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ORIGINAL ARTICLE

## Effect of dexmedetomidine on plasma brain-derived neurotrophic factor: A double-blind, randomized and placebo-controlled study

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### Abstract

**Background.** Dexmedetomidine (DEX) has neuro-protective effects, but the clinical mechanism remains unclear.

**Method.** Forty patients were randomly divided into two groups: group A (control) and group B (treated with DEX). Plasma concentrations of brain-derived neurotrophic factor (BDNF) were determined in blood samples using enzyme-linked immunosorbent assays at five time points: T1 (baseline), T2 (15 minutes after intubation and before the surgery was started), T3 (the end of surgery), T4 (10 minutes after extubation in the post-anesthesia care unit), and T5 (24 hours after the surgery). Changes in bispect (BIS) index, heart rates, and doses of anesthetics used for induction were also recorded.

**Results.** Baseline plasma concentrations of BDNF did not differ between group A and group B; 15 minutes after induction, concentrations of plasma BDNF were significantly reduced in group A. Twenty-four hours after surgery, the concentration was still higher in group B than in group A. In contrast, plasma concentrations of BDNF at other time points tested did not differ between the two groups.

**Conclusion.** It appears that DEX could reverse the reduced plasma concentrations of BDNF caused by anesthetics, and this effect lasted for 24 hours after surgery.

**Key words:** Anesthetic drugs, brain-derived neurotrophic factor (BDNF), dexmedetomidine

### Introduction

As a member of the neurotrophin family of growth-promoting proteins, brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival, axon growth, and synaptic plasticity (1). In rodents, BDNF is highly correlated with learning, memory, and other advanced neuronal functions (2). Elevation of BDNF in the central nervous system (CNS) may significantly attenuate neuronal injuries caused by ischemia and also be beneficial for the treatment of degenerative diseases (3). Importantly, BDNF is detectable in blood, and a positive correlation has been found between serum and cortical BDNF concentrations (4,5). Thus, determinations of serum BDNF concentrations could help to investigate changes of BDNF concentrations in the CNS.

Anesthetics are known to inhibit neuronal activity in the CNS (6) and cause sedation, amnesia, and post-operative cognitive dysfunction. Further studies have shown that such drugs could inhibit the release of BDNF from cortical neurons (7). It has been proven clinically that perioperative use of anesthetics could lead to decreased plasma concentrations of BDNF in patients (8).

The highly selective  $\alpha_2$ -adrenoceptor agonist, dexmedetomidine (DEX) has marked effects on hypnosis, anti-anxiety, and analgesia (9). Recent animal studies have revealed that DEX also has neuro-protective effects (10–12), due in part to the elevation of BDNF concentrations in the cortex and hippocampus (13). However, in humans, the impact of DEX on BDNF concentrations remains elusive. Therefore, we investigated the effect of DEX on plasma BDNF

concentrations in patients who underwent general anesthesia and were classified as physical status I and II patients (American Society of Anesthesiologists (ASA)).

### Subjects and methods

Our trial was registered in the Chinese clinical trial registry with the registration number ChiCTR-TRC-12002714 and approved by the ethics committee of The Second Xiangya Hospital, Central South University. All patients agreed to join our research project and signed an informed consent statement.

From 1 August 2012 to 31 December 2012 in The Second Xiangya Hospital, Central South University, ASA physical status I and II patients, who were scheduled for lumbar discectomy, were enrolled. Remembering that adult plasma BDNF concentrations are correlated with age, gender, and body mass index (BMI) (14), we planned to choose only male patients, from 40 to 60 years old, and with a BMI of 20 to 30. Patients with a history of alcohol abuse or use of antipsychotic drugs, as well as those with underlying organ disease or psychiatric illness, were not considered.

Patients received 5 mg diazepam orally, 30 minutes before entering the operating room. In the waiting room, they were randomly allocated to one of the two groups by drawing lots; lidocaine cream was applied to the skin of each patient's arms in order to attenuate the pain of puncture. Two intravenous catheters were inserted, one in each of the patient's arms; one was used exclusively for the measurement of BDNF plasma concentrations and the other for anesthesia and volume management.

After entering the operating room, 250 mL of Ringer's lactate was administered to ensure rapid volume expansion. Routinely, we monitored (Dash 3000, GE Company, Milwaukee, WI, US) a five-lead ECG, non-invasive blood pressure, heart rate and peripheral capillary oxygen saturation. BIS Index (BIS<sup>TM</sup> Complete 2-Channel Monitor and 4 Electrode Sensor, both from Covidien, Mansfield, MA, US) was used to measure the depth of anesthesia.

In order to maintain the double-blind nature of the study, an anesthetist who did not participate in our research program prepared the 'study drug solutions' containing either DEX 2 µg/ml or 0.9% saline, while a member of our research team supervised the whole anesthesia management. In group B, 0.7 µg/kg DEX was administered by intravenous infusion for 15 minutes, and propofol (Diprivan, AstraZeneca, Paddington, London, UK) was administered until the patient's eyelid reflex was lost. Then, sulfentanil (EuroCept, Ankeveen, The Netherlands) 0.15 µg/kg

and cis-atracurium 0.1 mg/kg were infused intravenously until neuromuscular relaxation was achieved. The same anesthetist carried out the intubation. In group A, however, an equal amount of 0.9% saline instead of DEX was administered, while the rest of the steps were the same as for group B. Another member of the research team was in charge of recording the doses of propofol and sulfentanil used for induction, changes in BIS values, and heart rates during induction.

Anesthesia was maintained by the continuous infusion of propofol; sulfentanil and cis-atracurium were administered intermittently for analgesia and muscular relaxation, respectively. In group B, 0.6 µg/kg/h DEX was additionally administered by continuous infusion. Controlled mechanical ventilation was adjusted to maintain the  $P_{ET}CO_2$  between 4.7 and 6.0 kPa, and BIS index was monitored between 35 and 45.

The infusion of all anesthetics and DEX was halted at skin closure, when 6–8 µg sulfentanil was given to each patient in order to reduce post-operative pain.

Five venous blood samples (5 mL each) were drawn from each patient: at T1 (baseline), T2 (15 minutes after intubation before the operation was started), T3 (after skin closure), T4 (10 minutes after extubation in the PACU), and T5 (24 hours after surgery). Blood samples were placed in ethylene diamine tetraacetic acid (EDTA) tubes and centrifuged for 15 minutes at 3,000 rpm. The plasma obtained was stored at  $-70^{\circ}C$  until required for subsequent analysis of its contents. BDNF plasma concentrations were measured by enzyme-linked immunosorbent assays (ELISA) (Human BDNF Immunoassay, R&D system, Minneapolis, US). Using this assay, the minimum detectable concentration of BDNF is less than 20 pg mL<sup>-1</sup>.

### Statistical analysis

For the design of this study, an estimation of the required minimum sample size was determined based on results of our pre-experimental investigations (not included in the real study) and on a previous study (8). Using type I error (0.05) and type II error (0.1), a power of test of 90%, the number of cases calculated per group would be 17. Thus, we recruited 20 patients in each group in order to prevent unforeseen difficulties.

Data were expressed as mean  $\pm$  standard deviation, maximum or minimum. Plasma BDNF concentrations were compared between the two groups and within each group, by using the non-parametric Mann-Whitney *U* test. A *t* test was used for comparison of doses of induction anesthetics and changes of the heart rates and BIS index at each time point

Table I. BDNF plasma concentrations.

	Group A (n = 19)	Group B (n = 18)
T1	196.1 ± 36.7 (141.4–268.6)	173.8 ± 40.0 (113.7–274.6)
T2	120.9 ± 17.6 (92.5–159.5)	167.3 ± 36.8 <sup>a</sup> (109.4–264.9)
T3	167.3 ± 19.9 (113.6–192.5)	165.3 ± 34.9 (119.2–255.6)
T4	154.9 ± 28.6 (107.8–194.5)	164.8 ± 29.4 (114.2–254.4)
T5	126.8 ± 28.2 (90.4–190.4)	176.0 ± 26.9 <sup>a</sup> (149.4–260.4)

T1 = baseline; T2 = 15 minutes after intubation before the operation started; T3 = skin closure; T4 = 10 minutes after extubation in the PACU; T5 = 24 hours after the operation. <sup>a</sup>*P* < 0.05 versus control.

between the two groups. *P* < 0.05 was considered to be statistically significant. All data were analyzed with SPSS 19.0 software (IBM Company, Armonk, New York City, US).

## Results

Forty patients were enrolled. Data from three patients were excluded: one from group A due to a change of the surgical procedure, and the other two from group B due to technical problems of blood processing. In group A, BDNF plasma concentrations were 196.1 ± 36.7 pg/ml at baseline and decreased to 120.9 ± 17.6 pg/ml 15 minutes after anesthesia induction (Table I). At the time point of skin closure, the BDNF plasma concentration increased to 167.3 ± 19.9 pg/ml and remained high (154.9 ± 28.6 pg/ml) 5 minutes after extubation. Twenty-four hours after the operation, the BDNF plasma concentrations fell below the baseline (126.8 ± 28.2 pg/ml). In group B, the baseline BDNF plasma concentration was 173.8 ± 40.0 pg/ml, which was comparable with that in group A. Fifteen minutes after anesthesia induction, the BDNF concentration tended to decrease (167.3 ± 36.8 pg/ml). However, it was still higher than in group A. Twenty-four hours after the operation, BDNF plasma concentrations were maintained at 176.0 ± 26.9 pg/ml, which was higher than in group A. Both at skin closure and 10 minutes after the extubation, BDNF plasma concentrations increased to 165.3 ± 34.9 pg/ml and 164.8 ± 29.4 pg/ml, but there were no differences between the two groups.

Table II. Changes in patients' heart rates.

	Group A	Group B
Baseline	78 ± 6.6	78 ± 7.0
Study drug injection	78 ± 6.8	63 ± 4.2 <sup>a</sup>
Anesthesia induction	65 ± 4.4	53 ± 2.7 <sup>a</sup>
Intubation	93 ± 7.0	86 ± 9.1 <sup>a</sup>

<sup>a</sup>*P* < 0.05 versus control.

In general, heart rates were lower in group B than in group A at the time point of injection of DEX, anesthesia induction, and intubation (Table II). The lowest heart rate in group B was 49 bpm after anesthesia induction, and it returned to 70 bpm after intra-tracheal intubation. There was no serious hypotension recorded.

BIS values were recorded during the operation (Table III). Compared with group A, the BIS values in group B were lower at the procedures of intubation and skin cut. At the other time points checked there were no differences between the two groups.

Basic characteristics, duration of the surgery, and the amount of bleeding and volume therapy did not differ between the two groups. However, doses of propofol and sufentanil for induction were lower in group B than in group A (Table IV).

## Discussion

This study demonstrated that DEX did reverse anesthetic-induced reductions of BDNF plasma concentrations. BDNF in blood could readily be detected, and according to previous studies it is highly correlated with BDNF concentrations in the brain (3,4). It is mainly stored in platelets (15) and may also be synthesized and secreted by visceral epithelia (16), vascular endothelia (17), and inflammation cells (18) (activated T-helper Th1 and Th2 CD4<sup>+</sup> cell lines, especially). There is evidence to suggest that intravenous

Table III. BIS value variation during surgery.

	Group A	Group B
Baseline	98.6 ± 0.5	98.2 ± 0.6
Anesthesia induction	40.3 ± 2.3	39.1 ± 3.5
Intubation	64.5 ± 4.3	51.4 ± 2.8 <sup>a</sup>
Skin cut	54.3 ± 4.9	46.8 ± 2.5 <sup>a</sup>
Skin closure	59.6 ± 4.4	59.5 ± 3.2

<sup>a</sup>*P* < 0.05 versus control.

Table IV. Duration of surgery, amount of bleeding and volume therapy, and the dose of induction anesthetics.

	Group A	Group B
Duration of surgery (min)	109.3 ± 7.1	104.6 ± 10.6
Bleeding (mL)	102.1 ± 10.3	103.9 ± 9.2
Volume therapy (mL)	1442.1 ± 161.0	1436.1 ± 173.9
Propofol for induction (mg)	92.1 ± 15.1	36.9 ± 6.0 <sup>a</sup>
Sulfentanil for induction (mg)	36.8 ± 5.06	20.4 ± 5.1 <sup>a</sup>

<sup>a</sup>*P* < 0.05 versus control.

administration of BDNF labeled with <sup>125</sup>I can result in entry into the CNS to promote neuron protection and regeneration, and after intracerebroventricular injection of exogenous BDNF an efflux of BDNF from brain to blood was also detected (4). Clinically depressed patients were found to have lower levels of BDNF, both in the cortex (19) and in plasma (20). In healthy individuals, Bernward Winter (21) demonstrated that the improvement of short-term learning was highly correlated with an elevation in the serum concentration of BDNF. It appears that elevation of blood concentrations of BDNF could contribute to a better neural function. Therefore, one can suppose that if DEX could increase BDNF concentrations in plasma, it might produce neurological benefits.

Anesthetics could inhibit the release of BDNF from cortical neurons (7). This reduction of plasma BDNF concentrations was proven to cause BDNF-dependent neuroapoptosis in the neonatal rat brain (22), which indicated that the BDNF signal was crucial to the CNS and could partly explain the mechanisms of neurotoxicity induced by anesthetics (23).

Without the interference of noxious stimuli and with strict management to maintain the BIS index within a narrow range, 15 minutes after induction may be the best time to assess the effects of the DEX and anesthetics on plasma BDNF. Our present study, together with other studies (8), showed that the administration of anesthetics could reduce the BDNF concentrations in plasma in both groups. We believe that measurements of BDNF concentrations in plasma may reflect, to some extent, the effect of anesthetics on BDNF expression in CNS. In contrast, DEX was proven to have neuro-protective effects, and it could attenuate the cognitive impairment induced by anesthetics (24) and elevate the BDNF levels in the hippocampus (12). In the present study, we found that when combined with DEX, anesthetics-induced reduction of BDNF appeared to be reversible. This could be explained by two mechanisms: Firstly, DEX administration obviously permitted a reduction in the doses of propofol and

sulfentanil used for induction, as was also demonstrated in other studies (25). Thus, DEX may weaken the attenuated effect of the anesthetics on the release of BDNF. Secondly, DEX itself might increase the BDNF levels both in CNS (proven in animal research (12)) and in plasma. However, further studies are still needed to figure out the actual peripherally or centrally acting site of DEX and anesthetics.

At the time point of skin closure and 10 minutes after extubation in the PACU, the BDNF plasma concentrations in both groups increased markedly compared to the concentrations 15 minutes after induction. We supposed that these changes resulted from the gradual reduction in the depth of anesthesia and analgesia, as the infusion of all the drugs was stopped at the beginning of the skin closure. Neuronal excitability recovered gradually, which might have caused a rapid release of BDNF in the CNS.

The change of BDNF plasma concentrations 24 hours after surgery may well reflect the long-lasting effects of anesthetics on patients. In our present study, it was found that after anesthesia the BDNF plasma concentrations were decreased 24 hours after surgery, which is consistent with results from previous research (8). Importantly, we showed that DEX combined with general anesthesia reversed the decrease of the BDNF plasma concentration induced by anesthetics. Clinical trials (26) with large sample sizes have already reported that postoperative sedation with DEX instead of propofol or midazolam is associated with significantly lower rates of postoperative delirium (which is a form of neurological impairment) and care costs. We believe that this elevation of plasma BDNF concentrations might serve as a potential mechanism to explain the neuro-protective effect of DEX in humans.

Perioperative noxious stimuli are known to be important factors affecting the post-operative neurologic recovery. In the present study, we found that compared with group A, the DEX-treated patients in group B had more stable heart rates and BIS values in the face of intubation and skin cut, most probably because of the anti-sympathetic effect of DEX. Whether it is correlated with the elevation of BDNF concentrations needs to be clarified.

A limitation of our research was that we did not carry out stratified research of the population (only well-selected male patients were enrolled), and the number of patients used was limited and thus might not be representative of the general population. We did not extend our investigation to include studies of our patients' cognition functions, because patients (aged 40–60 years old) rarely suffer from postoperative cognition dysfunction after the surgery of lumbar discectomy.



Overall, our experiments showed that DEX combined with general anesthesia could reverse the reduced BDNF plasma concentrations caused by anesthetics during and 24 hours after surgery. Whether the elevation of plasma BDNF is beneficial to the patient remains to be unequivocally established.

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