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Original Article

Effects of dexmedetomidine on endothelial progenitor cells and its therapeutic application in patients with traumatic brain injury

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Abstract: Objective: To investigate the role of dexmedetomidine (DEX) in the treatment of traumatic brain injury (TBI) and its effect on endothelial progenitor cells (EPCs). Methods: Seventy-six patients with TBI were randomly and equally divided into control and observation groups. Patients in the observation group were intravenously injected with DEX before administering anesthesia and after the surgery, while those in the control group were not given any drug in this prospective study. Prior to and 1 month after the surgery, the levels of serum S100β and neuron specific enolase (NSE) were measured using enzyme-linked immunosorbent assay; the hemodynamic parameters including end-diastolic blood flow velocity (Vd), peak systolic blood flow velocity (Vs), mean blood flow velocity (Vm), pulsatility index (PI), and resistance index (RI) of the middle cerebral artery were measured using transcranial Doppler ultrasound; the number of endothelial microparticles (EMPs) and EPCs in the peripheral blood were measured using flow cytometry; and the proliferation rate and adhesion level of EPCs were also measured. Three months after the surgery, patients' rehabilitation was evaluated according to Glasgow outcome score (GOS). Results: After surgery, compared to the control group, the levels of serum S100β (P=0.007) and NSE (P=0.031) decreased in the observation group; the hemodynamic parameters Vd (P=0.032), Vs (P=0.003), Vm (P<0.001), and PI (P=0.017) increased, while RI (P=0.033) decreased; the number of EMPs in the peripheral blood decreased (P<0.001); the number of EPCs in the peripheral blood (P<0.001), proliferation (P<0.001) and adhesion level (P<0.001) improved. Three months after surgery, the GOS score of the observation group was significantly higher than that of the control group (P=0.004). Conclusion: Pre-operative and post-operative DEX therapy can reduce the serum levels of S100β and NSE, stabilize the blood flow of patients with TBI, reduce the content of EMPs and improve the number of EPCs in the peripheral blood as well as the function of EPC.

Keywords: Dexmedetomidine, traumatic brain injury, endothelial progenitor cells, hemodynamics, S100β, neuron specific enolase, endothelial microparticles

Introduction

Traumatic brain injury (TBI) is a major disease emerging with the development of modern society. Every year in the United States, 2 to 2.5 million people are treated for TBI, of which 52,000 die [1]. Patients with moderate or severe TBI often need craniotomy hematoma clearance or decompression of bone flaps. Thus, it is important to choose appropriate anesthetics for reducing brain injury. Dexmedetomidine (DEX), a highly selective α_2 adrenergic receptor agonist, is an effective sedative, analgesic, and anesthetic agent [2]. In addition, DEX has anti-inflammatory, anti-oxidative, and anti-apoptotic effects, and has been applied in a series of brain injury diseases, including cerebral infarction, cerebral hemorrhage, and epilepsy [3, 4]. DEX has also been proven to provide good brain protection in TBI animal models. For example, Wu et al. found that DEX can not only inhibit cell death and brain tissue damage, but also reduce axonal injury and synaptic degeneration in a mouse TBI model [5]. However, there is still a lack of reports on the effect of DEX in the clinical application of TBI, and hence, whether DEX provides protection to the brain remains unclear.

It has been observed that vascular endothelial cell injury and secondary ischemia occurring within hours to days after trauma may be the main factors affecting the prognosis of TBI [6]. And it is an effective measure to treat TBI that using different drugs to prevent and treat endothelial injury and improve cerebral blood flow perfusion [7]. Endothelial progenitor cells (EPCs) are precursors of endothelial cells, and they participate in the repair of vascular injury. The number and function of EPCs are closely related to the recovery of blood supply and affect the prognosis of TBI [8-10]. To sum up, this study enrolled patients with TBI, observed the effect of DEX on the hemodynamic parameters and endothelial injury, and analyzed its effect on the number and function of EPCs in peripheral blood, which may provide good theoretical support for its clinical application.

Materials and methods

General data

From March 2017 to December 2018, 76 patients with TBI admitted to Jingzhou First People's Hospital were enrolled for this prospective study. The patients were divided into control and observation groups according to the random number table method, with 38 cases in each group. General data of the two groups were collected and compared, including age, gender, body mass index, Glasgow Coma Score (GCS), acute physiology and chronic health evaluation system II (APACHE II) score, etiology, and injury type. This study was approved by the Ethics Committee of Jingzhou First People's Hospital, and all patients signed an informed consent.

Inclusion criteria: (1) patients with a clear history of head trauma, admitted within 24 hours of onset, having a GCS ≤12 at admission, and confirmed of TBI using a cranial CT [11]; (2) patients who met the surgical indications and planned to undergo a craniotomy for hematoma removal or decompressive craniectomy. Exclusion criteria: patients with (1) multiple injuries to the neck, chest, or abdomen; (2) heart failure, respiratory failure, or shock; (3) liver and kidney dysfunction; (4) drug allergies to DEX, propofol, remifentanil, and cis-atracurium.

Therapeutic method

Routine examinations of the patients were performed after admission. Anesthesia was performed after the vital signs such as breathing, blood pressure, heart rate, and pulse oxygen saturation were stabilized, and then craniotomy for hematoma removal or decompressive craniectomy was performed. On this basis, the patients in the observation group were intravenously injected with DEX (SINOPHARM Co., Ltd. Sichuan) before administering the anesthesia (at a dose of 1 μg/kg/h for 10-15 min) and after surgery (at a dose of 0.5 μg/kg/h for 3 d). The control group was not given any therapeutic drug.

Observation indicators

Determination of serum S100β and neuron specific enolase (NSE) contents: Before and 1 month after the surgery, 2 mL fasting venous blood samples were collected from patients in both the groups. After a short rest at room temperature, the samples were centrifuged at 12,000 rpm for 10 min, and the supernatant was collected. Enzyme-linked immunosorbent assay kit was used to detect the serum levels of S100β (Jiangsu Jingmei Company, China) and NSE (Jiangsu Jingmei Company, China). The procedure was carried out in accordance with the company instructions. The absorbance values of each well were determined using a microplate reader (Thermo Scientific, USA).

Measurement of hemodynamic parameters: The hemodynamic parameters of middle cerebral artery were measured by transcranial Doppler ultrasonography (Shenzhen Dedicated Company, China) at bilateral temporal windows before and 1 month after the surgery. The frequency was 2 MHz. The indices included end-diastolic blood flow velocity (Vd), systolic peak blood flow velocity (Vs), mean blood flow velocity (Vm), pulsation index (PI), and resistance index (RI).

Detection of EMPs in the peripheral blood: Before and 1 month after the surgery, 2 mL of fasting venous blood samples were collected into citrate anticoagulant tubes from the patients in both the groups, and were centrifuged for 10 min at 3,000 rpm. Then 50 μL of supernatant plasma was collected, and 0.5 μL FITC-labeled anti-CD42 antibody (Pharmingen,

USA) and 0.5 μL PE-labeled anti-CD31 antibody (Pharmingen, USA) were added to the supernatant. Low-speed shaking was performed for 20 min at room temperature in dark. Then, 1 mL PBS solution was added to mix, and the number of $CD31^+CD42^-$ particles with a diameter less than 1 μm were detected using flow cytometry (BD Biosciences, USA).

Detection of EPCs in the peripheral blood: Before and 1 month after the surgery, 1 mL fasting venous blood samples were collected into citrate anticoagulant tubes from patients in both the groups, and human peripheral blood mononuclear cells were separated by density gradient centrifugation using a kit (Beijing Solarbio). Then a mononuclear cell suspension was prepared. The 10 μL PE-labeled anti-CD34 antibody (Pharmingen, USA) and FITC-labeled anti-KDR antibody (Pharmingen, USA) were added in turn and incubated at 4°C for 30 min in dark. Sample was centrifuged for 5 min at 2000 r/min, and the supernatant was discarded. The cells were washed twice, and suspended with PBS again. The number of EPCs of $CD34^+KDR^+$ was analyzed using flow cytometry.

Culture and identification of EPCs in the peripheral blood: Human peripheral blood mononuclear cells were isolated and inoculated into 24-well plates which were pre-coated with fibronectin (Hematological Technologies, USA). The inoculated amount was $5\times10^6/cm^2$. The cells were cultured on a 100 U/mL M199 medium containing 20% fetal bovine serum (Gibco Company, USA). After 3 days, the culture medium was changed and the cells were collected on the 7th day for subsequent detection. Cell slides were prepared routinely and fixed using polyformaldehyde (BOSTER Biological Technology Co. Ltd., Wuhan, China). The cells were dripped with 2.4 mg/mL Dil-ac-LDL dye (Molecular Probe Company, USA) and 10 mg/mL FITC-UEA-I dye (Molecular Probe Company of the United States), incubated at 37°C for 1 h in dark. Then a laser confocal microscope (Leica, Germany) was used to observe and photograph.

Detection of proliferation level of the EPCs: EPCs were collected on the 7th day and inoculated into 96-well plates at a density of 1×10^5/mL. After culturing for 92 h, 20 μL MTT solution (5 g/L) (Sigma Company, USA) was added. After incubation at 37°C for 4 h, the culture medium was discarded and 100 μL DMSO (Sigma, USA) was added. The optical density was measured using a microplate reader (Thermo Scientific, USA) at 570 nm.

Detection of adhesion level of the EPCs: EPCs were collected on the 7th day and inoculated in 24-well plates which were pre-coated with fibronectin, at a density of 5×10^4/mL for 30 min. The cells were washed for three times with PBS and then observed under an optical microscope (200×, Olympus, Japan). Three different visual fields were randomly selected to count the number of adherent cells and calculate the average viscosity cell number.

Glasgow outcome scale (GOS)

Three months after the surgery, patients' rehabilitation was evaluated using the GOS score. Five points were awarded for return to normal life; 4 for having the ability to live alone, but with a certain degree of disability; 3 for conscious, but requiring care from others, with obvious disability; 2 for only the smallest degree of physical reaction, unable to perform normal activities; and 1 for death due to illness.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. All measurement data conformed to normal distribution passing the Shapiro-Wilk test and were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent sample t-test was used for comparison between the two groups, and paired t-test was used for comparison between different time points in the same group. Count data were expressed as the number of patients/percentage (n/%). X^2 test was used for comparison between the two groups. $P<0.05$ was used as the level of significance.

Results

General data

There were no significant differences in age, gender, body mass index, GCS, APACHE II scores, cause of disease, and type of injury between the two groups (all $P>0.05$, **Table 1**). In addition, no adverse drug reactions such as apnea, abnormal heart rate, and myoclonus occurred in either group during the surgery and during the period of DEX administration post-surgery.

Table 1. Comparison of general information ($\bar{x}$ ± sd, n)

Group	Control group (n=38)	Observation group (n=38)	t/X^2	P
Age (year)	39.6±6.1	38.9±6.5	0.490	0.625
Gender (male/female)	25/13	27/11	0.244	0.622
Body mass index (kg/m^2)	22.41±3.03	22.90±2.86	0.725	0.471
GCS (score)	5.82±1.42	5.59±1.17	0.771	0.443
APACHE II (score)	16.56±4.55	16.19±4.23	0.367	0.715
Cause of disease (n)			0.291	0.864
Car accident	27	29		
Downfall	7	6		
Blunt injury	4	3		
Type of injury (n)			1.100	0.777
Traumatic intracerebral hematoma	7	9		
Acute subdural hematoma with brain contusion and laceration	6	8		
Acute subdural hematoma	10	7		
Extensive brain contusion and laceration	15	14		

Note: GCS, Glasgow Coma score; APACHE, acute physiology and chronic health evaluation scoring system.

Table 2. Comparison of serum S100β and NSE levels ($\bar{x}$ ± sd)

Group	Control group (n=38)	Observation group (n=38)	t	P
S100β (μg/L)				
Before surgery	2.47±0.43	2.52±0.39	0.531	0.597
After surgery	1.95±0.31*	1.74±0.35*	2.769	0.007
NSE (μg/L)				
Before surgery	19.66±3.28	20.10±3.07	0.604	0.548
After surgery	15.22±2.70*	13.89±2.56*	2.204	0.031

Note: *P<0.05, compared with the same group before surgery. NSE, neuron specific enolase.

Serum S100β and NSE levels

The levels of serum S100β and NSE in both groups after the surgery were lower than those before the surgery (both P<0.05). Before the surgery, the levels of serum S100β and NSE were not significantly different between the groups (both P>0.05). However, post-operatively, the levels of serum S100β and NSE in the observation group were lower than those in the control group (both P<0.05, **Table 2**).

Hemodynamic indices

The Vd, Vs, Vm, and PI increased post-operatively in both groups, while RI decreased (all P<0.05). Before the surgery, there were no significant differences in the above indices between the two groups (all P>0.05). However, post-operatively, Vd, Vs, Vm, and PI were higher in the observation group than those in the control group, while RI was lower than that in the control group (all P<0.05, **Table 3**).

EMPs in the peripheral blood

The number of EMPs in the peripheral blood of patients in both groups after the surgery was significantly lower than that before the surgery (both P<0.05). Before the surgery, there was no significant difference in the number of EMPs in the peripheral blood between the two groups (P>0.05). However, post-operatively, the observation group showed the lower number of EMPs than the control group (P<0.05, **Table 4**).

Identification of EPCs

EPCs can absorb both FITC-UEA-I dye (green) and Dil-ac-LDL dye (red), showing a double-positive staining (yellow, **Figure 1**).

Number and function of EPCs in the peripheral blood

The number, proliferation, and adhesion of EPCs in the peripheral blood of both groups were significantly improved after surgery when compared with those before the surgery (all P<0.05). Before the surgery, there was no significant difference in the above indices between

Table 3. Comparison of hemodynamic indices ($\bar{x}$ ± sd)

Group	Control group (n=38)	Observation group (n=38)	t	P
Vd (cm/s)				
Before surgery	24.66±5.78	24.91±6.20	0.182	0.856
After surgery	35.27±8.44*	39.66±9.03*	2.189	0.032
Vs (cm/s)				
Before surgery	72.29±8.05	71.80±9.33	0.245	0.807
After surgery	84.61±9.84*	92.09±11.52*	3.043	0.003
Vm (cm/s)				
Before surgery	40.65±4.38	41.77±3.92	1.175	0.244
After surgery	51.46±5.23*	57.02±4.88*	4.791	<0.001
PI				
Before surgery	0.87±0.12	0.80±0.19	1.920	0.059
After surgery	1.03±0.27*	1.19±0.30*	2.444	0.017
RI				
Before surgery	0.69±0.10	0.71±0.13	0.752	0.455
After surgery	0.58±0.17*	0.50±0.15*	2.175	0.033

Note: *P<0.05, compared with the same group before surgery. Vd, end-diastolic blood flow velocity; Vs, systolic peak velocity; Vm, mean blood flow velocity; PI, pulsatility index; RI, resistance index.

Table 4. Comparison of EMPs in the peripheral blood ($\bar{x}$ ± sd)

Group	Control group (n=38)	Observation group (n=38)	t	P
Before surgery	1552.40±136.55	1603.77±149.38	1.565	0.122
After surgery	1144.29±126.51*	830.63±95.27*	12.210	<0.001

Note: *P<0.05, compared with the same group before surgery. EMPs, endothelial microparticles.

the two groups (all P>0.05). However, postoperatively, the number, proliferation, and adhesion of EPCs in the peripheral blood of the patients in the observation group were significantly higher than those in the control group (all P<0.05, **Table 5**).

GOS score 3 months after the surgery

Three months after the surgery, the GOS score of the observation group (4.06±1.22) was significantly higher than that of the control group (3.28±1.09) (t=2.939, P=0.004, **Figure 2**).

Discussion

Trauma-induced brain injury is related to direct violence, but it mainly attributed to secondary injury, including free radical production, cytokine release, activation of calcium ion and related protease activity, and changes in neurotransmitters. DEX can act on the α_2 receptors of locus coeruleus in the central nervous system and inhibit the release of norepinephrine. It can function as a sedative, an analgesic, an anti-anxiety and hypnotic agent, and is widely used in clinical anesthesia [12]. DEX has been proven to protect neurons by inhibiting inflammation, resisting to apoptosis, and reducing autophagy, thus alleviating cerebral ischemia-reperfusion injury [13, 14]. In addition, some *in vitro* and *in vivo* studies have also shown that DEX has protective effects against TBI [15, 16]. For example, Wang et al. found that by inhibiting the activation of inflammatory molecules NF-κB and NLRP3, DEX can reduce acute inflammatory response caused by trauma, and alleviate the damage to the blood-brain barrier and neuronal apoptosis [17]. In this study, the protective effects of DEX were investigated from the perspective of the vascular endothelium and the EPCs.

Trauma can lead to edema of the brain tissue, increase in intracranial pressure, vascular dys-regulation, spastic stenosis, and decrease in blood perfusion, and further aggravate pathological damage of the brain tissue. The results of the current study showed that the hemodynamic parameters were improved significantly after the surgery, which indicated that the hemodynamic disturbance was alleviated to some extent by the surgical treatment. This may be related to timely relief of the intracranial hypertension. More importantly, continuous DEX infusion before administering the anesthesia and after the surgery can further improve the hemodynamic parameters, suggesting that DEX has a certain inhibitory effect on the vascular dysfunction. In other reports, DEX as an adjuvant during general anesthesia can maintain the hemodynamic stability, which indirectly supports the conclusion of this study [18, 19].

In addition to inhibiting the release of vasoconstrictors, the mechanism of DEX behind stabi-

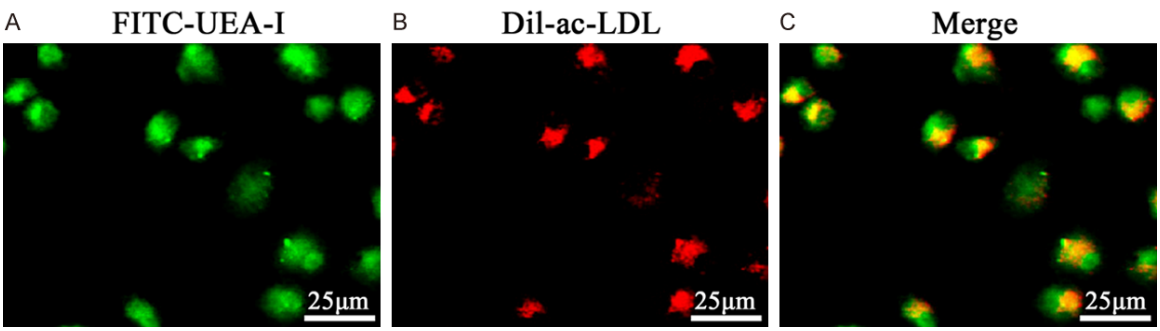

Figure 1. Identification of endothelial progenitor cells. A. FITC-UEA-I staining (green); B. Dil-ac-LDL staining (red); C. Double staining (yellow).

Table 5. Comparison of number and function of EPCs in the peripheral blood ($\bar{x}$ ± sd)

Group	Control group (n=38)	Observation group (n=38)	t	P
EPCs (n/mL)				
Before surgery	51.82±8.93	49.61±9.77	1.029	0.307
After surgery	95.20±12.73*	135.11±13.95*	13.03	<0.001
Proliferation (OD value)				
Before surgery	0.720±0.069	0.743±0.058	1.573	0.120
After surgery	0.846±0.093*	0.981±0.088*	6.500	<0.001
The number of adhesion cell (n/mL)				
Before surgery	22.74±1.76	23.10±1.45	0.973	0.334
After surgery	29.66±3.52*	34.08±2.99*	5.899	<0.001

Note: *P<0.05, compared with the same group before surgery. EPCs, endothelial progenitor cells; OD, optical density.

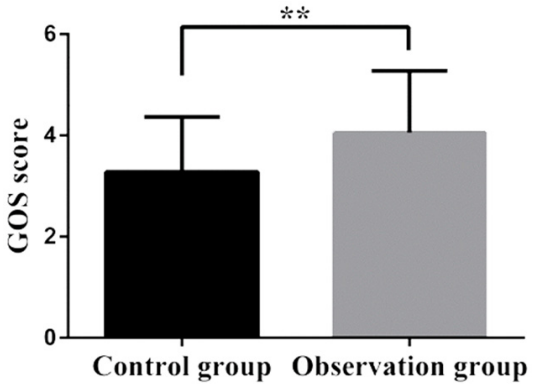

Figure 2. Comparison of GOS score 3 months after the surgery. **P<0.01. GOS, Glasgow outcome score.

lizing the hemodynamic parameters may also be related to the protection it offers to the endothelial cells [20, 21]. For example, Riquelme et al. found that the protective effect of DEX on ischemia-reperfusion injury of the heart may be attributed to its direct reaction on the endothelial cells [22]. EMPs are small vesicles released by the endothelial cells into the peripheral blood under the pathological stimuli. The diameter of these vesicles is 0.1-1 μm, which can specifically reflect the degree of endothelial injury. In order to confirm whether DEX is involved in endothelial protection, flow cytometry was used to detect the number of EMPs. The results showed that the number of EMPs in the observation group was significantly lower than that in the control group, indicating that DEX had protective effect on the endothelium. The specific mechanism is still unclear, but it may be related to the protection of glycogen encapsulation in endothelial cells and the activation of nitric oxide synthase [23, 24].

EPCs can directly differentiate into endothelial cells and secrete a series of factors that promote the repair of damaged endothelial cells. The number of EPCs in the peripheral blood is closely related to the prognosis of patients with TBI, for example, promoting EPC mobilization has been shown to accelerate the functional recovery in animal models [25-27]. The results of this study also show that DEX can increase the number of EPCs in the peripheral blood,

which may be one of the mechanisms of the endothelial protection by DEX. But whether DEX is directly involved in EPC mobilization remains unknown. Besides quantity, the function of EPCs is also an important factor in evaluating their angiogenic and repair abilities. *In vitro* cell-culture experiments showed that the proliferation and adhesion abilities of EPCs isolated and cultured in the observation group were more enhanced than those in the control group, suggesting that DEX adjuvant therapy had a positive effect on the proliferation and adhesion function of EPCs.

There were also some shortcomings to this study. Firstly, we only observed the related indicators one month after operation, but it is not clear whether the indicators show dynamic changes; and the survival rate and other indicators were not analyzed, thus whether DEX can improve the long-term prognosis needs to be further studied. Secondly, the mechanism of DEX on the up-regulation of the number of EPCs in the peripheral blood and on the improvement of their function has not been explored. In the future, *in vitro* experiments are needed to further clarify the direct mechanism of DEX.

In conclusion, DEX treatment before and after the surgery can reduce the serum levels of S100β and NSE, stabilize hemodynamic indices, restrain the content of EMPs in the peripheral blood, and improve the number and function of EPCs in the peripheral blood in TBI patients.

Disclosure of conflict of interest

None.

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