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Effect of Pregabalin in Preventing Secondary Damage in Traumatic Brain Injury: An Experimental Study

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Background: In this study we aimed to explore the effects of pregabalin on a traumatic brain injury model in rats.

Material/Methods: This study included 40 adult male Sprague-Dawley rats randomized into 4 groups, each of which contained equal numbers of animals. The control group had no head trauma and thus was not treated. The trauma group had head trauma but was not treated. The pregabalin group had no head trauma but was treated by pregabalin. The trauma + pregabalin group had head trauma treated with pregabalin. The biopsy samples taken from the study animals were histopathologically examined for the presence of edema, inflammation, and neuronal damage.

Results: All animals in the trauma group had edema, inflammation, and neuronal damage. Four subjects in the control group, 6 in the pregabalin group, and 4 in the trauma + pregabalin group had edema; inflammation was present in 1 subject in the control group, 3 subjects in the pregabalin group, and 3 subjects in the trauma + pregabalin group; neuronal damage existed in 1 subject in the control group, 1 subject in the pregabalin group, and 6 subjects in the trauma + pregabalin group. The trauma group had significantly higher edema and neuronal damage scores than the other groups. Similarly, inflammation was significantly more prevalent in the trauma group than the control and trauma + pregabalin groups.

Conclusions: The results of the present study indicated anti-edema, anti-inflammatory, and neuroprotective effects of pregabalin in an experimental head trauma model in rats. Pregabalin may thus be beneficial in humans with acute TBI by relieving concomitant edema and inflammation.

MeSH Keywords: Anticonvulsants • Brain Edema • Brain Injuries • Inflammation • Neuroprotective Agents

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Background

Despite medical and surgical advances, traumatic brain injury (TBI) following head trauma continues to be a significant health issue with constantly increasing rates worldwide [1]. TBI will reportedly surpass many other illnesses as one of the leading cause of mortality by 2020 [2]. In excess of 10 million people worldwide annually suffer this catastrophe, most commonly caused by traffic accidents (60%), falls (20–30%), assaults (10%), and work- or sports-related incidents (10%) [2]. The patient's life is often saved, but at the cost of a significant reduction in its quality. In addition to serious limitations of movement, most patients experience various cognitive and emotional disturbances caused by extensive brain damage. Difficulties in self-care are a very common problem for patients recovering from prolonged coma after a severe TBI, and a major factor reducing their quality of life [3].

The direct mechanical impact of trauma is responsible for focal and/or diffuse primary brain injury. Secondary brain injury, on the other hand, is a result of some complex interacting pathophysiological mechanisms, including excitotoxicity, oxidative and nitrosative stresses, peri-infarct depolarizations, inflammation, apoptosis, calcium-dependent cell injury, gene activation, and mitochondrial dysfunction, all of which occur hours or days after primary brain injury [4,5]. Inflammation, excitotoxicity, and brain edema all lead to increased intracranial pressure by inducing secondary brain injury, which is associated with increased morbidity and mortality if not promptly and effectively treated [6]. Appropriate and timely interventions can reportedly prevent secondary brain injury in TBI and thus reduce mortality rates [7].

A wide array of pharmaceuticals has been used in experimental and clinical trials to alter the events during the course of TBI, although none have shown much promise [8]. These include anticholinergics, excitatory amino acid antagonists, endogenous opioid antagonists, catecholamines, serotonin antagonists, modulators of arachidonic acid, antioxidants and free radical scavengers, steroid and lipid peroxidation inhibitors, platelet activating factor antagonists, anion exchange inhibitors, magnesium, gangliosides, calcium channel antagonists, growth factors, antihistamine agents, and stem cells [9–11].

Pregabalin is a structural analog of gamma-aminobutyric acid (GABA) [12]. It is a highly potent ligand of alpha-2-delta subunits of voltage-gated calcium channels (VGCC) exerting anticonvulsant, analgesic, and anxiolytic actions in animal models. After strongly binding to the alpha-2-delta subunit of the calcium channels of excited neurons, it reduces depolarization-induced calcium flow and thus the release of many excitatory neurotransmitters including glutamate, noradrenaline, and substance P [12–15].

Pregabalin is a substrate of the L-transporter system that is responsible for the transport of large amino acids in both the blood-brain barrier (BBB) and the intestinal system. It has been shown to cross the BBB in mice, rat, and monkey models [16,17].

Pregabalin exerts an anticonvulsant effect in many animal models [12,18]. It has also been shown to reduce nociceptive behaviors in animal models of neuropathic and inflammatory pain. However, it has not been shown to emotionally affect acute nociception. It reduced allodynia to a significant extent in a vincristine-induced neuropathic pain model [19]. Preclinical studies have shown that pregabalin exerted anxiolytic-like effects in a dose-dependent manner [20]. The present study aimed to determine the neuroprotective, anti-inflammatory, and anti-edema effects pregabalin in TBI.

Material and Methods

Subjects

Forty healthy adult male Sprague-Dawley rats weighing 300–350 g and not used for any other study were used as the study subjects. They were offered standard pellets and tap water until the day of the experiment. The cages of the animals received daylight, allowing alternating day-night cycles. The International Declaration on Animal Welfare proclaimed in 1978 at the UNESCO headquarters in Paris was complied with by the experiments performed in the study. The study was approved by the local ethics committee for animal experiments in Düzce University (dated 01.12.2010 and numbered 2010/26).

Procedure

All animals were weighed before induction of anesthesia that was achieved by intraperitoneal administration of 50 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis, Eczacıbaşı, Istanbul, Turkey). The intensity of anesthesia was checked by corneal reflex and tail-pinch method, followed by measurement of physiological parameters of the subjects, including respiratory rate, pulse rate, and rectal temperature, before the start of the experiment (0^{th} hour). Physiological signs were re-checked at 24^{th} hour of the induction of head trauma. The mean values 0^{th} and 24^{th} hour measurements of physiological parameters did not differ significantly.

The animals were randomized into 4 groups each containing 10 animals: The control group had no head trauma and thus was not treated. The trauma group had head trauma but was not treated. The pregabalin group had no head trauma but was treated by pregabalin. The trauma + pregabalin group had head trauma treated with pregabalin.

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Induction of head trauma

The animals were first placed in prone position. Then, a midline incision through skin was made to expose the bregma and lambdoid sutures. Sutures were completely exposed by stripping periosteum to both sides. A 10-mm wide and 3-mm thick steel disc was placed between coronal and lambdoid sutures in the midline. Then, the animals were placed on a sponge floor (12×12×43 cm) in the prone position. Head trauma was induced by dropping a 450-g steel rod off a height of 2 m through a tube with an internal diameter of 19 mm and an external diameter of 25 mm in a weight-drop device developed by Marmarou et al. [21]. Following induction of head trauma, 7 subjects developed respiratory arrest and 4 dilated papilla or seizure. Airway was immediately opened and cardiopulmonary resuscitation initiated and continued until after spontaneous breathing of sufficient depth resumed. Skin incisions were then sutured using a 2/0 silk sutures and the animals with adequate respiratory effort were transported back to their cages. Two rats died at the time of trauma and thus 2 new rats were enrolled and subject to trauma to equalize the number of rats in all groups.

Pregabalin treatment

Pregabalin (Lyrica, Pfizer, ABD) 25 mg/kg was administered intraperitoneally 7 times at 30 minutes, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, and 72 hours after trauma and resuscitation.

Obtaining tissue samples

At 84th hour of trauma, induction 5–6 mL intracardiac blood samples were obtained from the subjects anesthetized by intraperitoneal ketamine hydrochloride 60 mg/kg. The animals were then sacrificed, decapitated, and their brainstems were removed and fixed in 10% formaldehyde.

Histopathological examination

Hippocampal and pons-cerebellum samples were obtained, fixed in 10% buffered formaldehyde, sliced into axial sections, and stained with hematoxylin-eosin. They were then subject to histopathological examination for the presence and severity of bleeding, presence and severity of edema, presence, severity, and location of inflammation and myelinolysis, neuronal damage (pink ischemic neurons-perineuronal vacuolation), retraction ball-diffuse axonal injury, and presence and extent of vascular congestion.

Observing free red blood cells in the brain parenchyma or ventricle suggested a hemorrhage. The severity of the latter was graded under a microscope in the area with a magnification of 20× in the following manner: 1+ when hemorrhage was <10%, as 2+ when hemorrhage was 10–50%, and as 3+ when hemorrhage was >50%. Brain edema was detected when there existed microcystic areas formed by distended extracellular spaces and separation of the parenchymal cells. Its severity was graded under a microscope in the area with a magnification of 20× in the following manner: 1+ when edema was <10%, as 2+ when edema was 10–50%, and as 3+ when edema was >50%. Presence of polymorphonuclear leukocytes, lymphocytes, plasma cells, and eosinophils was indicative of inflammation. Myelinosis was deemed present when there was formation of a white area caused by myelin loss within the white matter, or when there were histiocytic cells.

Statistical analysis

Predictive Analysis Software (PASW) Statistics 18.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for all statistical analyses. Numerical variables are expressed as mean standard deviation and median (min-max) while categorical variables are presented as number and percentage. Kruskal-Wallis test was used for the comparison of numerical variables with non-normal distribution between multiple independent groups. Categorical variables with non-normal distribution were compared with Monte Carlo Simulation across multiple independent groups. Mann-Whitney U-test with Bonferroni correction and Fisher's exact test with Bonferroni correction were used for subgroup analyses of the numerical and categorical variables, respectively. Statistical significance was normally set at $p<0.05$ and it was set at $p<0.08$ for the Bonferroni correction.

Results

In contrast to edema that was periventricular for most of the time, hemorrhage was usually located subpially, in the parenchyma and ventricle. Table 1 summarizes the histopathological findings of the whole study population.

Four subjects in the control group had edema at the level of 1+. Hemorrhage was subpially located in 3 subjects while 1 subject had neuronal damage. Two subjects had inflammation. The control group had subpial hemorrhage and neuronal damage; the decapitation procedure inflicted minimal trauma (iatrogenic) to neuronal tissue (Figure 1).

The trauma group had 10 subjects with 2+ edema. While 1 subject had parenchymal hemorrhage, the remaining 9 had subpial, parenchymal, and ventricular hemorrhage (Figure 2). All samples in this group demonstrated signs of inflammation and neuronal damage. The neuronal damage was 1+ in 5 subjects and 2+ in the rest of this group.

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Table 1. Histopathological findings in all study subjects.

Groups	Edema	Inflammation	Neuronal Damage	Bleeding	Location of Bleeding
C-1	+	–	–	+	Subpial
C-2	+	–	+	+	Subpial
C-3	+	+	–	–	
C-4	+	–	–	+	Subpial
C-5	–	–	–	–	
C-6	–	–	–	–	
C-7	–	–	–	–	
C-8	–	–	–	–	
C-9	–	–	–	–	
C-10	–	–	–	–	
T-1	**++**	**+**	**+**	**+**	**Subpial, parenchymal, ventricular**
T-2	**++**	**+**	**+**	**+**	**Subpial, parenchymal, ventricular**
T-3	**++**	**+**	**+**	**+**	**Subpial parenchymal, ventricular**
T-4	**++**	**+**	**+**	**+**	**Parenchymal**
T-5	**++**	**+**	**++**	**+**	**Subpial, parenchymal, ventricular**
T-6	**++**	**+**	**++**	**+**	**Subpial, parenchymal, ventricular**
T-7	**++**	**+**	**++**	**+**	**Subpial, parenchymal, ventricular**
T-8	**++**	**+**	**++**	**+**	**Subpial, parenchymal, ventricular**
T-9	**++**	**+**	**++**	**+**	**Subpial, parenchymal, ventricular**
T-10	**++**	**+**	**+**	**+**	**Subpial, parenchymal, ventricular**
T+P-1	+	+	+	+	Subpial, parenchymal
T+P-2	–	–	+	–	
T+P-3	–	–	+	–	
T+P-4	+	–	–	+	Subpial
T+P-5	+	–	+	+	Subpial, parenchymal
T+P-6	–	–	–	+	Subpial, parenchymal
T+P-7	–	+	+	+	Subpial, parenchymal
T+P-8	–	–	+	+	Subpial, parenchymal
T+P-9	+	–	+	+	Subpial, parenchymal, ventricular
T+P-10	–	+	–	+	Subpial, parenchymal, ventricular
P-1	–	–	+	+	Subpial
P-2	+	–	–	–	
P-3	–	+	–	+	Subpial
P-4	+	–	–	+	Subpial
P-5	+	+	–	–	
P-6	+	–	–	–	
P-7	+	–	–	–	
P-8	–	–	–	–	
P-9	+	+	–	–	
P-10	–	–	–	–	

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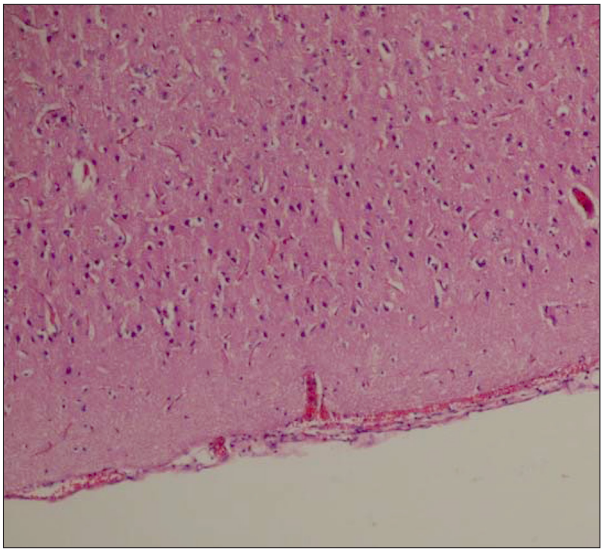

Figure 1. An example of iatrogenic subpial bleeding in the control group.

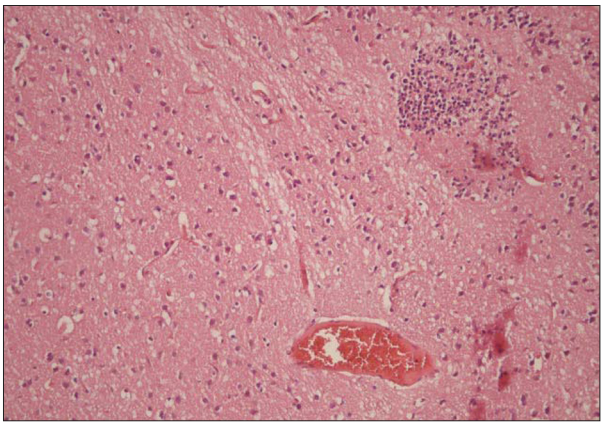

Figure 2. Edema, ventricular, and parenchymal bleeding in the trauma group.

The pregabalin group contained 6 subjects with 1+ edema. That group had 3 subjects with inflammation. In addition, 3 subjects had subpial hemorrhage. Here again, subpial hemorrhage was indicative of minimal trauma to neuronal tissue during decapitation procedure (iatrogenic).

The trauma + pregabalin group had 4 subjects with 1+ edema and the rest had no brain edema. Hemorrhage localization was subpial and parenchymal in 5 subjects, subpial, parenchymal, and ventricular in 2, and subpial in 1. Two subjects had no hemorrhagic foci at all. Three subjects in this group, as opposed to the remaining 7, had inflammation (Figure 3). Six subjects had 1+ neuronal damage and 4 had no neuronal damage.

Table 2 presents the results of the comparisons between the study groups' histopathological assessment scores. Kruskal-Wallis test revealed significant differences between all groups

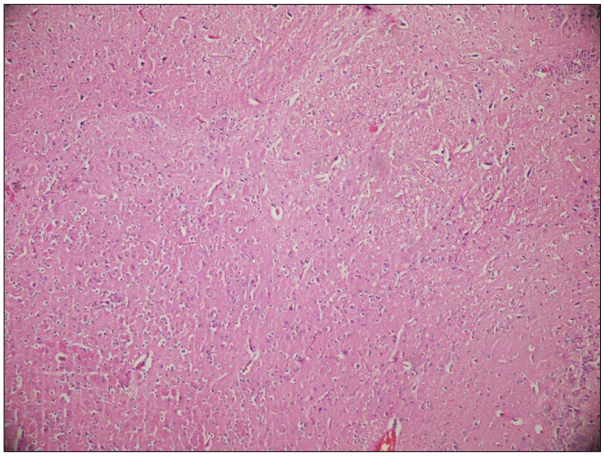

Figure 3. Decreases in edema, inflammation, and neuronal damage in the trauma + pregabalin group.

with respect to mean values of edema, inflammation, neuronal damage, and hemorrhage; the trauma group had significantly different results from all other groups. As the next step, paired comparisons using the Mann-Whitney U test revealed the following (Table 2, Figure 4):

1. No significant difference was found between the control and pregabalin groups;
2. No significant difference was found between the control and trauma+ pregabalin groups;
3. No significant difference was found between the pregabalin and trauma + pregabalin groups;
4. There was a significant difference between the control and trauma groups with respect to the means of all variables;
5. There was a significant difference between the trauma and trauma + pregabalin groups with regard to the means of all variables;
6. There was a significant difference between the trauma and pregabalin groups.

Lack of a significant difference between the control group and the pregabalin group (without trauma) and presence of a significant difference between the trauma + pregabalin groups and the trauma group both indicated that the results of the experiment were significantly in favor of pregabalin. The comparison of the trauma group and the trauma + pregabalin group with respect to edema ($Z=-4.119$, $P<001$), inflammation ($Z=-3.199$, $P<0.007$), neuronal damage ($Z=-2.936$, $P<0.07$), and hemorrhage ($Z=-1.453$, $P<0.481$) also significantly favored the neuroprotective and anti-edema properties of pregabalin.

Discussion

Two main objectives are pursued in the management of patients with head trauma. One of them is to restore neurological and systemic equilibrium, and the other is to ascertain the

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Table 2. Results of histopathological evaluation in the study groups.

	Control group	Trauma group	Pregabalin group	Trauma + pregabalin group	p
Edema score	0.40±0.51[b]	2.00±0.00[a,c,d]	0.60±0.51[b]	0.40±0.51[b,a]	<0.001
Neuronal damage score	0.10±0.31[b]	1.50±0.52[a,c,d]	0.10±0.31[b,a]	0.60±0.51[b]	<0.001
Bleeding score	0.30±0.48[b]	1.00±0.00[c,a,d]	0.30±0.48[b,a]	0.80±0.42[b]	<0.001
Presence of inflammation	0.10±0.31[b]	1.00±0.00[a,c,d]	0.30±0.48[b]	0.30±0.48[b]	<0.001

Values are presented as mean±standard deviation (median) or number (%), where appropriate. The table shows the results of the comparison of multiple groups with Kruskal-Wallis test and the results of the paired comparisons performed with the Mann-Whitney U test. [a] Different from the control group. [b] Different from the trauma group. [c] Different from the pregabalin group. [d] Different from the trauma + pregabalin group.

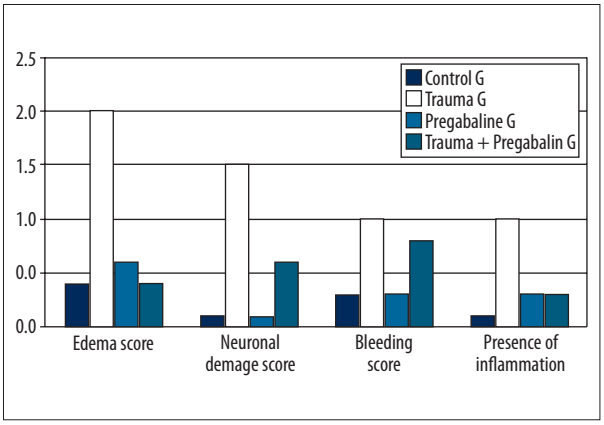

Figure 4. Comparison between the trauma and pregabalin and trauma + pregabalin groups show the difference significantly (all P<0.001).

degree of neurological impairment at the shortest time possible. Interventions to achieve these goals include providing sufficient, albeit excessive, cerebral perfusion pressure, reduction of intracranial pressure, and prevention or at least minimizing secondary cerebral injury caused by hypoxia, hypotension, epilepsy, electrolyte imbalance, coagulation defects, and infection [22].

Vasogenic edema in the course of TBI, which is a result of disruption of the blood-brain barrier, is not the sole culprit responsible for the clinical deterioration, but rather ischemia-induced edema at cellular level also contributes to the clinical picture [23]. Ischemia-induced (neurotoxic) edema is a result of sodium-calcium imbalance resulting from excessive secretion of free radicals and excitatory amino acids [24,25]. Mortality and morbidity of TBI can be reduced dramatically as long as secondary brain injury can be prevented by eliminating some, if not all, contributing factors [26].

Glutamate is a neurotransmitter with multiple antitoxic effects, which has an important role in development of secondary injury after TBI. An increase in the extracellular of glutamate levels after trauma may lead to over-excitation of glutamate receptors and cell death [26]. Excitatory amino acids glutamate and aspartate cause intracellular calcium overload, which in turn triggers a process ending up with free radical formation and lipid peroxidation and causes the activation of the calmodulin-mediated nitric oxide synthesis that prevents mitochondrial respiration and produces toxic hydroxyl radicals [27]. Excess intracellular calcium causes impaired oxidative phosphorylation, toxic radical formation, increased cellular enzymes, dissolution of cellular metabolism, and ultimately, death [28].

Free radical formation and oxidative injury are key players in the pathophysiology of acute brain injury; the events following injury critically depend on the presence of peroxynitrite-induced lipid peroxidation during that time [29].

Pregabalin is a highly potent compound that has a newly described action mechanism and that is effective in many conditions such as epilepsy, anxiety, and neuropathic pain. Despite being a GABA structural analog, it has no direct action on GABA-like mechanisms. It is a novel ligand of alpha-2-delta (α2-δ) subunits of voltage-gated calcium channels (VGCC) exerting anticonvulsant, analgesic, and anxiolytic actions in animal models. After potently binding to alpha-2-delta subunit of the calcium channel, it reduces depolarization-induced calcium flow and thus the release of many excitatory neurotransmitters [26,30–34].

Pregabalin strongly binds to calcium channels via its α2-δ subunit and ultimately results in a reduction of the release of various neurotransmitters such as glutamate, noradrenalin, serotonin, dopamine, and substance P [35]. Thus, it leads to

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clinical improvement by reducing secondary damage through decreased excitatory neurotransmitter release.

Shim et al., in an animal study using cardiopulmonary bypass with deep hypothermic circulatory arrest in rats, demonstrated that neurologic scores were significantly better in the pregabalin-treated group than in the control group, and in the cerebral cortex the percentage of necrotic neurons was significantly less in the pregabalin-treated group than in the control group [34].

Free radicals and excessively released excitatory amino acids also cause impaired sodium and calcium balance, resulting in ischemic (or neurotoxic) edema [36–38].

Yoo-kyung Kim et al., in a focal cerebral ischemia/reperfusion study, carried out a middle cerebral artery (MCA) occlusion and established reperfusion 24 hours later. Twenty minutes before the occlusion they administered pregabalin isoform gabapentin via intravenous route at doses of 0.1 mg/kg, 0.5 mg/kg, and 5 mg/kg. At the end of the study the authors demonstrated that gabapentin reduced infarct volume and brain edema while exerting a neuroprotective action in all groups, but especially in the gabapentin 5 mg/kg group [39].

Kee-Yong Ha et al. explored the neuroprotective effects of pregabalin in spinal cord injuries in rats and showed via histopathological and biochemical parameters that pregabalin had anti-inflammatory and antiapoptotic effects. They recommended use of pregabalin as a neuroprotective agent in SCI [40,41].

Celik et al. explored the role of pregabalin in sciatic nerve injury and found that the pregabalin-treated groups had a significantly superior histopathological regeneration in peripheral nerve injuries compared with the control group. In addition, SFI increases and TGF-B gene expression up-regulation were also significantly better in the pregabalin groups [42].

Our study demonstrated that all subjects in the whole trauma groups and 4 subjects in the trauma+ pregabalin group had edema. In addition, the trauma group had a significantly higher edema score (2.00±0.00 *vs.* 0.40±0.51, p<0.001). Furthermore, all rats in the trauma group had signs of inflammation, whereas only 3 subjects in the trauma+ pregabalin group had inflammation (1.00 *vs.* 0.30±0.48, P<0.001). We also determined a significant difference in the neuronal damage score (1.50±0.52 *vs.* 0.60±0.51, P<0.001). These results suggest that pregabalin effectively prevented post-traumatic edema, inflammation, and neuronal damage.

Conclusions

This study concluded that pregabalin had histopathological demonstrable anti-edema, anti-inflammatory, and neuroprotective effects in rats after administration to limit diffuse brain damage during the acute phase of experimental brain injury. We suggest that pregabalin may also be beneficial in acute TBI in humans via its anti-edema and anti-inflammatory actions.

Declaration of interest

The authors report no conflicts of interest.

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