ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▸ 2025:32(3):184-190 ▸ doi: 10.17343/sdutfd.1629663

Neuroprotective Effects of Dexpanthenol Against Chest Trauma-Induced Brain Injury in Rats

Serife TASAN[1], Sanem ASCI[2], Halil ASCI[3]

[1] Department of Pathology, Faculty of Veterinary Medicine, Burdur Mehmet Akif Ersoy University, Burdur, Türkiye
[2] Department of Neurology, Private Meddem Hospital, Isparta, Türkiye
[3] Department of Pharmacology, Faculty of Medicine, Suleyman Demirel University, Isparta, Türkiye

Cite this article as: Tasan S, Asci S, Asci H. Neuroprotective Effects of Dexpanthenol Against Chest Trauma-Induced Brain Injury in Rats. Med J SDU 2025;32(3):184-190.

Abstract

Objective
Chest trauma-induced brain injury (CTB) occurs as a result of the formation of inflammatory markers in the lung and blood. Vitamin B5, derived from dexpanthenol (DEX), has antioxidant, anti-inflammatory, and antiapoptotic properties. This study aimed to investigate the protective effects of DXP on CTB.

Materials and Methods
Forty Wistar Albino males were divided into four groups as sham, CTB (Dropping a 200g weight from a height of 1 meter onto the anterior chest wall), CTB+DXP (500mg/kg, ip), and DXP. After 48 hours, rats were sacrificed under anesthesia, and the brain tissues were put into 10% formaldehyde solution for histopathological and immunohistochemical examination.

Results
In the CTB group, rats exhibited significant hemorrhage, increased TNF-α, Cas-3, and decreased MBP expressions in the brain compared to the control group. DXP treatment significantly reducted hemorrhage areas and reversed immunoexpressions.

Conclusion
CTB may develop in brain tissue by causing inflammation, apoptosis, and myelin sheath damage. These adverse effects can be reversed with DXP treatment.

Keywords: Acute chest trauma, brain, dexpanthenol, inflammation, apoptosis

Introduction

Chest trauma (CT) is a common cause of morbidity and mortality that can result in both direct lung damage and systemic inflammatory consequences. Following CT, alveolar rupture, pulmonary hemorrhage, and edema disrupt pulmonary function and initiate an inflammatory cascade. This cascade releases pro-inflammatory cytokines and oxidative molecules into the circulation, leading to extrapulmonary complications including cardiac, renal, and cerebral damage. Recent evidence suggests that this systemic response may compromise the blood-brain barrier (BBB), allowing inflammatory mediators to infiltrate the central nervous system (CNS) and cause secondary brain injury, referred to as chest trauma-induced brain injury (CTB) (1–5).

Correspondence: S.T. / vethekserifeagirca@gmail.com
Received: 30.01.2025 • Accepted: 11.06.2025
ORCID IDs of the Authors: S.T: 0000-0002-1469-3464; S.A: 0000-0002-1283-2096; H.A: 0000-0002-1545-035X

The pathogenesis of CTB involves neuroinflammation, neuronal apoptosis, and myelin sheath degradation. Tumor necrosis factor-alpha (TNF-α) and Caspase-3 (Cas-3) are well-known biomarkers representing inflammation and apoptosis, respectively. Similarly, myelin basic protein (MBP) serves as a sensitive marker of demyelination in CNS injuries. Damage to myelin not only disrupts signal transmission but may also contribute to long-term neurological deficits (6–11).

Dexpanthenol (DXP), a biologically active alcohol derivative of pantothenic acid (vitamin B5), has been recognized for its regenerative, anti-inflammatory, antioxidant, and anti-apoptotic effects. DXP has shown efficacy in wound healing, ischemic injuries, and oxidative tissue damage, including in CNS-related models. Its ability to penetrate the BBB and modulate neuroinflammatory pathways makes it a promising therapeutic candidate in brain injuries secondary to systemic trauma (12–18).

Despite the established systemic benefits of DXP, its neuroprotective potential in the context of CT-induced secondary brain injury has not been explored. Therefore, this study aims to evaluate the histopathological and immunohistochemical effects of DXP on inflammation, apoptosis, and myelin damage in a rat model of CTB.

Material and Method

Animals and Experimental Design

Experimental design of all experimental procedures was performed following the guidelines for animal research from the National Institutes of Health (approval no: 06/300). The animals were housed at 21-22 °C and 60% ± 5% humidity with a 12-hour light:12-hour dark cycle and fed with standard commercial feed ad libitum and water during the experiments. Totally, weighing 300-350 grams, forty Wistar Albino males were divided into four groups. Groups were;

- Sham group (n=10); 0.5-1 ml saline intraperitoneally (ip) injection was applied to rats, and no CT was induced under anesthesia.

- CTB group: A 200-gram weight was dropped from a height of 1 meter onto the rats' thoracic wall to induce trauma, after which 0.5–1 ml of saline was administered intraperitoneally under anesthesia in the CTB group.

- CTB+DXP group: A 200-gram weight was dropped from a height of 1 meter onto the rats' thoracic wall to induce trauma, after which 500 mg/kg ip DXP (Bepanthen, Bayer, Turkey) was administered under anesthesia.

- DXP group: 500mg/kg ip DXP administered, and no CT was induced under anesthesia.

After 48 hours, rats were sacrificed under anesthesia, and the brain tissues were put into 10% formaldehyde solution for histopathological and immunohistochemical examination. For all experimental procedures, 80-90 mg/kg ketamine (Ketalar, Pfizer, Turkey) and 8-10 mg/kg xylazine (Xylazinbio 2%, Bioveta, Czech Republic) were used for anesthesia.

Chest Trauma Procedure

A modified bilateral pulmonary contusion model was employed by dropping a 200g weight from a height of 1 meter onto the anterior chest wall as described by Raghavendran et al. (19). The resulting energy (E) was calculated using the formula E = mgh (where E is energy, g is gravitational acceleration- 9.8 m/s^2, h is height- 100 cm, and m is the dropped weight- 0.2 kg), yielding a transferred energy to the chest wall of 1.96 joules.

Histopathological Method

Every group of rats in the study was euthanized at the conclusion. The rat brains were removed from the skull by carefully opening it during necropsy with great care

Table 1 Subarachnoid hemorrhage histopathological scores

0	Normal meningeal and parenchymal structure
1	No blood in the subarachnoid space, ventricles, or brain parenchyma
2	No localized or diffuse thin subarachnoid hemorrhage, intraventricular, or intraparenchymal hemorrhage
3	No diffuse or localized thick subarachnoid blood layers, intraventricular, or intraparenchymal hemorrhage
4	Intraventricular or intraparenchymal hemorrhage in association with subarachnoid hemorrhage, regardless of thickness or location

to prevent damage to the brain tissue. All groups' brain samples underwent careful gross examination. They were preserved in a 10% buffered formalin solution after this inspection. Brain tissues were embedded in paraffin after undergoing a routine tissue processing procedure. Using an automated rotary microtome, serial sections of 5 microns in thickness were taken from each tissue. The hematoxylin and eosin (HE) staining method was used to stain one series of sections and examined under a light microscope.

As in the Mielke et al. study (2020) (20), histopathological results were assessed using the standards given in Table 1. The scores ranged from 0 to 4.

Immunohistochemical Method

Sections produced on slides coated with poly-L-lysine were subjected to streptavidin-biotin peroxidase immunohistochemical staining method. Primary antibodies against Cas-3 (Anti-Caspase-3 antibody [EPR18297] (ab184787)), MBP (Anti-Myelin Basic Protein antibody [IGX3421] (ab209328)), and TNF-α (Recombinant Anti-TNF alpha antibody [EPR21753-109] (ab205587)) were used to stain brain sections for immunohistochemical analysis. All of the primary antibodies used in the immunohistochemistry analyses were obtained from Abcam (UK) and diluted using antibody dilution solutions at a ratio of 1/100. The immunohistochemical procedure was performed in accordance with the manufacturer's instructions. The secondary kit was the Mouse and Rabbit Specific HRP/DAB Detection Kit -Micropolymer (ab236466) from Abcam (Cambridge, UK). Other procedures were followed as directed, although for the negative controls, antibody dilution solutions were applied to the sections at the primary antibody stage rather than the primary antibodies.

On a 0-3 scale, the IHC expressions received scores. Hence, 0 denotes no expression, 1 focal and mild staining, 2 diffuse and weak staining, and 3 diffuse and prominent staining. Image J 1.46r software (The National Institutes of Health, Bethesda, MD) was used to determine the positive immunohistochemistry reaction. Microphotography was conducted using the Database Manual Cell Sens Life Science Imaging Software System (Olympus Corporation, Tokyo, Japan) with an Olympus CX41 type microscope.

Statistical Analysis

For statistical analysis, we used the GraphPad Prism 10 (Version 10.1.0) (GraphPad Software, USA) program. Initially, the data were analyzed for normality of distribution using the Shapiro-Wilk test. Since the data showed a normal distribution ($p>0.05$), comparisons between the groups were made with one-way analysis of variance (ANOVA). The Tukey test was used to identify differences between groups, with values of $p<0.05$ considered statistically significant. For nonparametric data, the Mann-Whitney U test and Dunnett's C test were used to detect differences between groups.

Results

During histopathological examination, slight to moderate hyperemia in meningeal vessels was observed in the sham group. In the CTB group, rats exhibited significant and widespread hemorrhage. In the CTB+DEX group, it was observed that DEX treatment resulted in significant reductions in hemorrhage areas. Normal brain histology was observed in the DEX group (Fig. 1). Statistically significant differences were observed between the control group and the CTB and DXP groups; between the CTB group and both the CTB+DXP and DXP groups; as well as between the CTB+DXP and DXP groups ($p < 0.001$). These findings indicate that CTB and DXP administrations induce significant histopathological alterations and that the addition of DXP to CTB substantially modulates the effects of CTB.

Immunohistochemical Findings

At the immunohistochemical examinations, negative or very slight Cas-3 and TNF-α expressions with marked MBP expressions in the brain were observed in the sham and DXP groups. While decreased MBP and increased Cas-3 and TNF-α expressions were noticed in the CTB+DXP group. The DXP group's expressions matched those of the control group with markers in terms of similarity (Fig.2-3-4).

In terms of TNF-α expression levels, the CTB group demonstrated significantly higher expression compared to the control, CTB+DXP, and DXP groups ($p < 0.001$). Additionally, the CTB+DXP group showed statistically significant differences in expression levels compared to both the control and DXP groups. These findings suggest that CTB administration increases TNF-α expression in brain tissue, while DXP may partially attenuate this pro-inflammatory response. (Fig.2).

In terms of Cas-3 expression levels, the CTB group exhibited significantly higher expression compared to the control, CTB+DXP, and DXP groups ($p < 0.001$). Furthermore, the CTB+DXP group demonstrated significantly higher expression levels than the DXP group. These findings indicate that CTB administration increases Caspase-3 expression in the brain,

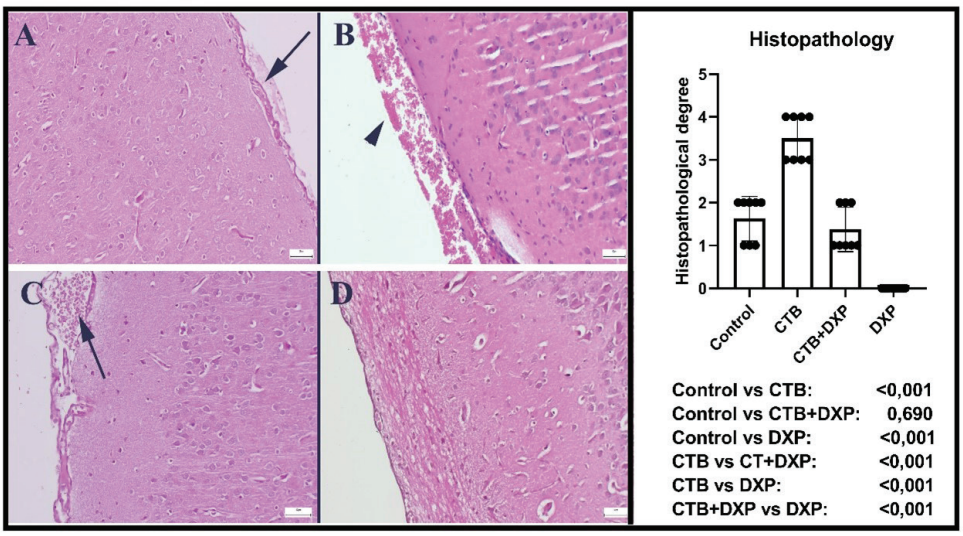

Figure 1

Representative histopathological figures and statistical analysis of histopathological scores of brains between the groups. (A) Mild hyperemia (arrow) in meningeal vessels in the sham group. (B) Marked hemorrhage foci (arrowheads) in the brain of a rat in the CTB group. (C) Markedly reduced hemorrhage area in the CTB+DEX group. (D) Normal brain and meningeal structure in a rat in the DEX group, HE, Scale bars=50µm. Values are presented as means±standard deviation. A one-way ANOVA test was used. * P≤0.05, ** P≤0.01, *** P≤0.001

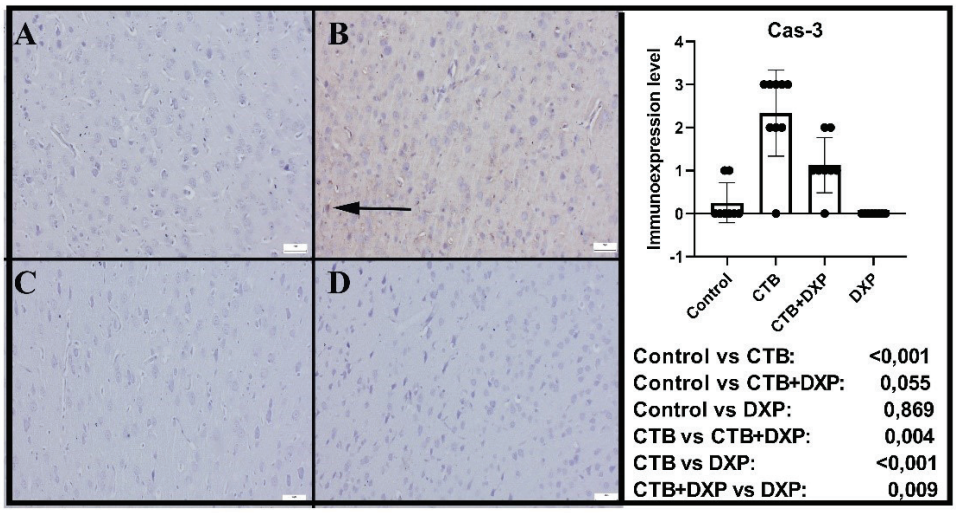

Figure 2

TNF-α immonoexpressions and statistical analysis of immunohistochemical scores of the brain tissues. (A) Negative TNF-α in the sham group. (B) Significant increase in TNF-α and expressions (arrows) in the CTB group. (C) Decreased TNF-α expression in the CTB+DEX group. (D) Negative TNF-α expressions in the DEX group, streptavidin-biotin peroxidase method, scale bars=50 µm. Values are presented as means±standard deviation. A one-way ANOVA test was used. * P≤0.05, ** P≤0.01, *** P≤0.001

suggesting an enhancement of apoptosis, while DXP appears to partially attenuate this effect. (Fig.3).

In terms of MBP expression levels, the CTB group showed statistically significant differences compared to both the CTB+DXP and DXP groups, as well as the control group ($p < 0.001$). No significant differences were observed in the other comparisons. These findings suggest that CTB administration significantly increases MBP expression in brain tissue, while DXP may modulate this effect in a suppressive manner. (Fig.4).

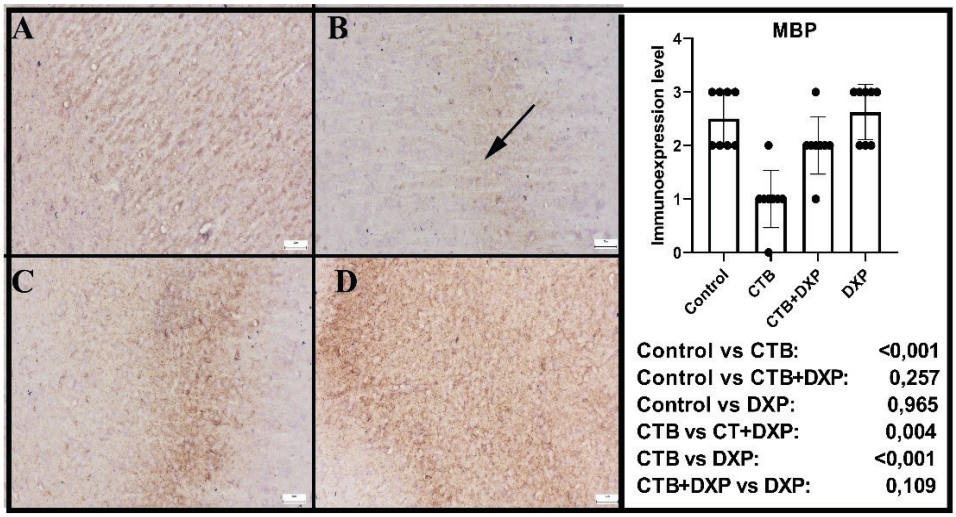

Figure 3

Cas-3 immonoexpressions and statistical analysis of immunohistochemical scores of the brain tissues. (A) Negative TNF-α in the sham group. (B) Significant increase in Cas-3 and expression (arrows) in the CTB group. (C) Decreased Cas-3 expression in the CTB+DEX group. (D) Negative Cas-3 expressions in the DEX group, streptavidin-biotin peroxidase method, scale bars=50 μm. Values are presented as means±standard deviation. A one-way ANOVA test was used. * P≤0.05, ** P≤0.01, *** P≤0.001

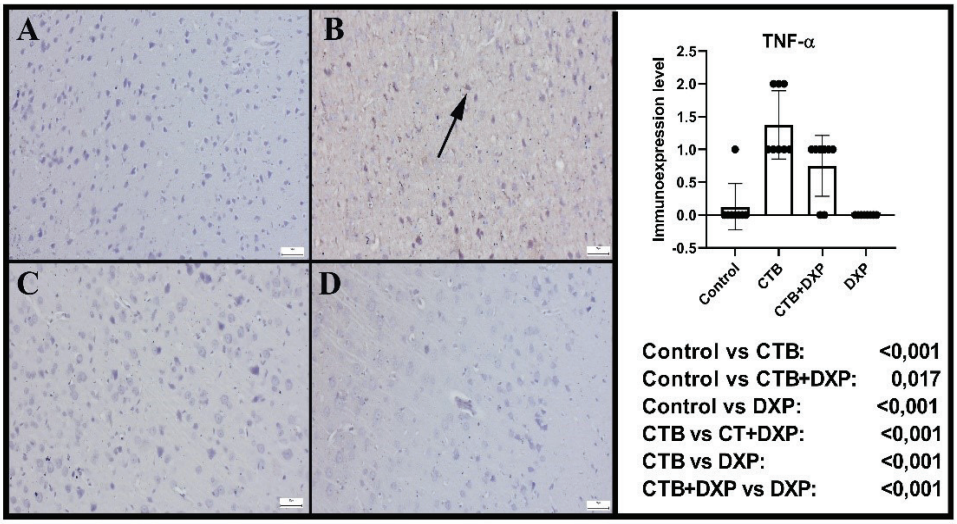

Figure 4

MBP immonoexpressions and statistical analysis of immunohistochemical scores of the brain tissues (A) Marked expression of MBP in the sham group. (B) Significant decrease in MBP expressions (arrows) in the CTB group. (C) Increase in MBP expressions in the CTB+DEX group. (D) Marked expressions MBP expressions in the DEX group, streptavidin-biotin peroxidase method, scale bars=50 μm. Values are presented as means±standard deviation. A one-way ANOVA test was used. * P≤0.05, ** P≤0.01, *** P≤0.001

Discussion

Chest trauma (CT) is a well-established cause of systemic inflammation and oxidative stress due to pulmonary parenchymal damage. While the pulmonary effects of CT are widely studied, its secondary impacts on remote organs such as the brain remain under-recognized. The present study demonstrates, for the first time, that CT can lead to histopathologically and immunohistochemically verifiable damage in the brain, and that dexpanthenol (DXP), a pantothenic acid derivative, offers measurable neuroprotection (21-23).

Histological analyses revealed severe hemorrhagic lesions in the cerebral cortex, particularly in the frontal regions, of the CTB group. This aligns with prior reports that systemic trauma may lead to cerebrovascular fragility and breakdown of the blood-brain barrier (BBB) through inflammatory mediators like TNF-α and IL-6 (24–26). The reduction of hemorrhagic areas in DXP-treated animals suggests the compound's vasoprotective and anti-inflammatory properties, likely mediated through oxidative stress reduction and stabilization of endothelial junctions (17,18).

The increase in TNF-α and Cas-3 expressions in CTB animals underscores the prominent role of inflammation and apoptosis in secondary brain injury. TNF-α is a proinflammatory cytokine that contributes to BBB permeability and leukocyte infiltration, whereas Cas-3 is a terminal executor of apoptosis, especially in neurons (13–15). DXP treatment significantly suppressed these markers, indicating its ability to modulate neuroinflammation and apoptosis pathways. This is consistent with prior findings demonstrating DXP's protective role in ischemia-reperfusion and sepsis-induced neural injury models (16,18,27).

Importantly, MBP expression, a marker of myelin integrity, was significantly reduced in the CTB group. Myelin disruption impairs axonal conductivity and contributes to long-term neurological deficits. The partial restoration of MBP levels in the DXP group suggests that this agent may preserve oligodendrocyte function and inhibit demyelination. This effect is highly relevant given that myelin damage is a critical determinant of cognitive and motor dysfunctions in trauma-induced brain injury (9–11).

The regional localization of injury and recovery—most prominent in the frontal cortex and periventricular regions—supports the hypothesis that CT-associated systemic inflammation preferentially affects highly vascularized and metabolically active brain regions. Future studies involving molecular signaling analysis (e.g., NF-κB, MAPK, or PI3K/Akt pathways) and behavioral assessments would be valuable in confirming and extending these findings.

Clinically, the findings of this study may have translational implications for emergency medicine and neurocritical care. Since DXP is already used in parenteral forms for wound healing and is known to cross the BBB, it represents a readily available, safe, and cost-effective candidate for early intervention in trauma cases.

Conclusion

In conclusion, this study demonstrates that chest trauma induces neuroinflammation, neuronal apoptosis, and myelin sheath damage, particularly in the frontal cortex. Dexpanthenol significantly attenuates these pathological changes, likely through its antioxidant, anti-inflammatory, and anti-apoptotic effects. These findings warrant further exploration of DXP as a neuroprotective agent in systemic trauma settings and support its potential inclusion in emergency trauma care protocols.

Conflict of Interest Statement
Authors must disclose any potential conflict of interest.

Ethical Approval
In this study, all experiments were performed under the guidelines for animal research from the National Institutes of Health and were approved by the Committee on Animal Research of Suleyman Demirel University, Isparta (Ethic No:09.05.2024/300).

Funding
In this study, consumables and analytical support were provided by the Süleyman Demirel University Scientific Research Projects Coordination Unit (Project No: TSG-2024-9515), while the costs of animal care and fees were covered by the Süleyman Demirel University Scientific Research Projects Coordination Unit (Project No: TSG-2023-9010).

Availability of Data and Materials
Data sharing not applicable.

Artificial Intelligence Statement
The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions
ST: Data curation; Formal analysis; Investigation;

Validation; Visualization; Writing-original draft.

SA: Investigation; Validation; Writing-original draft.

HA: Methodology; Data curation; Formal analysis; Writing- review & editing.

References

1. Požgain Z, Kristek D, Lovrić I, Kondža G, Jelavić M, Kocur J, et al. Pulmonary contusions after blunt chest trauma: clinical significance and evaluation of patient management. Eur J Trauma Emerg Surg 2018;44:773–7.
2. Lewis BT, Herr KD, Hamlin SA, Henry T, Little BP, Naeger DM, et al. Imaging manifestations of chest trauma. Radiographics 2021;41(5):1321–34.
3. Mert Ü, Andruszkow H, Hildebrand F. Chest trauma: Classification and influence on the general management. In: Textbook of Polytrauma Management: A Multidisciplinary Approach. Cham: Springer International Publishing; 2022. p. 161–84.
4. Bezerra FS, Lanzetti M, Nesi RT, Nagato AC, Silva CPE, Kennedy-Feitosa E, et al. Oxidative stress and inflammation in acute and chronic lung injuries. Antioxidants 2023;12(3):548.
5. Di Bella D, Ferreira JP, Silva RDNO, Echem C, Milan A, Akamine EH, et al. Gold nanoparticles reduce inflammation in cerebral microvessels of mice with sepsis. J Nanobiotechnol 2021;19:1–1
6. Li R, Ye JJ, Gan L, Zhang M, Sun D, Li Y, Wang T, Chang P. Traumatic inflammatory response: pathophysiological role and clinical value of cytokines. Eur J Trauma Emerg Surg 2024;50(4):1313-1330.
7. Hazeldine J, Foster M. The immune and inflammatory response to major traumatic injury. In: Blast Injury Science and Engineering: A Guide for Clinicians and Researchers. Cham: Springer International Publishing; 2023. p. 14
8. Walsh SA, Hoyt BW, Rowe CJ, Dey D, Davis TA. Alarming Cargo: The Role of Exosomes in Trauma-Induced Inflammation. Biomolecules 2021;31;11(4):522.
9. Smirnova EV, Rakitina TV, Ziganshin RH, et al. Comprehensive atlas of the myelin basic protein ınteraction landscape. Biomolecules 2021;3;11(11):1628.
10. Shenfeld A, Galkin A. Role of the MBP protein in myelin formation and degradation in the brain. Bio. Comm 2022;67(2): 127–13.
11. Shang Y, Wang Y, Guo Y, Ren L, Zhang X, Wang S, et al. Analysis of the risk of traumatic brain injury and evaluation of neurogranin and myelin basic protein as potential biomarkers of traumatic brain injury in postmortem examination. Forensic Sci Med Pathol 2022;18(3
12. Karakuyu NF, Özmen Ö. Dexpanthenol Inhibits ınflammation and apoptosis in LPS-ınduced acute lung ınjury by reducing ıncreased VCAM-1 and caspase-3 expressions in rats. KVJ 2022;15(3):303-10.
13. Zhou Y, Fan R, Botchway BO, Zhang Y, Liu X. Infliximab can improve traumatic brain injury by suppressing the tumor necrosis factor alpha pathway. Mol Neurobiol 2021;58(6):2803–11.
14. Gu M, Mei XL, Zhao YN. Sepsis and cerebral dysfunction: BBB damage, neuroinflammation, oxidative stress, apoptosis, and autophagy as key mediators and the potential therapeutic approaches. Neurotox Res 2021;39:489–503.
15. Zhou R, Sun X, Li Y, Huang Q, Qu Y, Mu D, et al. Low-dose dexamethasone increases autophagy in cerebral cortical neurons of juvenile rats with sepsis associated encephalopathy. Neuroscience 2019;419:83–99.
16. Graff-Radford J, Lesnick T, Rabinstein AA, Gunter J, Aakre J, Przybelski SA, et al. Cerebral microbleed incidence, relationship to amyloid burden: The Mayo Clinic Study of Aging. Neurology 2020;94(2):e190–e199.
17. Karatoprak DE, Engin R, Sahin S, İclek İ, Durak MA. Investigation of neuroprotective efficacy of dexpanthenol in an experimental head injury model. J Korean Neurosurg Soc 2024.
18. Gülmez A, Bektaşoğlu PK, Tönge Ç, Yaprak A, Türkoğlu ME, Önder E, et al. Neuroprotective effects of dexpanthenol on rabbit spinal cord ischemia/reperfusion injury model. World Neurosurg 2022;167:e172–e183.
19. Raghavendran K, Davidson BA, Helinski JD, Marschke CJ, Manderscheid P, Woytash JA, et al. A rat model for isolated bilateral lung contusion from blunt chest trauma. Anesthesia & Analgesia 2005;101(5):1482-9.
20. Mielke D, Bleuel K, Stadelmann C, et al. The ESAS-score: A histological severity grading system of subarachnoid hemorrhage using the modified double hemorrhage model in rats. PLoS One 2020;15(2), e0227349.
21. Dogrul BN, Kiliccalan I, Asci ES, Peker SC. Blunt trauma related chest wall and pulmonary injuries: An overview. Chin J Traumatol 2020;23(3):125–38.
22. Oestreich MA, Seidel K, Bertrams W, Müller HH, Sassen M, Steinfeldt T, et al. Pulmonary inflammatory response and immunomodulation to multiple trauma and hemorrhagic shock in pigs. PLoS One 2022;17(12):e0278766.
23. Noorbakhsh MR, Kriley IR. Management of severe respiratory failure in complex trauma patients. J Emerg Crit Care Med 2018;2(3).
24. Xu J, Zhan T, Zheng WK, Huang YK, Chen K, Zhang XH, et al. Hydroxysafflor yellow A acutely attenuates blood-brain barrier permeability, oxidative stress, inflammation, and apoptosis in traumatic brain injury in rats. Acta Cir Bras 2021;35:e351202.
25. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: Effects and mechanisms. CNS Neurosci Ther 2021;27(1):36–47.
26. Qin D, Wang J, Le A, Wang TJ, Chen X, Wang J. Traumatic brain injury: Ultrastructural features in neuronal ferroptosis, glial cell activation and polarization, and blood-brain barrier breakdown. Cells 2021;10(5):1009.
27. Kose A, Parlakpinar H, Ozhan O, Ermis N, Yildiz A, Vardi N, et al. Therapeutic effects of dexpanthenol on the cardiovascular and respiratory systems following cecal ligation and puncture-induced sepsis in rats. Biotechnic Histochem 2020;95(6):428–37.