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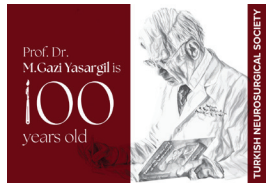


# Assessing Dexmedetomidin's Efficacy in Traumatic Brain Injury Treatment Using a Rat Experimental Model

Yasar OZTURK[1], Ismail BOZKURT[2,3], Orkhan MAMMADKHANLI[4], Yahya GUVENC[5],Salim SENTURK[6], Guven GUNEY[7], Manuel De Jesus Encarnación RAMÍREZ[8], Ozlem GULBAHAR[9]

[1]Yenimahalle Training and Research Hospital, Department of Neurosurgery, Ankara, Türkiye
[2]Medical Park Ankara Hospital, Department of Neurosurgery, Ankara, Türkiye
[3]Yuksek Ihtisas University, Faculty of Medicine, Department of Neurosurgery, Ankara, Türkiye
[4]Trakya University, School of Medicine, Department of Neurosurgery, Edirne, Türkiye
[5]Marmara University, School of Medicine, Department of Neurosurgery, Istanbul, Türkiye
[6]Memorial Spine Center, Neurosurgery Clinic, Istanbul, Türkiye
[7]Hitit University School of Medicine, Department of Pathology, Corum, Türkiye
[8]Russian People's Friendship University, Department of Neurosurgery, Moscow, Russia
[9]Gazi University, Faculty of Medicine, Department of Medical Biochemistry, Ankara, Türkiye

**Corresponding author:** Orkhan MAMMADKHANLI ✉ dr.mammadkhanli@gmail.com

## ABSTRACT

**AIM:** To elucidate the effects of nasal and intraperitoneal dexmedetomidine (DexN and DexP, respectively) administration in an animal model, and to explore the underlying action mechanisms on the treatment of traumatic brain injury (TBI).

**MATERIAL and METHODS:** A total of 31 Wistar albino rats served as a weight-drop model to induce experimental TBI. The two treatment groups received DexN and DexP on the day of the trauma and then after 5 days. The Garcia test was performed for the neurological evaluation along with histopathological and biochemical analyses.

**RESULTS:** The rats in the treatment group displayed better neurological outcomes, as evidenced by a higher Garcia test score ($p<0.001$). DexP group presented with increased anti-inflammatory and neuroprotective effects in comparison to DexN ($p<0.001$). DexN group demonstrated a reduction in the neuron specific enolase (NSE) levels ($p=0.023$), indicating that it inhibited the neuronal destruction.

**CONCLUSION:** The present study support the hypothesis that a psychoactive drug, Dex, which has been conventionally used for sleep disorders and is also known for its cognitive-enhancing properties, may have beneficial effects after TBI owing to its anti-inflammatory, anti-oxidative, and neuroprotective properties.

**KEYWORDS:** Traumatic brain injury, Dexmedetomidine, Neuroprotective agents, Anti-inflammatory agents, Rats

**ABBREVIATIONS: BBB:** Blood-brain barrier, **CASP3:** Caspase-3, **Den N:** Dexmedetomidine nasal, **DEX:** Dexmedetomidine, **DexP:** Dexmedetomidine peritoneal, **GSH-PX:** Glutathione peroxidase, **H&E:** Hematoxylin and eosin, **Hpf:** Highpower field, **NSE:** Neuron-specific enolase, **S100B:** S100 calcium-binding protein B, **TBARS:** thiobarbituric acid reactive substances, **TBI:** Traumatic brain injury

Yasar OZTURK : 0000-0003-0923-5941
Ismail BOZKURT : 0000-0002-6719-5522
Orkhan MAMMADKHANLI : 0000-0003-3299-4196
Yahya GUVENC : 0000-0002-4813-0854
Salim SENTURK : 0000-0003-0524-9537
Guven GUNEY : 0000-0001-8324-2870
Manuel De Jesus Encarnación RAMÍREZ : 0000-0003-3541-0635
Ozlem GULBAHAR : 0000-0003-0450-4305

## INTRODUCTION

Traumatic brain injury (TBI) is an acute biomechanical brain injury caused by an abrupt trauma, often resulting from falls, accidents, or direct impacts. The associated symptoms range from mild ones, such as headaches and brief confusion, to severe ones, including neurological deficits, coma, or even death. TBI involves complex pathological processes, including white matter degeneration, neuronal loss, abnormal protein formation, neurotransmitter imbalances, and chronic neuroinflammation (3). It is a major public health concern affecting all age groups. Despite the advancements made in diagnostics and clinical care domains, the underlying pathological process remains poorly understood, which hinders the development of effective treatments. In addition, co-occurring external injuries often complicate TBI assessments. Understanding the mechanisms of brain injury and recovery is thus crucial for therapeutic advancements.

Dexmedetomidine (DEX), a selective α-2 adrenergic agonist, exhibits sedative, analgesic, and neuroprotective properties via reduction in the sympathetic activity and enhancement of neuroprotection. Recently, DEX has gained attention for its anti-inflammatory and antioxidant effects in TBI models (6). This study evaluated the potential neuroprotective benefits of DEX and compared the efficacy of intranasal versus systemic administration in experimental TBI.

## MATERIAL and METHODS

### Study Approval

Appropriate Institutional Review Board approval was obtained prior to conducting the study (Ankara Research and Training Hospital Ethics Committee, no: 0019/23102014/317), and the study was conducted in accordance with the "Principles of Laboratory Animal Care" (NIH publication 82-23, revised in 1985 and further updated in 1996). The ARRIVE Essential 10 checklist (available at https://arriveguidelines.org/resources/author-checklists) was applied as the reporting guideline. Thirty-one healthy adult male Wistar rats (n=31) weighing 250–300 g were housed in a temperature-controlled environment (24 ± 2°C) with a 12-hour (h) photophase and administered with an *ad libitum* access to standard chow and water. The rats were randomly assigned into four groups: control (n=7), trauma (n=8), DEX nasal (DexN) (n=8), and DEX peritoneal (DexP) (n=8).

### Animal Preparation and Experimental Protocol

Marmarou et al. initially established a model of diffuse cortical injury (8), which was subsequently modified in the present study by the integration of a steel plate, so as to reduce the incidence of post-traumatic seizures. To induce anesthesia, the rats were administered intraperitoneally with 60 mg/kg of ketamine hydrochloride (Alfamine 10%, Egevet Veterinary Services) and 5 mg/kg of xylazine (Alfazyne 2%, Egevet Veterinary Services).

In order to reveal the coronal and lambdoid sutures, a vertical scalp incision was created. Thereafter, a circular aluminum plate (approximately 10-mm diameter, 3-mm thickness) was affixed to the cranium by using bone wax. Subsequently, a 450 g cylindrical lead weight was dropped onto the exposed bony surface from a height of 70 cm through a tube.

No additional intervention was performed in the control group from this point onward and this group only received 2 mL of saline on the day of trauma and then a day later. The DEX group was administered DEX at a dosage of 25 mcg/kg/day immediately following the trauma and then on the following day via intranasal and intraperitoneal routes. In a previous study, equivalent doses of IV and IN showed equally effective outcomes and fewer side effects in the IN administration group. Accordingly, in this study, the same dosage was used (11).

### Neurological Examination

An 18-point scale proposed by Garcia et al. was used for neurological evaluation (5). This assessment involved the following six parameters: spontaneous activity, symmetry in four limb movements, forepaw outstretching, climbing, body proprioception, and response to vibrissae touch.

### Brain Tissue Extraction and Histological Analysis

A week after the TBI, the brain tissues were extracted *en bloc* under anesthesia, thereby ensuring no additional trauma. The specimens for histological and biochemical analyses were collected from the right frontal lobe close to the interhemispheric fissure. The tissue samples were fixed in 10% phosphate-buffered formaldehyde for 24 h. Subsequently, the specimens were sliced vertically into sections of 4-mm thickness and then placed in cassettes. These sections remained in an ethanol bath for 24 h for fixation, followed by infiltration with paraffin wax. Finally, the samples were sectioned into 5-µm-thick horizontal sections.

Before staining with hematoxylin and eosin (H&E), the sections were kept in 10% buffered formaldehyde for 24 h. A pathologist (blinded to the treatment and control groups) evaluated the sections under a light microscope (Nikon Eclipse 80i) focusing on neuron loss, inflammation, congestion, and gliosis. Anti-inflammatory and neuroprotective analyses served as the main focus, as evidenced by the histopathological scoring system given in Table I. Congestion was analyzed by counting the number of congested vascular structures per high-power field (hpf), whereas the number of inflammatory cells was used for inflammation analysis.

The parameters employed in this analysis were specifically selected for their reproducibility and low susceptibility to bias. The loss of neurons and the presence of gliosis were used to quantify the neuroprotective effect. The number of neurons was considered as 100% in healthy control rats under 5 hpf. Thereafter, quartiles were used to grade the amount of neurons in the test subjects. Similarly, no gliosis was detected in the healthy subjects, and this effect was compared with that observed in the TBI rats. The scoring system was composed of 12 points, with "12" indicating a healthy subject and "0" indicating the most severe injury. Congestion and inflammation points made up for the anti-inflammatory analysis, whereas neuron loss and gliosis made up for the neuroprotective effect.

**Table I:** Scoring System Used in the Pathological Analysis

| Histopathological analysis | | Value | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| Anti-inflammatory | Congestion[1] | >3 | 2-3 | 1 | None |
| | Inflammation | Small groups of inflammatory cells within the parenchyma | Few inflammatory cells within the parenchyma | Perivascular inflammatory cells | No inflammation |
| Neuroprotective | Neuron loss[2] | >75% | 50-75% | 25-50% | <25% |
| | Gliosis[3] | Extended | Limited | Mild | None |

*[1]The number of congested vascular structures observed per 1 high-power field (hpf).*
*[2]The specimens obtained from the control group underwent evaluation at the 5 hpf stage. In comparing with other groups, the average number of neurons was taken into account at 60 neurons, expressed in percentage terms as 100%.*
*[3]The control group was evaluated as normal at 3 points. The maximum gliosis was scored as 0. 1-2 points were scored in between.*

### Biochemical Analysis

Biochemical analyses were performed by blinded biochemists. The levels of neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), caspase-3 (CASP3), thiobarbituric acid reactive substances (TBARS), and glutathione peroxidase (GSH-PX) were determined. Tissue samples were mixed with an isotonic solution (0.9% NaCl) and then centrifuged. A commercially available solid-phase enzyme immunoassay kit (Shang Hai Yehua Biological Technology Co., Ltd.) was used for the measurements.

### Statistical Analysis

Shapiro–Wilk normality test was applied to determine the normality of the data, whereas Mann–Whitney U-test was used for comparison between the groups. Normally distributed groups were analyzed with one-way ANOVA and non-parametric ANOVA (Kruskal–Wallis) for non-parametric values. $P<0.05$ was considered to indicate statistical significance. After the Kruskal–Wallis test, the Dwass–Steel–Critchlow–Fligner method was employed for post-hoc analysis. All statistical analyses were conducted using the Jamovi program (version 2.3.21).

## RESULTS

One rat in control group died on the night after the intervention, necessitating the omission of all subsequent analyses.

The mean values and standard deviation results for all four groups are detailed in Table II. Table III presents the Garcia Score Test, along with the anti-inflammatory and neuronal protective impacts, as well as the overall histopathological score.

The trauma group exhibited statistically significant ($p\leq0.001$) poorer outcomes compared to the control group across all four parameters (i.e., Garcia score, anti-inflammatory, neuroprotective, and total histopathologic effect).

The evaluation of the Garcia score via the DexP method and the DexN method yielded identical outcomes. The DexP method demonstrated a more pronounced anti-inflammatory effect relative to the DexN method. With regard to the total histopathological score, the DexP method was more efficacious than the DexN method. In all histopathological analyses (i.e., inflammation, congestion, neuronal loss, gliosis, and overall histopathologic score), the results demonstrated statistically significant better outcomes when compared to those of the trauma group (Table IV). In consideration of the neuroprotective effect, an analysis of the results of additional biochemical markers indicated that DexN demonstrated a more favorable outcome. Biochemical analysis indicated a significant increase in the NSE, S100B, CASP, and TBARS and a decrease in the GSH-PX levels in the trauma group when compared to both the control and trauma groups (Table II). The p-values for S100B, TBARS, and GSH-PX levels among the control, trauma, and pharmacologically treated (DexN and DexP) groups were >0.05, indicating the absence of statistically significant differences between the groups for these variables (S100B: $p=0.212$, CASP3: $p=0.085$, TBARS: $p=0.160$, and GSH-PX: $p=0.149$, respectively). The non-parametric ANOVA results for the groups with non-parametric distributions (i.e., NSE, CASP3, and GSH-PX) were analyzed. The Kruskal–Wallis test for the NSE levels revealed statistically significant differences between the groups ($\chi^2(3) = 9.56$, $p=0.023$). This finding supports the hypothesis about the presence of significant differences in the NSE levels among the control, trauma, and pharmacologically treated (Groups 3 and 4) groups. The Kruskal–Wallis test for the GSH-PX and CASP3 levels indicated no significant differences between the groups ($\chi^2(3)= 5.34$, $p=0.149$ and $\chi^2(3)=6.61$, $p=0.085$, respectively). Pairwise comparisons were conducted using Dwass–Steel–Critchlow–Fligner tests. The results of the pairwise comparisons for NSE indicated a statistically significant difference between the control and trauma groups ($p=0.010$). The differences among the other groups were not statistically significant (Dex N vs Trauma: $p=0.392$; Dex P vs Trauma: $p=1.000$; DexN vs Control: $p=0.967$; DexP vs Control: $p=0.124$; DexN vs DexP: $p=0.456$).

## DISCUSSION

This present study aimed to assess the effects of DEX in an experimental TBI model by using the Marmarou method (8), with the addition of a steel plate to prevent cranial fractures

**Table II:** Descriptive Values of Biochemistry Markers and Comparison Between Groups (*nonparametric ANOVA Test was Performed For Non-Normal Distributions)

| Biochemical markers | Group name | n | Mean | SD | ANOVA/ Non parametric ANOVA* | |
|---|---|---|---|---|---|---|
| | | | | | df2/$\chi^2$ | p-value |
| NSE (ng/ml) | Control | 7 | 6.29 | 1.46 | 9.56 | 0.023* |
| | Trauma | 8 | 9.77 | 2.25 | | |
| | Dex N | 8 | 7.54 | 4.74 | | |
| | Dex P | 8 | 9.91 | 8.37 | | |
| CASP3 (ng/ml) | Control | 7 | 10.54 | 3.82 | 6.61* | 0.085* |
| | Trauma | 8 | 11.93 | 2.12 | | |
| | Dex N | 8 | 9.84 | 3.74 | | |
| | Dex P | 8 | 13.06 | 3.46 | | |
| TBARS (pg/ml) | Control | 7 | 128.68 | 49.29 | 13.6 | 0.160 |
| | Trauma | 8 | 184.40 | 83.34 | | |
| | Dex N | 8 | 139.99 | 28.16 | | |
| | Dex P | 8 | 176.77 | 90.70 | | |
| GSH-PX (U/ml) | Control | 7 | 79.06 | 68.55 | 5.34* | 0.149* |
| | Trauma | 8 | 100.69 | 41.79 | | |
| | Dex N | 8 | 114.06 | 22.55 | | |
| | Dex P | 8 | 127.25 | 80.83 | | |
| S100B(pg/ml) | Control | 7 | 162.92 | 63.10 | 13.8 | 0.212 |
| | Trauma | 8 | 182.16 | 53.98 | | |
| | Dex N | 8 | 179.13 | 73.55 | | |
| | Dex P | 8 | 187.29 | 107.24 | | |

**Non-parametric values are presented as median ± interquartile range (IQR) and subjected to statistical analysis using the Kruskal–Wallis test.* ***NSE:*** *Neuron-specific enolase,* ***CASP3:*** *Caspase-3,* ***TBARS:*** *Thiobarbituric acid reactive substances,* ***GSH-PX:*** *Glutathione peroxidase, and* ***S100B:*** *S100 calcium-binding protein B.*

**Table III:** Distribution of Garcia score, Anti-Inflammatory Effect, Neuroproductive Effect and Total Histopathologic Scores according to Groups

| Groups | Anti-Inflammatory | Neuroprotective | Histopathological score | Garcia Test | Garcia score* p-value |
|---|---|---|---|---|---|
| Control | Min: 5.90<br>Max: 6.00<br>Median: 6.00 | Min: 5.90<br>Max: 6.00<br>Median: 6.00 | Min: 11.90<br>Max: 12.00<br>Median: 12.00 | Min: 17.90<br>Max: 18.00<br>Median: 18.00 | **<0.001** |
| Trauma | Min: 1.00<br>Max: 2.00<br>Median: 2.00 | Min: 2.00<br>Max: 4.00<br>Median: 2.50 | Min: 4.00<br>Max: 6.00<br>Median: 2.00 | Min: 14.90<br>Max: 15.00<br>Median: 15.00 | - |
| DexN | Min: 1.00<br>Max: 4.00<br>Median: 3.00 | Min: 2.00<br>Max: 4.00<br>Median: 4.00 | Min: 4.00<br>Max: 8.00<br>Median: 6.50 | Min: 17.90<br>Max: 18.00<br>Median: 18.00 | **<0.001** |
| DexP | Min: 3.00<br>Max: 4.00<br>Median: 4.00 | Min: 3.90<br>Max: 4.00<br>Median: 4.00 | Min: 7.00<br>Max: 8.00<br>Median: 8.00 | Min: 17.90<br>Max: 18.00<br>Median: 18.00 | **<0.001** |

***Mann Whitney U test for comparison with trauma group.***

**Table IV:** Comparison Between Groups according to Histopathological Parameters

| Histopathological parameters | Dex N Control | Dex N Trauma | Dex N Dex P | Trauma Control | Control DexP | Trauma DexP | Kruskal-Wallis | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $\chi^2$ | p-value |
| Inflammation | 0.064 | 0.001 | 0.156 | 0.001 | 0.954 | 0.001 | 23.2 | **<0.001** |
| Congestion | 0.001 | 0.001 | 0.245 | <0.001 | <0.001 | <0.001 | 29.5 | **<0.001** |
| Neuronal loss | 0.962 | 0.001 | 0.245 | 0.001 | 0.114 | <0.001 | 23.3 | **<0.001** |
| Gliosis | 0.019 | <0.001 | 0.750 | <0.001 | 0.004 | <0.001 | 27.6 | **<0.001** |
| Total score | 0.109 | 0.002 | 0.070 | 0.001 | 0.002 | 0.001 | 26.6 | **<0.001** |

linked to increased mortality and seizures. The rats received either nasal or intraperitoneal DEX, while the control groups were not treated. Three comprehensive analyses focusing on the neurological status, histological evaluation, and biomarker assessment were performed to elucidate the neuroprotective and anti-inflammatory effects of DEX.

The secondary neuroinflammatory phase of TBI is complex and lays the foundation for long-term effects. NSE, S100B, CASP3, TBARS, and GSH-PX have been previously demonstrated to help assess the level of severity of TBI and prognosis (2,3,10). Hence, these biomarkers are valuable in providing insight into the pathophysiology of TBI while shedding light on potential therapeutic agents. However, the NSE levels were lower in the DexP group, with a statistically significant difference (p=0.023). This result advocates the neuroprotective effect of Dex when administrated nasally.

A glycolytic enzyme specific for neurons is NSE, which has been proven to be a reliable biomarker for neuron damage. Elevated NSE levels have been correlated with worse outcomes after TBI (4). Our results suggested reduced levels of NSE after DexN when compared with the control group (Figure 1).

S100B, a glial protein primarily released by astrocytes after CNS trauma, rises rapidly following TBI, peaking within hours, and then normalizing within 24 h. Its elevated levels are correlated with injury severity and neuroinflammation, which makes it a potential therapeutic target (9). In this study, the DexN group exhibited lower S100B levels compared to the trauma group (179.13 ± 73.55 vs. 182.16 ± 16), albeit the intergroup differences were not statistically significant (p=0.212).

CASP3, a key enzyme in apoptosis, is markedly activated following TBI, indicating neuronal cell death. Elevated CASP3 levels have been associated with poor neurological outcomes, highlighting its value as a predictive biomarker (4). In this study, the CASP3 levels were lower in the DexN group than in the control group (9.84 ± 3.74 vs. 10.54 ± 3.82), while the DexP group showed higher levels (13.06 ± 3.46). Although intergroup differences were not statistically significant (p=0.085), the findings suggest that intranasal DEX may help reduce apoptosis.

Considering the significant alterations in the NSE and CASP3 levels observed in DexN, this treatment exhibited neuroprotective properties.

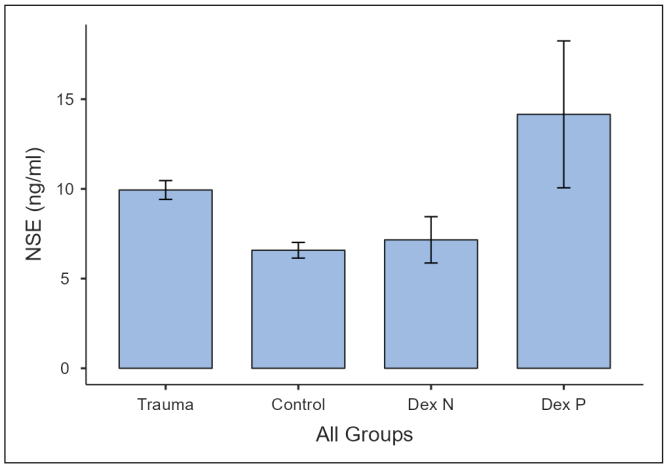


**Figure 1:** Bar plot showing the level of the neuron-specific enolase (NSE) among all the groups.

TBARS are markers of lipid peroxidation induced by oxidative stress following TBI, with elevated levels associated with worsening neuronal injury and poorer outcomes (1,4). In this study, the TBARS levels in the DexN group were similar to those in the control group (139.99 ± 28.16 vs. 128.68 ± 49.29), while the DexP group exhibited higher levels (176.77 ± 90.70). Although intergroup differences were not statistically significant (p=0.160), the results imply that DexN may help mitigate lipid peroxidation and prevent any secondary neuronal damage.

GSH-PX is an antioxidant enzyme that plays a role in reducing oxidative stress by decreasing hydrogen peroxide levels. In the context of TBI, diminished GSH-PX activity has been demonstrated to indicate a disruption in the antioxidant defense system. Decreased GSH-PX levels have been associated with elevated oxidative stress and adverse outcomes in TBI patients, underscoring the potential importance of maintaining antioxidant balance for neuroprotection. In the groups treated with pharmacological agents, both DexN and DexP were increased in comparison to that in the control group (114.06 ± 22.55 and 127.25 ± 80.83 vs 100.69 ± 41.79, respectively) (Figure 2). However, the Kruskal–Wallis analysis did not yield any statistically significant results (p=0.149). Despite the lack of any statistical significance, the increased GSH-PX level could contribute to reduced morbidity and mortality related

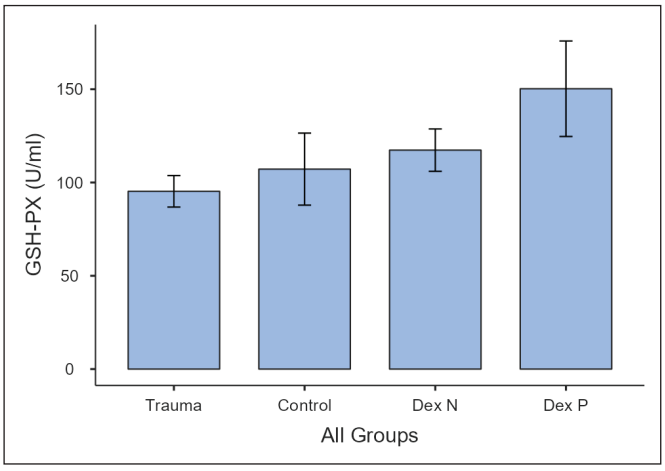


**Figure 2:** Bar plot showing the level of the glutathione peroxidase (GSH-PX) among all the groups.

to trauma. These findings could be interpreted to suggest that DEX plays a primary role in oxidative stress. Furthermore, the antioxidant effects of DexN are superior to those of DexP.

Histopathological analysis of the brain following a TBI revealed significant pathological changes related to congestion, inflammation, neuronal loss, and gliosis. Each of these factors plays a pivotal role in the comprehensive pathological response to TBI and can affect the outcomes and the clinical course of the injury.

To assess the anti-inflammatory effects of treatment, congestion, and inflammation served as indicators. Similarly, to evaluate the neuroprotective effect, neuron loss and gliosis were employed as markers. The anti-inflammatory effect of DexP was found to be more pronounced than that of DexN. With regard to the neuroprotective and antioxidant effects, an examination of the results of other biochemical markers revealed that DexN exhibited a more favorable outcome.

In terms of the total histopathological score, the DexP drug demonstrated a superior outcome compared to DexN. Our findings are similar to that of a past study in which Dex was used IP after cortical injury in the experimental mice. Dex alleviated early neurological impairment and brain swelling while reducing inflammation, enhancing tight junction protein expression, and mitigating secondary blood–brain barrier (BBB) damage and cell death. These neuroprotective effects have been linked to the suppression of NF-κB and NLRP3 pro-inflammatory pathways. These findings highlight Dex's potential in reducing acute post-traumatic inflammation within 3 days of the injury (11). A recent review article concluded that Dex's neuroprotective effects primarily stem from its ability to suppress inflammation, reduce apoptosis and autophagy, protect the BBB, and stabilize cellular structures. These mechanisms when considered alongside the results of the present study demonstrate significant benefits for neurological recovery in brain injury patients (7).

These results demonstrated that the peritoneally administered DEX drug exhibited a more pronounced anti-inflammatory effect, outperforming the nasally administered DEX drug in terms of histopathological examination. The latter drug, when administered nasally, demonstrated a reduction in the NSE and CASP3 levels, indicating the inhibition of neuronal destruction. Furthermore, an increased level of GSH-PX was recorded, which plays a role in activating the antioxidant system. The drugs administered via both routes exhibited varying degrees of positive outcomes, with a statistically significant difference observed in their Garcia scores, specifically in the neurological assessment ($p<0.001$).

### Strengths and Limitations

This study is limited by several factors. The study's limited sample size restricts the generalizability and statistical significance of the findings. Furthermore, the evaluation of dose-response was not feasible owing to the small sample size. However, the use of two different routes of administration represents a strength of this study considering that this study aimed to assess the efficacy of DexP and DexN treatment and to identify the precise mechanism by which Dex exerts its effects. Nonetheless, further investigation is necessary to achieve this goal.

## CONCLUSION

The results demonstrated that, following nasal administration, a reduction was noted in the NSE and CASP3 levels, which indicates that the drug inhibited neuronal destruction. In addition, increased levels of GSP-PX were noted, which play an important role in preventing oxidative stress. In contrast, peritoneal administration resulted in a superior outcome in terms of histopathological score when compared to nasal administration. Furthermore, a neurological examination revealed that both routes were associated with positive outcomes.

The present results support the hypothesis that a psychoactive drug, DEX, may impart beneficial effects following TBI through its anti-inflammatory, antioxidant, and neuroprotective effects.

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### Declarations

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**Availability of data and materials:** The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

**Disclosure:** The authors declare no competing interests.

**AUTHORSHIP CONTRIBUTION**

Study conception and design: YO, IB, YG, SS

Data collection: IB, YG, SS

Analysis and interpretation of results: OM, GG, OG

Draft manuscript preparation: OM

Critical revision of the article: OM, IB

Other (study supervision, fundings, materials, etc...): IB, OM, MDJER, YG, SS, OG

All authors (YO, IB, OM, YG, SS, GG, MDJER, OG) reviewed the results and approved the final version of the manuscript.

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