Published online 2021 October 20 **Original Article**

Effect of Dexmedetomidine on Oxidative Stress Response and Expression of Intracellular Adhesion Factor-1 (ICAM-1) and S100B in Patients with Traumatic Brain Injury

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Received 2021 October 01; **Revised** 2021 October 19; **Accepted** 2021 October 24.

Abstract

Background: To study the effect of dexmedetomidine on oxidative stress response and the expression of intracellular adhesion factor-1 (ICAM-1) and S100B in patients with traumatic brain injury (TBI).

Objectives: This study aimed to discusses the effects of dexmedetomidine on oxidative stress response and ICAM-1 and S100B expression in patients with TBI to investigate its protective effect on oxidative stress and brain damage in patients with TBI.

Methods: The TBI patients treated in our hospital from May 2017 to April 2020 were enrolled in the study and divided into control and treatment groups by the random number table method. The treatment group was administered with dexmedetomidine injection via an intravenous pump based on the conventional treatment in the control group. Glasgow coma scale (GCS) and Glasgow outcome scale (GOS) were used to evaluate the patients' injury, recovery, and prognosis. ELISA method was employed to detect four oxidative stress index levels, including serum superoxide dismutase (SOD), lipid peroxidation (LPO), malondialdehyde (MDA), and total antioxidant capacity (TAC), as well as ICAM-1 and S100B levels upon admission and at different time points after the operation.

Results: On the 3rd and 14th day after the operation, the treatment group had a higher GCS score, compared to the control group ($P<0.05$). Furthermore, on the 30th, 90th, and 180th days after discharge, the treatment group had a higher GOS score than the control group ($P<0.05$). On the 3rd, 5th, and 14th days after operation, the treatment group had higher SOD activity than the control group ($P<0.05$). Immediately after the operation, on the 3rd, 5th, and 14th after the operation, the treatment group had higher LPO levels than the control group ($P<0.05$). Moreover, on the 3rd, 5th, and 14th days after the operation, blood MDA levels gradually decreased in both groups, which was lower in the treatment group than that in the control group ($P<0.05$). On the 3rd, 5th, and 14th after the operation, the treatment group had higher TAC activity in the blood, compared to that in the control group ($P<0.05$). On the 3rd, 5th, and 14th days after the operation, the treatment group had lower S100B levels than that in the control group ($P<0.05$).

Conclusion: Dexmedetomidine can relieve TBI-induced oxidative stress state and reduce the levels of brain injury markers (ICAM-1, S100B), which has a protective effect on the brain tissue with TBI.

Keywords: Dexmedetomidine, Intracellular adhesion factor-1, Oxidative stress, S100B, Traumatic brain injury

1. Background

Traumatic brain injury (TBI) is a common acute and severe case in neurosurgery. Cerebral hemorrhage and brain laceration induced by TBI can cause dysfunction of varying degrees in patients, such as cognitive decline or affective disorders. For patients with mild and moderate TBI, these symptoms are often difficult to detect in the early stage, which can therefore cause permanent damage to the patient and seriously affect patients' quality of life (1-5). Dexmedetomidine is a new type of α_2-adrenergic receptor agonist with high selectivity and specificity. Due to its strong sedative and analgesic effects, it is used to assist general anesthesia and reduce stress response during trachea intubation. Its sedative, analgesic, and anti-anxiety effects show dose-dependence (6-8). Recent studies have shown that dexmedetomidine can reduce the nerve damage caused by ischemia-reperfusion, and its mechanism of action is related to anti-inflammatory and anti-oxidative damage effects (9-12). Under traumatic diseases, such as TBI, patients are often in a relatively strong oxidative stress state. In this state, a large number of reactive oxygen species produced by oxidative stress can cause lipid peroxidation damage to cell membranes, which in turn leads to organ damage; therefore, it is unfavorable to patients' prognosis (13-15). Intracellular adhesion molecule-1 (ICAM-1) and S100B protein are both important indices for evaluating brain damage after TBI (16, 17).

2. Objectives

This study aimed to discusses the effects of dexmedetomidine on oxidative stress response and ICAM-1 and S100B expression in patients with TBI to investigate its protective effect on oxidative stress and brain damage in patients with TBI.

3. Methods

3.1. Case collection and grouping

The TBI patients treated in our hospital from May 2017 to April 2020 were enrolled in the study and divided into control and treatment groups by

the random number table method. General information, such as age, gender, cause of injury, and type of brain injury was recorded, and the Glasgow coma scale (GCS) was used to score the patients' injury. During the follow-up period, Glasgow Outcome Scale (GOS) was also employed to score the patient's prognosis. The inclusion criteria were traumatic brain injury that was diagnosed by CT or MRI and approved by the hospital ethics committee, as well as the patients' or their family members' consent to participate in the study.

On the other hand, the patients with local or systemic infection; liver, kidney, or heart organ dysfunction; cerebral infarction and hemorrhage before TBI; cognitive impairment, such as dementia before TBI; autoimmune diseases; coagulation dysfunction; TBI complicated with other serious physical injuries; drug allergies or risk of allergies; and age ≥70 years old or <18 years old were excluded from the study.

3.2. Treatment methods

Both the control and the treatment groups underwent general anesthesia for hematoma aspiration or bone valve decompression according to injury type. Fentanyl (≤4μg/kg), propofol (≤1.5 mg/kg), and vecuronium bromide (0.1 mg/kg) were injected intravenously for anesthesia induction before tracheal intubation. Continuous intravenous infusion of remifentanil and propofol, as well as the intermittent infusion of vecuronium, were given to maintain anesthesia, and real-time monitoring was performed on indices, such as electrocardiogram, heart rate, central venous pressure, and end-expiratory carbon dioxide partial pressure. The treatment group was given an intravenous pump of dexmedetomidine injection (rate of 0.5μg/kg h) before anesthesia induction, which was continued until the 3rd day after operation. The control group was given normal saline by an intravenous pump at the same rate.

3.3. Measurement index

Venous blood was collected upon admission, immediately after the operation, as well as 3 and 14 days after the operation. The serum was centrifuged and collected. Enzyme-linked immunosorbent assay (ELISA) was used to detect the level of oxidative stress indexes. The measurement indices include superoxide dismutase (SOD), lipid peroxidation (LPO), malondialdehyde (MDA), and total antioxidant capacity (TAC) (18).

If there were symptoms of TBI injury, venous blood was collected upon admission, after the operation, as well as 3, 5, and 14 days after the operation. It was then centrifuged to collect serum. A standard curve was established using an ELISA kit according to the instructions so that the relative concentration of patient serum ICAM-1 and S100B can be detected and calculated (19).

3.4. Statistical methods

The obtained data in this study were all processed in SPSS software (version 20.0) (IBM, USA), and the measurement data were expressed as mean±SD. Moreover, an independent sample t-test was used for comparison between groups. The count data were expressed as percentages (%), and the Chi-square test was utilized for comparison between groups. Furthermore, repeated-measures ANOVA was employed to compare between times. Since there were significant changes in both groups in analysis, each time point data were also compared in this study. A p-value less than 0.05 was considered statistically significant.

4. Results

4.1. General information

This study included 87 patients with TBI. There were 42 cases in the control group with a mean age of 41.3±8.2 years (age range: 28-63 years). It should be noted that the majority of the patients (n=23) were male. Furthermore, the treatment group included 45 patients with a mean age of 42.6±9.2 years (age range: 25-66 years). The majority of the cases were male (n=26). According to the results of the Chi-square or t-test results, there was no statistical difference between the two groups regarding the basic information, such as age, gender, body mass index, and living habits (P>0.05). The TBI included in this study covers extensive brain contusion and laceration, complicated intracranial hemorrhage, or epidural hematoma. The ASA classification was Grade II or III. Furthermore, there was no statistical difference between the two groups in terms of the TBI type and ASA classification (P>0.05). Regarding anesthesia and operation time, the control group had an anesthesia time of 156.2±23.6 min and an operation time of 189.4±27.1 min. On the other hand, the treatment group obtained an anesthesia time of 150.7±25.3 min and an operation time of 195.5±25.9 min, which showed statistical differences between the two groups in this regard (P>0.05). In addition, the GCS scores of injury were determined at 6.6±1.3 and 6.4±1.1, respectively in the two groups, which revealed no statistical differences (P>0.05). The above information indicates no statistical difference in basic conditions of the two groups; moreover, the results after treatment are comparable (Table 1).

4.2. GCS score comparison

There was no significant difference between the two groups upon admission and one day after the operation in terms of the GCS scores (P>0.05). On the 3rd day after the operation, the treatment group had a higher GCS score, compared to the control group (P<0.05). On the 14th day after the operation, the

Table 1. Patients' basic information

Feature		Control group (n=42)	Treatment group (n=45)	t/χ^2	*P*
Age (year)		41.3±8.2	42.6±9.2	0.6939	0.4896
Gender	**Male**	23	26	0.080	0.831
	Female	19	19		
Body Mass Index (kg/m²)		22.5±2.6	23.2±2.3	1.332	0.1864
Living habit	**Smoking history**	11	13	0.284	0.790
	Drinking history	18	16		
Complications	**Hypertension**	9	7	0.355	0.837
	Diabetes	7	8		
	Hyperlipidemia	4	3		
TBI Type	**Extensive brain contusion and laceration**	26	25	0.449	0.799
	Complicated intracranial hemorrhage	8	11		
	Complicated epidural hematoma	8	9		
ASA classification	**Grade**	26	28	0.001	1.000
	Grade	16	17		
Anesthesia time (min)		156.2±23.6	150.7±25.3	1.047	0.2983
Operation time (min)		189.4±27.1	195.5±25.9	1.073	0.2861
GCS score		6.6±1.3	6.4±1.1	0.7764	0.4397

Table 2. Comparison of patients' GCS score

Group	GCS score				P**
	Upon admission	1 day after operation	3 days after operation	14 days after operation	
Control group (n=42)	6.62±1.32	7.22±1.61	7.91±1.32	8.80±1.23	0.001
Treatment group (n=45)	6.45±1.10	7.85±1.46	8.68±1.65	10.29±1.75	0.001
P*	0.439	0.065	0.028	0.002	

P*: t-test p-value; P**: Repeated measures ANOVA.

treatment group obtained a higher GCS score than the control group, which showed a statistical difference in the GCS score (P<0.05) (Table 2). Repeated measurements showed a statistically significant effect of time on the GCS score in the control group (F [3, 41]=0.517, P=0.001). In addition, there was a statistically significant effect of time on the GCS score in the treatment group (F [3, 44]=0.902, P=0.001).

4.3. Oxidative stress indexes

There was no statistical difference between the two groups upon admission regarding SOD, LPO, MDA, and TAC. As shown in Table 3, the treatment group has higher SOD activity, compared to the control group 3, 5, and 14 days after the operation (P<0.05). Repeated measurements showed a statistically significant effect of time on the SOD activity in the control group (F [3, 41]=18.84, P<0.001). Moreover, there was a statistically significant effect of time on the SOD activity in the treatment group (F [3, 44]=15.34, P<0.001). The treatment group obtained higher LPO levels than the control group immediately after the operation, as well as 3, 5, and 14 days after the operation (P<0.05). Repeated measurements showed a statistically significant effect of time on the LPO levels in the control group (F [3, 41]=0.019, P<0.001). Moreover, there was a statistically significant effect of time on the LPO levels in the treatment group (F [3, 44]=0.002, P<0.001). Immediately after the operation, there was a temporary increase in the MDA of both groups, which was lower in the treatment group than that in the control group (P<0.05). On the 3rd, 5th, and 14th days after the operation, the blood MDA levels of both groups gradually decreased, which were lower in the treatment group, compared to those in the control group (P<0.05). Repeated measurements showed no statistically significant effect of time on the MDA levels in the control group (F [3, 41]=27.34, P=0.354). Furthermore, there was a statistically significant effect of time on the MDA levels in the treatment group (F [3, 44]=1.035, P=0.001). There was a temporary decrease in the TAC activity of both groups after operation, and no statistically significant difference was observed between the groups in terms of the TAC activity. The treatment group had higher TAC activity in the blood, compared to the control group 3, 5, and 14 days after the operation (P<0.05). Repeated measurements showed a statistically significant effect of time on the TAC activity in the control group (F [3, 41]=0.571, P<0.001). Moreover, there was a statistically significant effect of time on the TAC activity in the treatment group (F [3, 44]=0.624, P<0.001)(Table 3, Figure 1).

4.4. I ICAM-1 level measurement results

There was no significant difference between the two groups upon admission in terms of the ICAM-1 level. Serum ICAM-1 levels of both groups decreased gradually over time from operation time to 14 days after the operation, and the treatment group had lower ICAM-1 levels, compared to the control group 5

Table 3. Oxidative stress indices (treatment time)

Index	Groups	Upon admission	Immediately after operation	3 days after operation	5 days after operation	14 days after operation	P**
SOD(U/mL)	Control group (n=42)	51.34±8.91	43.29±9.27	57.23±6.43	70.11±7.35	78.41±6.72	<0.001
	Treatment group (n=45)	50.28±9.33	46.31±8.10	68.82±7.45	78.04±7.88	96.22±6.83	<0.001
	t	0.541	-1.621	-7.743	-5.845	-12.250	
	P	0.589	0.108	<0.001	<0.001	<0.001	
LPO(μmol/L)	Control group (n=42)	4.28±0.25	5.05±0.31	5.59±0.35	6.42±0.33	8.30±0.22	<0.001
	Treatment group (n=45)	4.34±0.29	5.68±0.36	6.30±0.32	7.54±0.40	9.12±0.18	<0.001
	t	-1.030	-8.718	-9.884	-14.191	-19.080	
	P	0.305	<0.001	<0.001	<0.001	<0.001	
MDA(nmol/mL)	Control group (n=42)	4.81±0.62	5.94±0.81	5.37±0.65	4.54±0.69	4.13±0.66	0.354
	Treatment group (n=45)	4.77±0.68	5.26±0.62	4.91±0.39	4.00±0.58	3.56±0.52	0.001
	t	0.286	4.415	4.034	3.961	4.490	
	P	0.775	<0.001	0.001	0.002	<0.001	
TAC(U/L)	Control group (n=42)	3.25±0.73	2.67±0.68	3.51±0.83	3.88±0.80	3.95±0.56	0.043
	Treatment group (n=45)	3.11±.67	2.88±0.31	3.87±0.65	4.52±0.71	4.87±0.62	0.001
	t	0.932	-1.874	-2.260	-5.952	-7.246	
	P	0.353	0.064	0.026	0.002	<0.001	

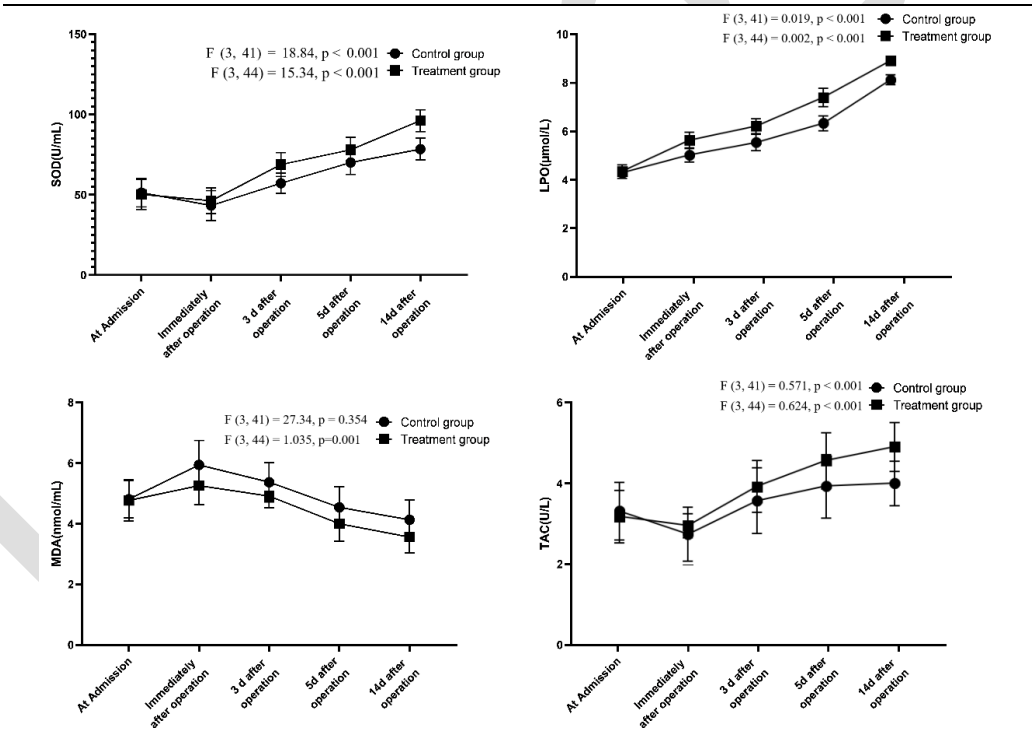

Figure 1. Oxidative stress indices

and 14 days after the operation (P<0.05). Repeated measurements showed a statistically significant effect of time on the ICAM-1 levels in the control group (F [3, 41]=117.34, P<0.001). Moreover, there was a statistically significant effect of time on the ICAM-1 levels in the treatment group (F [3, 44]=134.51, P<0.001) (Table 4, Figure 2).

4.5. S100B level measurement results

There was no significant difference between the two groups upon admission in terms of the S100B level. Serum S100B levels of both groups decreased gradually over time from operation time to 14 days after the operation, and the treatment group had lower S100B levels, compared to the control group 3, 5, and 14 days after the operation (P<0.05). Repeated measurements showed a statistically significant effect of time on the ICAM-1 levels in the control group (F [3, 41]=0.418, P<0.001). Moreover, there was a statistically significant effect of time on the ICAM-1

Table 4. ICAM-1 levels (ng/mL) of the two groups

Group	Upon admission	Immediately after operation	3 days after operation	5 days after operation	14 days after operation	P**
Control group (n=42)	978.12±38.41	735.55±31.80	529.20±22.82	313.59±83.12	162.23±59.12	<0.001
Treatment group (n=45)	926.75±53.32	772.46±46.92	428.16±55.05	243.61±66.05	103.41±41.16	<0.001
t	1.638	-11.115	10.002	8.359	9.417	
P	0.105	0.268	3.951	<0.001	<0.001	

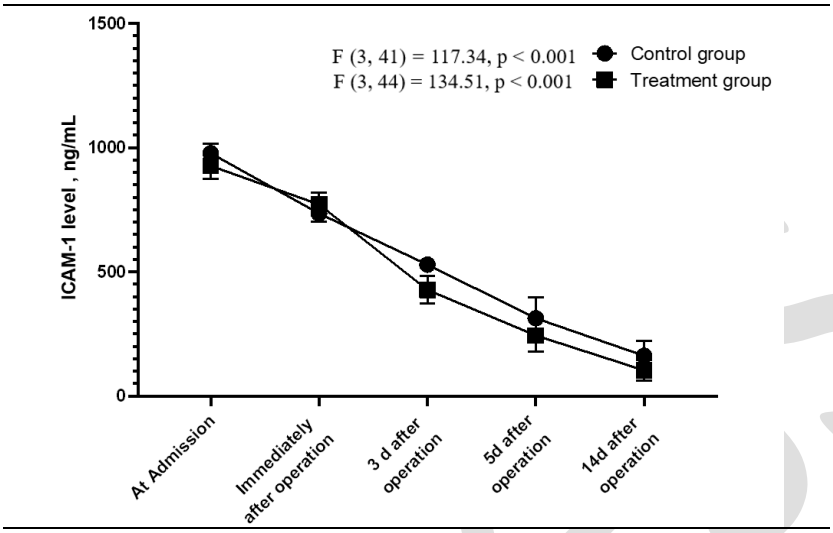

Figure 2. ICAM-1 level measurement results

levels in the treatment group (F [3, 44]= 0.501, P<0.001) (Table 5, Figure 3).

4.6. GOS score comparison after discharge

The GOS scores were compared and analyzed after discharge. Furthermore, 38 and 40 cases were followed up in the control and treatment groups, respectively, at discharge, as well as 30, 90, and 180 days after discharge. The treatment group had higher GOS scores than the control group at discharge; however, it showed no statistical difference (P>0.05). On the 30th and 90th days after discharge, the treatment group had a higher GOS score, compared to the control group (P<0.05). Furthermore, 180 days after discharge, the treatment group had a higher GOS score than the control group, which showed no statistical difference (P<0.05) (Table 6).

Table 5. S100B levels of the two groups (μg/L)

Group	Upon admission	Immediately after operation	3 days after operation	5 days after operation	14 days after operation	P**
Control group (n=42)	2.32±0.18	2.04±0.14	1.79±0.20	1.53±0.22	1.04±0.41	<0.001
Treatment group (n=45)	2.38±0.21	1.98±0.16	1.51±0.15	1.26±0.18	0.78±0.36	<0.001
t	-1.126	1.856	5.051	6.283	6.148	
P	0.157	0.066	0.043	<0.001	0.002	

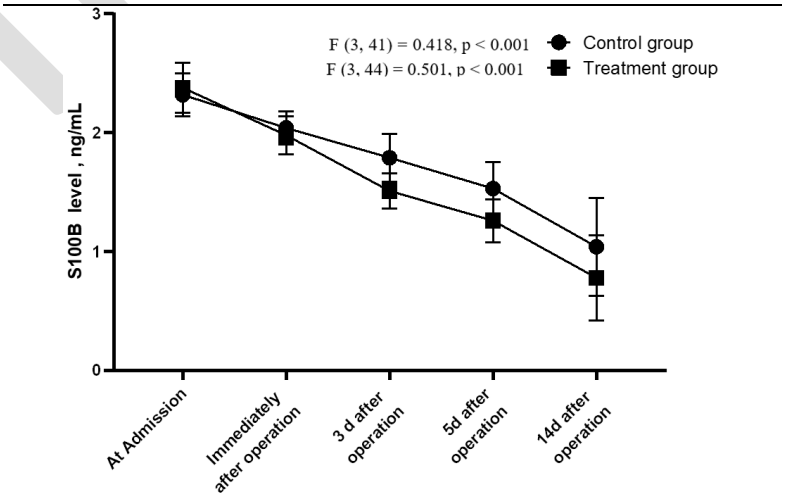

Figure 3 S100B level measurement results

Table 6. GOS score comparison

Group	GOS score				P**
	Upon discharge	30 days after discharge	90 days after discharge	180 days after discharge	
Control group (n=42)	3.42±0.60	3.51±0.31	3.71±0.76	3.91±0.70	0.451
Treatment group (n=45)	3.65±0.92	3.92±0.25	4.25±1.13	4.56±0.52	0.054
t	1.149	5.320	-5.381	-6.373	
P	0.254	0.023	0.020	<0.001	

5. Discussion

TBI-induced brain damage involves a variety of complex pathophysiological processes. The stress stimulation of TBI can excite the sympathetic-adrenaline system, which makes the body under stress and induces inflammation at the same time. The release of a large number of inflammatory factors can activate neutrophils and produce a large amount of oxygen free radicals so that the body is in a state of oxidative stress. Following TBI, brain microvascular endothelial cells are activated, making white blood cells accumulate locally due to the adhesion between brain microvascular endothelium. ICAM-1 as a single-chain glycoprotein in the immunoglobulin superfamily has little expression in the human vascular endothelium under normal circumstances. When TBI occurs, it can be excessively present in brain microvascular endothelium, glial cells, and other inflammatory parts, which is an important factor that regulates white blood cell adhesion to vascular endothelium and cerebral microcirculation disorders, playing an important role in the process of secondary brain injury after TBI.

S100B protein belonging to the S100 protein family is secreted by glial cells. When expressed at low levels, it can nourish nerve cells and glial cells; moreover, it plays a role in information transmission. When S100B is expressed at low levels, it can protect cells, prevent nerve cell apoptosis caused by oxidative stress, and stimulate the growth of nerve cell axons. When S100B levels are high, it has a significant effect on nerve cells and promotes their death. Under normal physiological conditions, most S100B exists in the cerebrospinal fluid. When brain tissue injury occurs, it enters the peripheral blood circulation due to increased permeability of the blood-brain barrier. Therefore, the expression level of S100B in the peripheral blood circulation can reflect the severity of brain tissue injury in TBI.

Dexmedetomidine can bind to α_2 receptors in the body to exert receptor agonism. α_2 receptors are widely distributed in the central nervous system, peripheral nervous system, as well as multiple organs and tissues. The α_2 receptors in brain tissues mainly exist in the Locus coeruleus of the brain stem, which is the main part of the brain to synthesize norepinephrine. Dexmedetomidine can regulate the epinephrine release through a negative feedback mechanism by binding to α_2 receptors throughout the body. Studies have shown that dexmedetomidine exerts a protective effect on brain tissue by regulating SOD activity and serum tumor necrosis factor levels in the brain tissue of rats with cerebral ischemia-reperfusion injury (20, 21), which can inhibit caspase-3 expression to protect brain tissue and improve neurocognitive function (22, 23). In this study, the GCS scores 3 and 14 days after the operation, and the GOS scores 30, 90, and 180 days after discharge show that the combined use of dexmedetomidine on the basis of conventional treatment can improve the recovery after TBI. In addition, this study indicates that the combined use of dexmedetomidine can increase SOD and TAC activities in the body, increase the LPO level, and reduce MDA level, which helps to relieve the oxidative stress state of the body after TBI and lower ICAM-1 and S100B levels in serum. The above results all suggest that dexmedetomidine has a protective effect on brain tissue, which is consistent with the results of other previous studies.

Dexmedetomidine was shown to decrease oxidative stress in a study conducted by Cekic et al., which was consistent with the results of the present study; however, they evaluated oxidative stress index. In a very similar study to our study with the same objectives, dexmedetomidine lessened injury to rat brains by ischemia-reperfusion and suppressed production of NF-kB and ICAM-1 in brain tissues, likely by suppressing oxidative stress. Moreover, the S100B level decreased, as well as that in our study.

6. Conclusion

In summary, this study shows that dexmedetomidine can alleviate the oxidative stress state after TBI and reduce the levels of brain damage markers (e.g., ICAM-1, S100B), which provides a clinical basis for the use of dexmedetomidine in the treatment of TBI patients. In addition, inflammation is an important pathological process in TBI, which is also an important cause of the body's oxygen stress state. The research team plans to further investigate the effect of dexmedetomidine on the inflammatory response in patients and its related mechanisms in the later stage to further explore the mechanism of action by which dexmedetomidine protects brain tissue after traumatic brain injury.

Acknowledgments

The authors express their gratitude to the Second Hospital of Jilin University, Changchun, China, for its support.

Footnotes

Authors' contributions: Mingxin Ji and Xinyu Li conceived the research idea and designed the study. Peng Zhao and Yunfeng Cui visited the dairy farms and collected the data. Mingxin Ji and Peng Zhao performed data analysis. Mingxin Ji, Yunfeng Cui and Xinyu Li wrote the paper.
Ethical Approval: Research experiments conducted in this article with humans were approved by the Ethical Committee and responsible authorities of our research organization (The Second Hospital of Jilin University) following all guidelines, regulations, legal, and ethical standards as required for humans.
Funding/Support: Not Applicable
Financial Disclosure: Not Applicable
Conflicts of Interest: The authors declare no conflict of interest.

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