

RESEARCH ARTICLE

Effect of Intraoperative Glucose Fluctuation and Postoperative IL-6, TNF- α , CRP Levels on the Short-term Prognosis of Patients with Intracranial Supratentorial Neoplasms

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Abstract

Objective: To investigate the effect of intraoperative glucose fluctuation and postoperative interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), C-reactive protein (CRP) levels on the short-term prognosis of patients with intracranial supratentorial neoplasms. **Materials and Methods:** Eighty-six patients undergoing intracranial excision were selected in The Second Hospital of Jilin University. According to the condition of glucose fluctuation, the patients were divided into group A (glucose fluctuation <2.2 mmol/L, $n=57$) and group B (glucose fluctuation ≥ 2.2 mmol/L, $n=29$). Glucose was assessed by drawing 2 mL blood from internal jugular vein in two groups in the following time points, namely fasting blood glucose 1 d before operation (T_0), 5 min after anesthesia induction (T_1), intraoperative peak glucose (T_2), intraoperative lowest glucose (T_3), 5 min after closing the skull (T_4), immediately after returning to intensive care unit (ICU) (T_5) and 2 h after returning to ICU (T_6). 1 d before operation and 1, 3 and 6 d after operation, serum IL-6 and TNF- α levels were detected with enzyme-linked immunosorbent assay (ELISA), and CRP level with immunoturbidimetry. Additionally, postoperative adverse reactions were monitored. **Results:** There was no statistical significance between two groups regarding the operation time, anesthesia time, amount of intraoperative bleeding and blood transfusion ($P>0.05$). The glucose levels in both groups at $T_1\sim T_6$ went up conspicuously compared with that at T_0 ($P<0.01$), and those in group B at T_2, T_4, T_5 and T_6 were significantly higher than in group A ($P<0.01$). Serum IL-6, TNF- α and CRP levels in both groups 1, 3 and 6 d after operation increased markedly compared with 1 d before operation ($P<0.01$), but the increased range in group A was notably lower than in group B ($P<0.05$ or $P<0.01$). Postoperative incidences of hypoglycemia, hyperglycemia and myocardial ischemia in group A were significantly lower than in group B ($P<0.05$), and respiratory support time obviously shorter than in group B ($P<0.01$). **Conclusions:** The glucose fluctuation of patients undergoing intracranial excision is related to postoperative IL-6, TNF- α and CRP levels and those with small range of glucose fluctuation have better prognosis.

Keywords: Glucose fluctuation - supratentorial neoplasms - interleukin-6 - tumor necrosis factor- α - C-reactive protein

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Introduction

A variety of factors affect perioperative glucose, especially the oxidative stress response. Glucose fluctuation can not only aggravate oxidative stress response, but also damage cardiovascular and renal functions. Perioperative hypoglycemia or hyperglycemia is a crucial factor that induces complications and death after brain surgery, so strict control of blood glucose can effectively shorten the hospital stays and improve the prognosis of patients (Miyake, 2014). The study revealed that glucose fluctuation could injure multiple organ function by damaging mitochondrial function, inhibiting immune system and up-regulating the level of proinflammatory cytokines (Franca et al., 2014; Teraguchi et al., 2014). Hence, monitoring intraoperative glucose

fluctuation and changes of postoperative inflammatory factors is conducive to judging the prognosis of patients. At present, there are no reports about the correlation between intraoperative glucose fluctuation and prognosis in patients without diabetes mellitus and undergoing intracranial excision. This study mainly investigated the effect of intraoperative glucose fluctuation and postoperative IL-6, TNF- α , C-reactive protein levels on the short-term prognosis of patients with without diabetes mellitus and undergoing intracranial excision.

Materials and Methods

General data

Eighty-six patients undergoing intracranial excision at the selective time were selected in The Second Hospital

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of Jilin University from Sep., 2011 to Sep., 2013. They were all at grading I-III according to American Society of Anesthesiologists (ASA), in which males and females were 58 and 28 cases, respectively. They were at the age of 20~64, with the median age of 47.6±4.8. Their body weight were 48~77 kg, with the mean of (67.5±5.4) kg and body mass index (BMI) <30 kg/m². There were 55 cases of meningioma and 31 cases of glioma. Exclusion criteria: (1) no injection of liquid glucose 4 h before operation to 4 h after operation or intraoperative glucose >14 mmol/L; (2) long-term administration of immunomodulator-related drugs; (3) having autoimmune disease; (4) having previous history of diabetes mellitus, hypertension and cardiovascular disease; (5) abnormal heart, liver and kidney function. According to the condition of glucose fluctuation, the patients were divided into group A (glucose fluctuation <2.2 mmol/L, n=57) and group B (glucose fluctuation ≥2.2 mmol/L, n=29). In group A, males and females were 39 and 18 cases, respectively. They were (44±17) years old, with the body weight of (57±16) kg. There were 36 and 21 patients respectively suffering from meningioma and glioma. In group B, males and females were 19 and 10 cases, respectively. They were (45±18) years old, with the body weight of (58±15) kg. There were 19 and 10 patients respectively suffering from meningioma and glioma. There was no statistical significance by comparison to the general data of patients in two groups like the gender, age and body weight ($P>0.05$), with comparability.

Methods

The patients in two groups were intramuscularly injected 0.5 mg of atropine and 0.1 g of phenytoin sodium 30 min before operation. Multifunctional vital sign monitor was used to routinely monitor the blood pressure (BP), electrocardiogram (ECG), heart rate (HR), oxygen saturation (SpO₂) and end-tidal carbon dioxide partial pressure (PETCO₂), and venous access was opened.

Anesthesia induction: The patients in both groups were respectively administrated midazolam (0.04~0.05 mg/kg), etomidate (0.2~0.3 mg/kg), fentanyl (1~2 µg/kg) and atracurium (0.8 mg/kg), and mechanical ventilation was performed after tracheal intubation. Respiratory rate (RR) was 12 times/min, tidal volume (VT) and oxygen flow rate being 8 mL/kg and 1.8 L/min, respectively. Besides, PETCO₂ was maintained in 30~40 mmHg.

Anesthesia maintenance: Propofol (4.0~6.0 mg·kg⁻¹·h⁻¹) and fentanyl (2~3 µg·kg⁻¹·h⁻¹) were intravenously injected, and atracurium was used for maintaining the muscles to be relax.

Glucose monitoring: 2 mL blood from internal jugular vein was drawn in two groups at the following time points, namely fasting blood glucose 1 d before operation (T₀), 5 min after anesthesia induction (T₁), intraoperative peak glucose (T₂), intraoperative lowest glucose (T₃), 5 min

Table 1. Comparison on the Intraoperative Conditions in Both Groups (x±s)

Groups	n	Operation time (min)	Anesthesia time (min)	Amount of intraoperative bleeding (mL)	Amount of blood transfusion (mL)
Group A	57	192±105	226±106	624±260	210±100
Group B	29	190±115	225±108	622±255	208±105

after closing the skull (T₄), immediately after returning to intensive care unit (ICU) (T₅) and 2 h after returning to ICU (T₆), and the same blood gas analyzer was applied to detect the glucose.

1 d before operation and 1, 3 and 6 d after operation, the blood from internal jugular vein of fasting patients in two groups was drawn, respectively. The levels of serum IL-6 and TNF-α as well as C-reactive protein (CRP) were detected respectively using enzyme-linked immunosorbent assay (ELISA) and immunoturbidimetry.

Observation indexes

Observation indexes in both groups were as follows: (1) intraoperative conditions, including operation time, anesthesia time, amount of intraoperative bleeding and blood transfusion; (2) glucose changes at different time points (T₀, T₁, T₂, T₃, T₄, T₅, T₆); (3) changes of serum IL-6, TNF-α and CRP levels 1 d before operation and 1, 3 and 6 d after operation; (4) incidence of postoperative adverse reactions, including myocardial ischemia, atrial fibrillation, hyperglycemia (>10 mmol/L, more than 3 times 6 d after surgery), hypoglycemia (<3.9 mmol/L, more than 3 times 6 d after surgery), respiratory support time and mortality.

Statistical data analysis

SPSS 17.0 statistical software was applied to analyze the data. The measurement data were compared using t test, and expressed with mean ± standard deviation (x±s). The enumeration data were compared using χ² test. $P<0.05$ was considered to be statistically significant.

Results

Comparison on the intraoperative conditions in both groups

There was no statistical significance between two groups regarding the operation time, anesthesia time, amount of intraoperative bleeding and blood transfusion ($P>0.05$) (Table 1).

Comparison on the glucose levels at different time points in both groups

The glucose levels in both groups at T₁~T₆ went up conspicuously compared with that at T₀ ($P<0.01$), and those in group B at T₂, T₄, T₅ and T₆ were significantly higher than in group A, in which significant differences were presented ($P<0.01$) (Table 2).

Table 2. Comparison on the Glucose Levels at Different Time Points in Both Groups (mmol/L, x±s)

Groups	n	T ₀	T ₁	T ₂	T ₃	T ₄	T ₅	T ₆
Group A	57	4.8±1.7	6.6±2.1**	7.0±2.2**	6.4±2.0**	6.5±1.7**	6.8±2.1	6.9±1.8**
Group B	29	4.6±1.8	6.7±2.0**	9.8±3.0***	6.5±2.1**	8.2±2.3***	8.4±3.2***	8.5±3.0***

Compared with T₀, ** $P<0.01$; Compared with Group B, *** $P<0.01$

Table 3. Comparison on the Levels of Serum IL-6, TNF- α and CRP in both Groups Before and after Operation (x \pm s)

Groups	Time	IL-6 (pg/mL)	TNF- α (pg/mL)	CRP (mg/L)
GroupA (n=57)	1 d before operation	30.28 \pm 12.79	7.46 \pm 2.39	6.71 \pm 2.86
	1 d after operation	86.87 \pm 43.46**#	34.68 \pm 23.27**#	95.64 \pm 43.21**#
	3 d after operation	68.66 \pm 34.53**#	26.29 \pm 16.45**#	77.35 \pm 39.08**#
	6 d after operation	41.69 \pm 18.35**#	16.77 \pm 13.96**#	39.67 \pm 24.59**#
	1 d before operation	28.71 \pm 14.18	7.24 \pm 2.16	6.52 \pm 2.68
	1 d after operation	108.59 \pm 47.76**	48.92 \pm 26.90**	118.41 \pm 49.32**
GroupB (n=29)	3 d after operation	87.38 \pm 41.26**	40.85 \pm 20.73**	96.47 \pm 46.83**
	6 d after operation	66.43 \pm 23.76**	33.85 \pm 18.54**	74.75 \pm 36.33**

Compared with 1 d before operation, ** P <0.01; Compared with Group B, # P <0.05, ## P <0.01

Comparison on the levels of serum IL-6, TNF- α and CRP in both groups before and after operation

Serum IL-6, TNF- α and CRP levels in both groups 1, 3 and 6 d after operation increased markedly compared with 1 d before operation (P <0.01), but the increased range in group A was notably lower than in group B (P <0.05 or P <0.01) (Table 3).

Comparison on the incidence of postoperative adverse reactions

Before operation, there were 5 patients suffering from myocardial ischemia and 4 from atrial fibrillation in group A, and 2 from myocardial ischemia and 2 from atrial fibrillation in group B. By comparison to incidences of myocardial ischemia and atrial fibrillation, significant difference was not presented (P >0.05). After operation, incidences of hypoglycemia, hyperglycemia and myocardial ischemia in group A were significantly lower than in group B (P <0.05), and respiratory support time obviously shorter than in group B (P <0.01) (Table 4).

Discussion

The stress reaction induced by perioperative operation and anesthesia performance can increase the blood glucose in patients with and without diabetes mellitus, whereas bowel preparation, prohibition of drinking water and improper hypoglycemic therapy can lead to the decrease of blood glucose. Under the condition of stress reaction, the levels of intraoperative and postoperative blood glucose are affected by various factors, such as abnormal regulation of neurohormone, a lot of released inflammatory cytokines, neuroendocrine change and insulin resistance (Nishimura et al., 1998; Wang et al., 2013). Glucose fluctuation can strengthen the aggregation of monocytes in vascular endothelium and damage the body multi-functional organ function (Watada et al., 2007). The study indicated that perioperative glucose fluctuation could increase the incidence of complications and mortality in

Table 4. Comparison on the Incidence of Postoperative Adverse Reactions [n (%)]

Groups	n	Hypog-lycemia	Hyper-lycemia	Myocardial ischemia	Atrial fibrillation	Respiratory support time (h, x \pm s)	Death
GroupA	57	1 (1.75)*	3 (5.26)*	7 (12.28)*	5 (8.77)	15.9 \pm 6.8**	2 (2.06)
GroupB	295	7 (2.4)	7 (2.4)	9 (3.03)	5 (1.72)	26.2 \pm 11.5	1 (3.45)

Compared with group B, * P <0.05, ** P <0.01

patients undergoing surgery, prolong hospital stays and affect long-term prognosis (Atkins et al., 2009; Wu et al., 2013). Hence, strictly monitoring perioperative glucose fluctuation is of great importance in judging the prognosis of patients undergoing surgery. The results in this study demonstrated that the glucose levels in both groups at T₁~T₆ went up conspicuously compared with that at T₀, and those in group B at T₂, T₄, T₅ and T₆ were significantly higher than in group A, illustrating that both operation and anesthesia performance can make the blood glucose of patients go up, and the range of glucose fluctuation in group B is more larger. Additionally, the incidences of postoperative hypoglycemia and hyperglycemia increased notably in group B, indicating that occurrence of postoperative hypoglycemia and hyperglycemia has a positive correlation with intraoperative glucose fluctuation, which may be related to decreased insulin secretion and glycogen synthesis as well as disorder of glucose uptake in peripheral tissue caused by insulin resistance.

As a multi-functional cytokine, IL-6 has a variety of biological functions and can induce the proliferation and differentiation of immunocytes. It plays an important role in both innate and acquired immunities in the body. Recent studies have revealed that abnormal expression of IL-6 and its receptors is closely related to tumorigenesis and progression, and has a crucial function in terms of tumor diagnosis and prognosis (Tripsianis et al., 2013; Holmer et al., 2014). TNF- α , a sort of polypeptide cytokine with various biological activities, is intimately associated with body immunoreactions, acute phase and inflammatory reactions. As a cytokine with the strongest anti-tumor activity, TNF- α can damage the vascular epithelial tissue surrounding solid tumors and inhibit tumor nutrient supply except for the cytotoxicity on tumor cells (El-Hussuna et al., 2013). As a sensitive marker for systemic inflammatory reaction, CRP can independently predict the occurrence, progression and prognosis of various critical diseases (Yu et al., 2013). The results in this study demonstrated that serum IL-6, TNF- α and CRP levels in both groups 1, 3 and 6 d after operation increased markedly compared with 1 d before operation, but the increased range in group A was notably lower than in group B, suggesting that IL-6, TNF- α and CRP levels are related to intraoperative glucose fluctuation. This mechanism probably lies in: (1) Glucose fluctuation can cause insulin resistance and stress hyperglycemia, promote serum IL-6, TNF- α and CRP to release and injure the function of many organs in the body, thereby affecting the prognosis of patients; (2) On one hand, both IL-6 and TNF- α mediate insulin resistance and aggravate stress reactions by increasing the levels of catecholamine, adrenocortical hormone and cortisol; On the other hand, they can induce postoperative

glucose fluctuation through inhibition of glucose transport in adipocytes (Hotamisligil et al., 1994); (3) By regulating NF- κ B and inducing TNF- α release, CRP can promote various factors to release and increase the expression of inflammatory genes so as to interfere insulin signal transduction and induce insulin resistance, consequently leading to increased blood glucose. Besides, it can also induce vascular injury reaction and enhance peripheral insulin resistance, thereby resulting in increased blood glucose (Gugapriya et al., 2014).

The study revealed that injury of vascular endothelial cells caused by fluctuated hyperglycemia was more serious than that by continuous hyperglycemia (Rassias, 2006; Mazze et al., 2012). In this study, the incidence of postoperative myocardial ischemia in group A was significantly lower than in group B. The reason may be the reactive oxygen species produced by glucose fluctuation can make vasoconstriction and platelet aggregation by inducing oxidative stress response, regulating gene expression of inflammatory factors and mediating vascular endothelial injury, finally leading to occurrence of myocardial ischemia. Additionally, the respiratory support time in group A was obviously shorter than in group B, which may be related to slowed absorption of ventilator-induced lung injury caused by adhesion, chemotaxis and phagocytosis of monocytes and neutrophils when blood glucose fluctuates (Rassias et al., 2002; Alba-Loureiro et al., 2007).

To sum up, the glucose fluctuation of patients undergoing intracranial excision is related to postoperative IL-6, TNF- α and CRP levels and those with small range of glucose fluctuation have better prognosis.

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