Protective effects of erythropoietin and methylprednisolone on lung damage after experimental head injury

Deneysel kafa travması sonrası gelişen akciğer hasarında, eritropoetin ve metilprednizolonun koruyucu etkisi

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Background: The effects of erythropoietin and methylprednisolone on pulmonary lipid peroxidation and myeloperoxidase activity in lung injury following experimental head trauma in rats.

Study design: Seventy-six female Wistar-Albino rats, weighing 180-220 gr, were evenly allocated into ten groups. A weight-drop method was used to achieve head trauma. Samples were obtained from the left lung 24-h after the injury. Lung tissue-associated myeloperoxidase activity and lipid peroxidation levels were measured. A one-way analysis of variance (ANOVA) was applied to test the differences in the lipid peroxidation levels and myeloperoxidase activities between groups. Then, post-hoc comparison was performed.

Results: Firstly, head trauma substantially elevated lipid peroxidation and myeloperoxidase activity in lung tissue in the severe trauma group ($p<0.05$). Secondly, methylprednisolone significantly decreased lipid peroxidation in trauma-moderate group ($p<0.05$), whereas in trauma-severe group erythropoietin was superior ($p<0.05$). Thirdly, erythropoietin was more effective than methylprednisolone in decreasing myeloperoxidase activity in both trauma groups ($p<0.05$).

Conclusion: Erythropoietin efficiently protected lung tissue against polymorphonuclear leukocytes infiltration and oxidative damage. Further studies are warranted to better clarify the management of lung injury in brain injury/death model to transfer sufficient data to clinical studies providing suitable donor lungs and better survival rates in recipients.

Key words: Brain injury/complications/physiopathology; lipid peroxidation; lung/metabolism/pathology; rats; respiratory distress syndrome, adult/etiology /pathology.

Amaç: Sıçanlarda kafa travması sonrası gelişen akciğer hasarında, eritropoetin ve metilprednizolonun akciğer lipid peroksidasyonu ve miyeloperoksidaz seviyesine etkileri araştırıldı.

Çalışma planı: Yetmiş altı adet 180-220 gr ağırlığında, dişi Wistar-Albino sıçan 10 gruba ayrıldı. Kafa travması oluşturmak için ağırlık düşürme yöntemi kullanıldı. Örnekler, hasar oluşturulduktan 24 saat sonra sol akciğerden alındı. Akciğer doku miyeloperoksidaz aktivitesi ve lipid peroksidasyon seviyeleri ölçüldü. Lipid peroksidasyon seviyelerindeki ve miyeloperoksidaz aktivitesindeki gruplar arası farklılıkları analiz etmek için tek yönlü varyans analizi (ANOVA) kullanıldı. Daha sonra, post-hoc karşılaştırma yapıldı.

Bulgular: Öncelikle, şiddetli travma grubunda lipid peroksidasyon seviyesi ve miyeloperoksidaz aktivitesi önemli ölçüde yüksek bulundu ($p<0.05$). İkincil olarak, metilprednizolon, orta travma grubunda lipid peroksidasyon seviyesini anlamlı ölçüde düşürüdü ($p<0.05$), buna karşın şiddetli travma grubunda eritropoietin daha üstündü ($p<0.05$). Son olarak, eritropoietin her iki travma grubunda da metilprednizolona göre daha etkin bir şekilde miyeloperoksidaz aktivitesini azalttı ($p<0.05$).

Sonuç: Eritropoietin, akciğer dokusunu polimorfonükleer lökosit infiltrasyonuna ve oksidatif hasara karşı etkili bir şekilde korumaktadır. Uygun donör akciğeri ve organ alıcılarında daha iyi sağkalım sağlamak için gerekli klinik çalışmalara yeterli veri transferi yapabilmek amacıyla, kafa travması/ölümü modelinde akciğerin tedavisini daha da açıklığa kavuşturacak ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Kafa travması/komplikasyon/fizyopatoloji; lipid peroksidasyonu; akciğer/metabolizma/patoloji; sıçan; erişkin respiratuvar distres sendromu/etyoloji/patoloji.

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Brain injured patients have an increased risk of extrcerebral organ failure, mainly pulmonary dysfunction.[1] Respiratory failure is a common finding in the intensive care unit (ICU) and in the management of complex cases in the operating room.[2] Since approximately one-third of these patients suffer respiratory problems, the efficient management of respiratory failure in patients with head trauma in ICU has vital importance in reducing organ failure.[3]

Direct pulmonary trauma following central nervous system injury requires immediate treatment to prevent further compromise of the patient's condition.[4] Treatment with free radical scavengers and antioxidants is a rational therapeutic strategy for stroke or central nervous system trauma.[5] In the present study, both erythropoietin and methylprednisolone were used to assess the probable free radical-scavenging effect and the anti-inflammatory effect against induced head injury.

We have recently showed that experimental head injury resulted in ultrastructural lung tissue injury.[6] The aim of the current study, first, was to determine whether any alteration in the levels of lipid peroxidation and myeloperoxidase activity existed following traumatic brain injury. The second aim was to verify to what extent erythropoietin and methylprednisolone sodium succinate decrease lung thiobarbituric acid reactive substances and the severity of polymorphonuclear granulocyte infiltration in lung tissue.

MATERIALS AND METHODS

The Institutional Review Board for the care of animal subjects approved the study. The care and handling of the animals were in accord with the "Principles of Laboratory animal care" (NIH publication No. 86-23, revised 1985).

Experimental groups. Seventy-six female Wistar-Albino rats, weighing 180-220 g, were randomly allocated into 10 experimental groups. Tissue samples were obtained 24 hours after induced brain trauma in all groups, except the control group. Impact of 200 g-cm brain injuries was produced in groups 3, 5, 6, and 9. Additionally, impact of 300 g-cm brain injuries was produced in groups 4, 7, 8 and 10.

Group 1 (C): Control group (n=8): Tissue samples were obtained immediately after thoracotomy and neither head trauma was inducted nor craniotomy was performed.

Group 2 (S): Sham-operated group (n=8): Scalp was closed after craniotomy and no trauma was stimulated.

Group 3 (Tm): Trauma-moderate group (n=8).

Group 4 (Ts): Trauma-severe group (n=8).

Group 5 (EPOtm): Erythropoietin (trauma-moderate) group (n=8): Erythropoietin was administered intraperitoneally by bolus injections of 1000 IU/rat, at once post trauma.

Group 6 (MPSStm): Methylprednisolone sodium succinate (trauma-moderate) group (n=8): Methylprednisolone sodium succinate was given intraperitoneally by bolus injections of 30 mg/kg, directly after achieving injury.

Group 7 (EPOts): Erythropoietin (trauma-severe) group (n=8): Erythropoietin was administered intraperitoneally by bolus injections of 1000 IU/rat, instantaneously post trauma.

Group 8 (MPSSts): Methylprednisolone sodium succinate (trauma-severe) group (n=8): Methylprednisolone sodium succinate was given intraperitoneally by bolus injections of 30 mg/kg, immediately after accomplishing trauma.

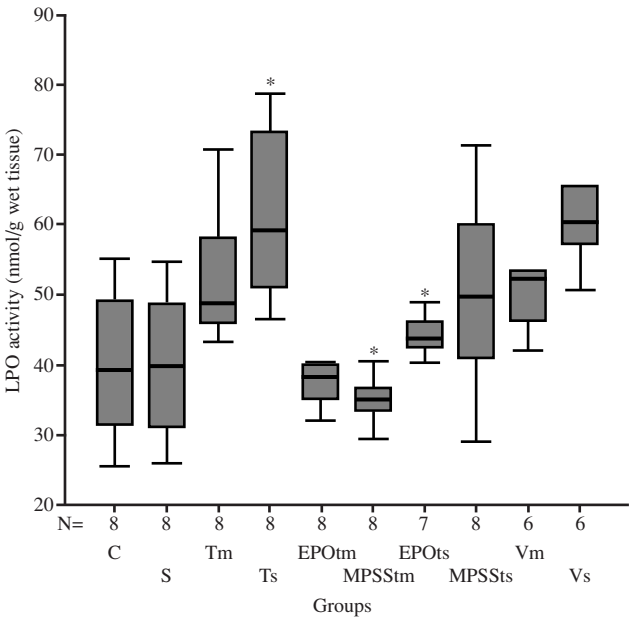

Fig. 1. Lung tissue lipid peroxide levels in all study groups expressed as nmol /g-wet tissue, mean ± SD. *: Take note that the severe trauma group has the highest lipid peroxidation level compared to that of control groups and the moderate trauma group. In addition, the methylprednisolone sodium succinate is more effective in lowering lipid peroxidation level in the moderate trauma group than the severe trauma group. Moreover, erythropoietin is more effective in decreasing the level of lipid peroxidation in the severe trauma group than the moderate trauma group.
C: Control group; EPO: Erythropoietin, EPOtm: Erythropoietin (trauma-moderate) group; EPOts: Erythropoietin (trauma-severe) group; LPO: Lipid peroxidation; MPSS: Methylprednisolone sodium succinate; MPSStm: Methylprednisolone (trauma-moderate) group; MPSSts: Methylprednisolone (trauma-severe) group. *: Significant results; S: Sham-operated group; SD; Standard deviation; TBI: Traumatic brain injury; Tm: Trauma-moderate group; Ts: Trauma-severe group; Vm: Vehicle-moderate group; Vs: Vehicle-severe group.

Table 1. Lung tissue lipid peroxide levels in each group following graded traumatic brain injury

Groups	n	Mean±SD (nmol/g-wet tissue)	*p*-value
Control group (C)	8	40.312±10.814	–
Sham-operated group (S)	8	40.237±10.622	–
Trauma-moderate group (Tm)	8	52.605±10.088	NS
Ts*	8	61.753±12.327	<0.05
Erythropoietin (trauma-moderate) group (EPOtm)	8	39.310±6.308	NS
MPSStm**	8	35.236±3278	<0.05
EPOts***	8	44.600±3.428	<0.05
Methylprednisolone (trauma-severe) group (MPSSts)	8	50.531±14.005	NS
Vehicle-moderate group (Vm)	6	52.985±9.808	–
Vehicle-severe group (Vs)	6	62.325±9.515	–
Total	76	47.519±12.817	–

SD: Standard deviation, NS: Non-significant. One-way analysis of variance (ANOVA) was applied to test for differences in lipid peroxidation levels between groups. Then, post-hoc comparison was performed. The differences were considered significant at a *p* value <.05. Ts*: Severe trauma group has the highest lipid peroxidation level compared to that of control groups and the moderate trauma group. MPSStm**: Methylprednisolone sodium succinate is more effective in lowering lipid peroxidation level in the moderate trauma group than the severe trauma group. EPOts***: Erythropoietin is more effective in decreasing lipid peroxidation level in the severe trauma group than the moderate trauma group. EPO: Erythropoietin; EPOts: Erythropoietin (trauma-severe) group; MPSS: Methylprednisolone sodium succinate; MPSStm: Methylprednisolone (trauma-moderate) group; Ts: Trauma-severe group;

Group 9 (Vm): Vehicle-moderate group (n=6): Saline (0.9%) was given intraperitoneally by bolus injections of 0.1 ml/rat, directly after injury.

Group 10 (Vs): Vehicle-severe group (n=6): Saline (0.9%) was administered intraperitoneally by bolus injections of 0.1 ml/rat, immediately following injury.

Surgical procedure. The surgical procedure was performed under general anaesthesia induced by intramuscular xylasine (Bayer, Istanbul, Turkey) (10 mg/kg) and ketamine hydrochloride (Parke Davis, Istanbul, Turkey) (60 mg/kg) injections. Rats were placed in prone position. Following midline longitudinal incision, scalp was dissected over cranium and retracted laterally. Coronal and sagittal sinuses were observed. Right frontoparietal craniectomies were carried out laterally to the sagittal sinus by dental drill system. The dura was exposed and left intact. Trauma of 200 g-cm and 300 g-cm impacts were produced by the method of Allen[7] in different groups, respectively. Rats were injured by two stainless steel rods (5 mm diameter, one weighing 200 g and the other 300 g). Weight dropped vertically through a calibrated tube from a height of 10 cm onto the exposed dura. Scalp was sutured with silk sutures. Body temperature was continuously monitored during the whole procedure with a rectal thermometer and maintained at 37 °C using a heating pad and an overhead lamp. Rats were neither intubated nor ventilated between brain damage and lung sampling. After returning to the cages, the rats were allowed food and water ad libitum.

Obtaining samples from lung parenchyma. Twenty-four hours after traumatic brain injury, animals in all groups, except the control group, were re-anaesthetized with the combination of ketamine and xylasine. Rats were placed supine on the operating table. Midline sternotomy and left thoracotomy were performed. The systemic circulation was perfused with 0.9% NaCl. Then, rats were killed with decapitation under general anaesthesia. Samples for lipid peroxidation level and myeloperoxidase activity were simultaneously obtained from the left pulmonary lobes. Lung samples were collected in randomly numbered containers and given to blinded observers. After evaluating the numbered tissues, results were collected in appropriate group lists.

Lipid peroxidation assay. The samples were thoroughly cleansed of blood and were immediately frozen and stored in a -70 °C freezer for assays of malondialdehyde. The levels of lipid peroxidation were measured as thiobarbituric acid-reactive material. The level of lipid peroxidation in the lung parenchyma was determined using the method of Mihara and Uchiyama.[8] Tissues were homogenized in 10 volumes (w/v) of cold phosphate buffer (pH 7.4). Half a millilitre of homogenate was mixed with 3 ml 1% H_3PO_4. After the addition of 1 ml 0.67% thiobarbituric acid, the mixture was heated in boiling water for 45 minutes. The colour was extracted into n-butanol, and the absorption at 532 nm was measured. Using tetramethoxypropane as the standard, tissue lipid peroxidation levels were calculated as nanomole per gram of wet tissue.

Determination of lung tissue-associated myeloperoxidase activity. Lung tissue-associated myeloperoxidase activity was measured by the modified method of Suzuki.[9] Frozen tissue samples were weighed and homogenized in 1:10 (w/v) ice-cold 10 mM TRIS

buffer (pH: 7.4) by the use of a dounce homogenizer. The homogenate (1 ml) was centrifuged at 10000xg for five times, and the pellet was re-suspended in equal volumes (1 mL) of 50 mM phosphate buffer (pH: 6.0) containing 0.5% Hexadecyltrimethyl ammonium bromide (HETAB) and 5 mM EDTA. The resulting suspension was centrifuged at 5000xg for 2 min and the supernatant was used for the activity measurement.

Myeloperoxidase activity was measured in a final volume of 1 ml containing 80 mM phosphate buffer (pH: 5.4), 0.5% HETAB, 1.6 mM synthetic substrate tetramethylbenzidine (TMB) initially dissolved in dimethylformamide, 2 mM H_2O_2 and the sample. The reaction was started at 37 °C by the addition of H_2O_2. Recording the increase of absorbance at 655 nm followed the initial rate of myeloperoxidase-catalyzed TMB oxidation. Myeloperoxidase activity was expressed as the amount of the enzyme producing one absorbance change per minute under assay conditions. Tissue-associated myeloperoxidase activity was calculated as units per gram of wet tissue.

Statistical method. All the data collected from the experiment were coded, recorded, and analyzed by using SPSS 11.5 statistical software package for Windows. The one-way analysis of variance (ANOVA) was used to compare lipid peroxidation levels and the activity of myeloperoxidase. Tukey's honestly significant difference (Tukey-HSD) test was applied to determine the statistically significant differences between the groups, as post-hoc. The differences were considered significant at a p value <0.05.

RESULTS

The results below were recorded:

Lipid peroxide levels are shown in Fig. 1 and Table 1:

Only severe trauma significantly increased lipid peroxides levels (p<0.05), compared to control and sham groups Additionally, methylprednisolone sodium succinate caused significant decline in lipid peroxidation level in the moderate trauma group similar to the moderate trauma vehicle and the erythropoietin moderate trauma groups (p<0.05). Moreover, erythropoietin caused significant decreases in lipid peroxide levels in severe trauma group compared to methylprednisolone severe trauma and severe trauma vehicle groups (p<0.05).

Lung tissue-associated myeloperoxidase activities are shown in Fig. 2 and Table 2:

Only severe trauma caused significant increases in myeloperoxidase activities (p<0.05). compared to the control and sham groups. Additionally, erythropoietin caused a significant decline in myeloperoxidase activities in both moderate and severe trauma groups. similar to the methylprednisolone moderate trauma, methylprednisolone severe trauma and the vehicle groups (p<0.05).

DISCUSSION

Respiratory failure is a common finding in the intensive care unit and in the management of complex cases in the operating room.[2] The development of lung injury is a critical independent factor affecting mortality in patients suffering traumatic brain injury and is associated with a worse long-term neurologic outcome in survivors.[10]

As approximately one-third of these paitients suffer respiratory problems, the efficient management of respiratory failure in patients with head trauma in ICU has vital importance[11] in reducing organ failure[3] and providing higher graft survival rates under conditions of donor shortage.[12]

Blunt traumatic brain injury represents one of the most important causes of death and disability in modern

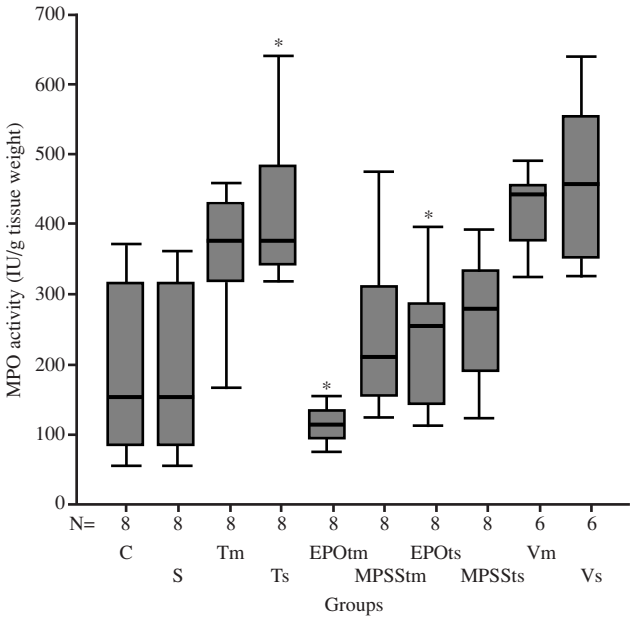

Fig. 2. Lung tissue myeloperoxidase activities in all study groups expressed as IU/g-wet tissue, mean±SD. *Take note that the severe trauma group has the highest myeloperoxidase activity compared to control, trauma moderate and treatment groups. In addition, erythropoietin is more effective in lowering myeloperoxidase activity in both moderate and severe trauma groups than methylprednisolone sodium succinate.

C: Control group; EPO: Erythropoietin; EPOtm: Erythropoietin (trauma-moderate) group; EPOts: Erythropoietin (trauma-severe) group; MPO: Myeloperoxidase; MPSS: Methylprednisolone sodium succinate; MPSStm: Methylprednisolone (trauma-moderate) group; MPSSts: Methylprednisolone (trauma-severe) group; *: Significant results; S: Sham-operated group; SD: Standard deviation; TBI: Traumatic brain injury; Tm: Trauma-moderate group; Ts: Trauma-severe group; Vm: Vehicle-moderate group; Vs: Vehicle-severe group.

Table 2. Lung tissue myeloperoxidase activities in each group following graded traumatic brain injury

Groups	n	Mean±SD (IU/g tissue weight)	*p*-value
Control group (C)	8	190.187±129.445	–
Sham-operated group (S)	8	189.500±128.351	–
Trauma-moderate group (Tm)	8	358.125±95.731	NS
Ts*	8	419.062±112.355	<0.05
EPOtm**	8	113.187±27.822	<0.05
Methylprednisolone (trauma-moderate) group (MPSStm)	8	241.625±119.418	NS
EPOts***	8	233.437±97.194	<0.05
Methylprednisolone (trauma-severe) group (MPSSts)	8	264.000±98.788	NS
Vehicle-moderate group (Vm)	6	420.250±61.625	–
Vehicle-severe group (Vs)	6	461.083±129.543	–
Total	76	281.066±147.411	–

SD: Standard Deviation, NS: Non-significant. The one-way analysis of variance (ANOVA) was applied to test for differences in the myeloperoxidase activity between groups. Then, post-hoc comparison was performed. The differences were considered significant at a *p* value <.05. Ts*: Severe trauma group has the highest myeloperoxidase activity compared to that of the control groups, trauma moderate group and the treatment groups. In addition, erythropoietin is more effective in lowering myeloperoxidase activity in both moderate (EPOtm**) and severe (EPOts***) trauma groups than methylprednisolone sodium succinate in both groups (MPSStm and MPSSts). EPO: Erythropoietin, EPOtm: Erythropoietin (trauma-moderate) group; EPOts: Erythropoietin (trauma-severe) group; MPO: Myeloperoxidase; MPSS: Methylprednisolone sodium succinate; Ts: Trauma-severe group.

society.[13] Acute lung injury is common in comatose victims with an isolated traumatic brain injury and is associated with an increased risk of death or a severe neurological morbidity.[14]

Cerebral hypoxia or ischemia and head trauma or seizures may all lead to severe neurogenic pulmonary injury.[15] The relative contribution of hydrostatic and permeability mechanisms to the development of human neurogenic pulmonary oedema had been identified.[5] In addition, elevated free radical production after central nervous system injury may also contribute to the formation of neurogenic pulmonary oedema.[16] It seems that neurogenic pulmonary injury is probably the result of a combination of all the pathogenetic mechanisms mentioned above.

Regarding lipid peroxidation, it is reported in detail in the literature in this field that oxygen radical formation after trauma results in cell membrane lipid peroxidation causing membrane lyses.[17] Additionally, it was reported that polymorphonuclear granulocyte infiltration also takes place after injury, which is determined by myeloperoxidase activity. Moreover, in some reports, it was clearly declared that the myeloperoxidase activity in lung tissue of animals after blunt chest trauma significantly increased.[18]

A previous study from our laboratory has shown that absolute ultrastructural damage took place at the pneumocyte type II cells. Additionally significant increase has been detected in lipid peroxidation level in lung tissue after traumatic brain injury.[6] In the current study, we investigated whether the levels of lipid peroxidation and myeloperoxidase activity following brain injury, could be diminished by erythropoietin and methylprednisolone sodium succinate. Neutrophil activation as assessed by myeloperoxidase activity in whole lung tissue, as well as lipid peroxidation, has significantly increased in the current weight-drop injury model compared to that of the control and sham-operated animals.

In a very specialized field dealing with lung transplantation, the paucity of suitable lung donors and the high early mortality as the result of primary graft failure remain major challenges.[19] It should be kept in mind that almost half of the organ donors have deceased from head trauma,[20] which mostly results in type II cell dysfunction.[21] As a result, it should be emphasized that it is of paramount importance to preserve donor organs as much as possible to achieve higher graft survival rates in the world's organ shortage.

Morbidity and mortality from lung failure will have lesser impact on patients as physicians treat the consequences of organ failure in the ICU.[3]

With regard to treatment, antioxidants may hypothetically act to avert propagation of tissue damage and improve both the survival and neurological outcome. Treatment with free radical scavengers and antioxidants is a rational therapeutic strategy for stroke or central nervous system trauma.[5]

Erythropoietin and methylprednisolone sodium succinate were used in order to avoid generation of tissue damage in the current head trauma model. Recent studies have revealed the significance of the non-erythropoietic effects of erythropoietin, mainly its free radical scavenging effect and holding back lipid peroxidation, hence diminishing oxidant injury.[22,23]

Glucocorticoids are the most potent and widely used anti-inflammatory agents. Methylprednisolone sodium succinate has been shown to have protective effect against traumatic spinal cord injury.[24] It was shown in another study that methylprednisolone has biphasic effect on alveolar capillary integrity after elevated cerebrospinal fluid pressure.[13] The features mentioned above were the main criteria for the selection of these agents used in this study.

In the current study, it was clearly shown that mostly erythropoietin was superior to the methylprednisolone in lowering both the lipid peroxidation levels and the myeloperoxidase activity in the studied trauma groups.

In conclusion, inhibitions of lipid peroxidation and myeloperoxidase activity by administration of erythropoietin could be a possible approach in the treatment or the prevention of lung injury in the patients with head trauma. This point might have a vital importance in a critical procedure like lung transplantation. An understanding of the mechanism of donor lung injury could lead to the development of new treatment strategies for the donor to reduce lung injury, increase the number of donors with acceptable lungs, and improve the results of lung transplantation.

Exact therapeutic agents and procedures have to be elucidated further to achieve more successful survival rates and to reduce graft failure rates in the recipients who have been transplanted the donor lungs harvested from patients who have suffered brain trauma.

In addition, this study highlights the need for continued efforts to identify optimal management strategies for patients with severe brain injury admitted to ICUs.

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