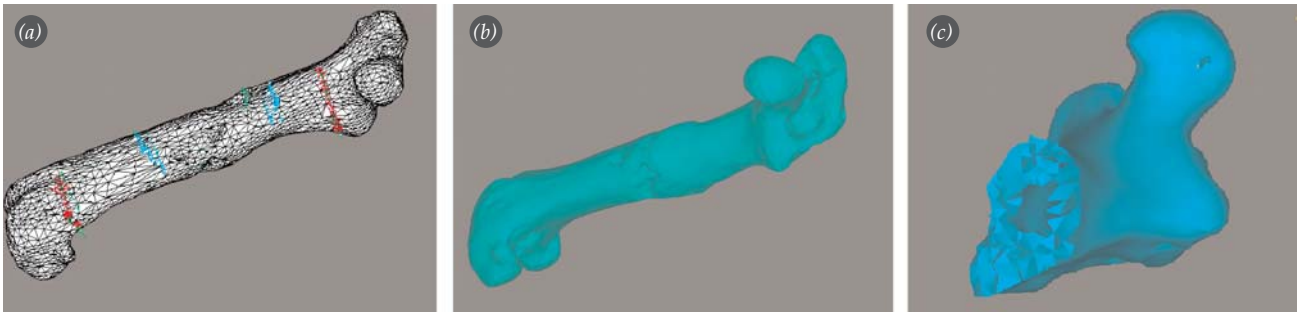

Fig. 3. **(a)** The elements formed for the analysis and loading areas for 4-point bend test, **(b)** generated femur model, and **(c)** sectional view of the femur model.

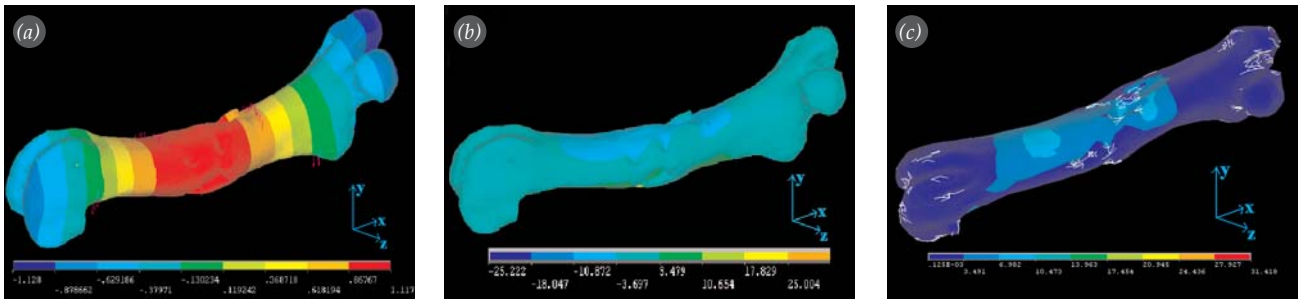

Fig. 4. **(a)** Deformation distribution in the loading area in a rat femur, **(b)** strain distribution after the loading, and **(c)** Von Mises strain distribution.

than in the control group ($p<0.05$). There was no significant difference between the groups with regard to maximum deformation ($p>0.05$). The mean bending rigidity was significantly higher in the head trauma group than in the control group ($p<0.05$). The head trauma group showed no significant difference from the control group in terms of strain energy and elasticity module ($p>0.05$).

According to both finite element method and experimental biomechanical testing, mean S_{max} value was significantly higher in the head trauma group than in the control group ($p<0.05$). While there was no difference between the groups relative to maximum deformity, head trauma group had significantly higher mean Von Mises strain values compared with the control group ($p<0.05$) (Table 2).

When the data acquired from the femur model created by finite element analysis method were compared with the parameters obtained from the experimental biomechanical study, no significant difference was found ($p>0.05$) except the δ_{max} mean values in Group 1 (Table 3).

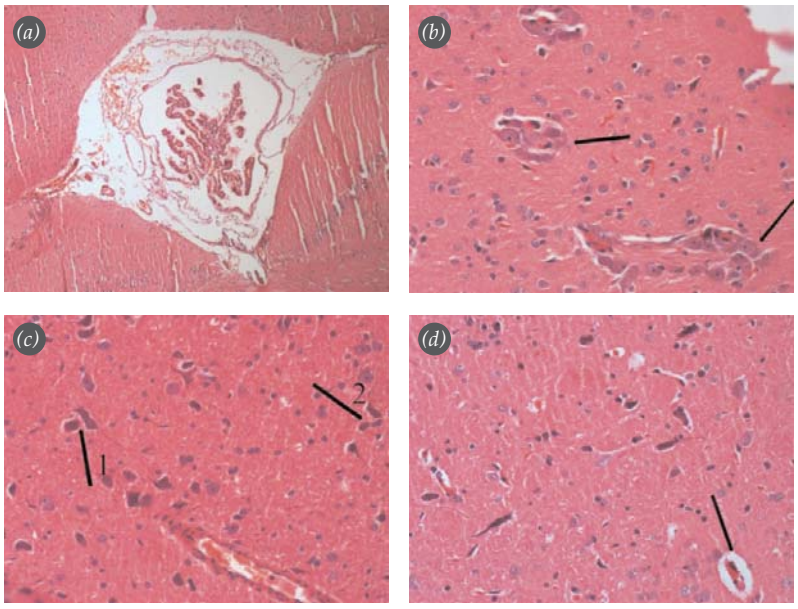

Fig. 5. Histological sections of brain tissue from rats showing: **(a)** ventricular dilatation and periventricular edema (H-E x10), **(b)** perivascular neuronal hyperplasia (H-E x40), **(c)** swollen red neurons (arrow 1) and dark-colored contracted neurons (arrow 2) (H-E x40), **(d)** vascular congestion and perivascular vacuolation (H-E x20).

Table 1
Results of experimental biomechanical test performed on femurs (mean±SD)

	Group 1 (control)	Group 2 (head trauma)	p value
Bending rigidity *(El; Nmm^2)*	2098.42±872.71	4105.36±2542.56	0.043
Maximum load *(N; P_{max})*	14.99±8.72	26.54±10.20	0.007
Strain energy *(U; Joule)*	29.71±23.851	67.194±70.410	0.089
Maximum deformation *(δ_{max}; mm)*	1.210±0.289	1.790±1.028	0.165
Maximum strain *(S_{max}; MPa)*	16.669±8.704	25.454±9.129	0.023
Elasticity module *(El; Nmm^2)*	192.32±70.482	316.785±207.586	0.143

Table 2
Results of finite element analysis performed on femurs (mean±SD)

	Group 1 (control)	Group 2 (head trauma)	p value
Maximum deformation *(δ_{max}; mm)*	0.768±0.211	1.183±0.804	0.290
Von Mises strain *(MPa)*	25.628±8.526	45.420±9.501	0.008
Maximum strain *(S_{max}; MPa)*	14.035±8.526	28.007±9.501	0.003

Table 3
Comparison of experimental biomechanical and finite element analysis results (mean±SD)

	Experimental biomechanics	Finite element analysis	p value
Maximum deformation *(δ_{max}; mm)*			
Group 1 (control)	1.210±0.2889	0.768±0.211	0.002
Group 2 (head trauma)	1.790±1.028	1.183±0.804	0.112
Maximum strain *(S_{max}; MPa)*			
Group 1 (control)	29.20±14.34	27.72±16.90	0.406
Group 2 (head trauma)	21.43±11.56	24.07±12.61	0.650

Discussion

The relationship between head trauma, speed of callus formation, and activation of cells stimulating bone growth are not yet clearly known.[11] It has been proposed that the presence of growth factors in the circulation following head trauma increases the osteogenic activity by autocrine and paracrine effects.[13] Newman et al.[11] associated fast fracture healing among head trauma patients with respiratory alkalosis development secondary to hyperventilation in those cases. Demonstration of increased calcium precipitation due to alkalosis in experimental studies

suggests that mildly basic environment may lead to fast callus formation and fracture healing.[11,21] According to Waisman and Schweppy,[22] head trauma disrupts normal hypothalamic function and leads to elevated dopamine secretion, which in turn increases secretion of growth hormone by inhibiting somatostatin release.

Formation of new bone and fracture healing is a process comprised of complicated mechanisms involving local growth factors, systemic mediators, and cytokine-mediated actions.[1] Head trauma has been shown to induce significant changes in the hypothalamo-pituitary region; hormonal response of patients with head trauma differs from those without head trauma. The acknowledged osteogenic effects in the sera of patients with traumatic brain injury are considered to be a result of factors released from the injured neural tissue or a part of central nervous system response associated with the head trauma.[7,10,22] Although osteoblast activation has been reported in sera of patients with brain or spinal cord injuries in the previous studies,[12,13,23] studies focusing on rat cell cultures have demonstrated significant increase in proliferation of mesenchymal stem cells among head trauma patients.[10] However, no direct clinical evidence suggesting a significantly improved fracture healing has been found in the sera of head trauma patients. The reason behind failure to identify a certain agent responsible for fracture healing may be due to multifactorial mechanism of the influence.[10,12,24] Contrary to the opinion proposing that central nervous system regulates bone formation, some authors believe that head trauma does not accelerate bone healing and that new bone formation in the fracture area is a form of heterotropic ossification. Garland et al.[25] found no evidence supporting a relationship between increased callus formation and rapid fracture healing among traumatic brain injury patients with a tibial or femoral fracture. The heterotropic ossification and myositis ossificans were suggested to be mistaken as increased callus formation in head trauma patients.[1,25-28]

Various models have been created in order to simulate head trauma in humans. However, it is considerably difficult to simulate diffuse brain injury *in vitro*.[20] Our study was based on the closed head trauma model designed by Marmarou et al.,[16,17] due to its similarity to the head trauma in humans. In our head trauma model, while the presence of swollen red neurons in rat brains are recognized as an evidence of neuronal damage, the appearance of dark-colored contracted neurons are associated with artifact development due to inadequate fixation or neuronal damage observed after hypoglycemia.[17] Other signs detected in brain tissues of rats after head trauma are the presence of thrombosed congestive capillary structures filled with erythrocytes and the accompanying perivascular vacuolation. These findings are associated with vasoconstriction or perivascular edema.[17,20] Moreover, detection of ventricular dilatation and periventricular edema on some sections may be due to post-traumatic brain injury.

Almost all the studies aiming to understand the stress-strain characteristics of bone, used bone models made of homogeneous, isotropic, and linear elastic material.[29-33] However, bone is a heterogeneous material which is consisted of different structural components. It is an anisotropic and non-linear tissue that can repair itself; adapt its shape, size, and inner composition to the varying mechanical requirements;[34] and respond with different mechanical characteristics against loads applied from varying directions.[35] Nonetheless, a linear elastic stress-strain relationship has been considered to be acceptable in bone.[36]

Retrieval of the normal mechanical power constitutes the most important appearance of healing fracture. In terms of biomechanics, bone fragility is evaluated with the following characteristics of a bone: strength, deformation, load-bearing capacity, and the amount of energy absorbed until fracture.[34] According to the data acquired at the end of the study, high P_{max}, S_{max}, and EI values indicate higher strength and resistance against bending forces in the head trauma group compared with the control group.

Absence of a statistically significant difference with regard to U and E values between head trauma and control groups in the experimental biomechanical study, may be associated with the number and sizes of femurs that received the biomechanical test. Different deformation values acquired from geometrically different femurs by biomechanical tests, may cause absence of statistically significant difference between U and E values.

The results we obtained from finite element analysis method and experimental biomechanical tests were generally consistent, which suggests that we were successful in creating a femur model that can reveal the characteristics of the bone without having bone samples. This femur model allows repeating different biomechanical test methods at choice as well as calculation of variations in the mechanical responses. Some factors that can influence the results of finite element analysis method are of great importance. One is that, the 3D structure of the bone in question should be generated separately for each model by computed tomography images. While creating the model, using as much as possible elements, makes it more comparable to the true geometry. Another factor is to describe the characteristics of bone materials in a more detailed fashion, while denoting the direction and application point of the force more accurately.[19]

In the analyses carried out with finite element analysis, mean S_{max} and Von Mises strain values were significantly higher in the head trauma group compared with the control group. Therefore, as with the results of the experimental biomechanical testing, head trauma may increase the mechanical strength of a healing bone.

Our femur model, which was created with finite element analysis, a noninvasive method, helps examination of the mechanical structure of the bone. Although the mechanism behind stimulation of fracture healing following head trauma is still unclear, our data acquired by experimental biomechanical and finite element analysis methods suggest that head trauma increases fracture healing.

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