



Research article

The change of circulating insulin like growth factor binding protein 7 levels may correlate with postoperative cognitive dysfunction



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HIGHLIGHTS

- Postoperative circulating IGFBP7 level increased and IGF-1 decreased.
- Up-regulation of IGFBP7 correlated with post-operative cognitive dysfunction.
- Lower IGF-1 level increased the risk of post-operative cognitive dysfunction.
- Elderly patients increased the risk of post-operative cognitive dysfunction.

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ABSTRACT

Insulin-like growth factor binding protein (IGFBP) 7 may be a critical regulator of memory consolidation. This study was performed to assess the relationship between circulating IGFBP7 levels and postoperative cognition dysfunction (POCD) in patients scheduled for elective head and neck carcinoma surgery under general anesthesia. Among one hundred and two patients included in this study, forty-four patients completed collection of all four blood samples and thirty-five patients were diagnosed with POCD. The results of Mini-Mental State Examination (MMSE) test and enzyme-linked immunosorbent assay showed that postoperative MMSE score and circulating insulin-like growth factor (IGF)-1 level were lower and circulating IGFBP7 level was higher than preoperative level. Circulating IGF-1 level was significantly lower and D-value of preoperative and postoperative day 1 circulating IGFBP7 levels (Δ IGFBP7¹) was significantly higher in the POCD group. Age preoperative MMSE, IGF-1 level and Δ IGFBP7¹ significantly correlated with POCD, but preoperative IGFBP7 level not. Logistic regression analysis revealed that older patients, lower preoperative MMSE score, IGF-1 level and higher IGFBP7 level significantly increased the risk of POCD, but Δ IGFBP7¹ not. Hence, circulating IGF-1 and IGFBP7 levels and their changes during operation under general anesthesia may correlate with POCD, but further investigation in larger samples is needed.

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1. Introduction

Postoperative cognitive dysfunction (POCD) manifests as a decline in brain function subsequent to surgical procedures with an increased incidence in elderly patients (≥ 60 years) [1,2]. Although POCD may last for a short period (days or weeks) in most patients after cardiac and non-cardiac surgery, POCD in some patients can last for months or longer [1–3], and even increase mortality [2,4]. One hypothesis for POCD pathogenesis is that anesthesia would

lead to tau hyperphosphorylation, thereby initiating or aggravating cognitive decline [5].

Insulin-like growth factor (IGF)-1 can induce inhibition of GSK-3 to result in tau dephosphorylation and increase microtubule binding of tau [6] and can decrease the β -amyloid ($A\beta$) level in the brain [7] by increasing the translating and clearing of $A\beta$. Evidence gathered from human studies showed a positive correlation between serum IGF-I levels and mental ability [8–13], while cognitive impairment has been found in human patients affected by growth hormone(GH)/IGF-I deficiency [14,15]. IGF-1 binding protein (IGFBP) 7 [16], a protein that attenuates the function of insulin-like peptide (ILP) signaling, is up-regulated in the brains of AD patients and in a mouse model for AD. Increasing hippocampal IGFBP7 levels leads to impaired memory consolidation and

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Table 1
Characteristics of the total patients and patients completing collection of all four blood samples.

	Total patients			Patients with blood collection			P ¹
	POCD group	Non-POCD group	P	POCD group	Non-POCD group	P	
number	35	67		18	26		0.447
Gender(men%)	26(74.29)	46(68.66)	0.554	14(77.78)	16(61.54)	0.256	0.864
Age(year)	70.31 ± 5.79	65.75 ± 5.36	0.0001	72.00 ± 5.70	64.15 ± 4.73	<0.0001	0.9636
Height(cm)	166.03 ± 8.00	166.43 ± 6.11	0.7766	167.00 ± 6.65	166.46 ± 7.07	0.8005	0.7523
Weight(kg)	63.31 ± 11.30	65.33 ± 9.49	0.3432	63.83 ± 12.53	63.83 ± 10.77	1.0000	0.7619
BMI(kg/m ²)	23.00 ± 4.05	23.59 ± 3.28	0.4290	22.69 ± 3.24	23.21 ± 3.72	0.6320	0.5427
Education level			0.309			0.273	0.681
Primary school(%)	10(28.57)	20(29.85)		5(27.78)	9(34.62)		
Middle school(%)	22(62.86)	34(50.75)		11(61.11)	10(38.46)		
College or university(%)	3(8.57)	13(19.40)		2(11.11)	7(26.92)		
History of DM(%)	4(11.43)	10(14.93)	0.626	2(11.11)	6(23.08)	0.312	0.490
History of hypertension(%)	20(57.14)	34(50.75)	0.539	10(55.56)	14(53.85)	0.911	0.858
History of smoking(%)	7(20.00)	12(17.91)	0.797	4(22.22)	6(23.08)	0.947	0.569
History of drinking(%)	5(14.29)	6(8.96)	0.410	2(11.11)	2(7.69)	0.698	0.757
History of cardiovascular diseases (%)	10(28.57)	19(28.36)	0.982	6(33.33)	6(23.08)	0.370	0.886
Albumin (g/liter)	41.20 ± 3.58	40.91 ± 3.70	0.7052	40.78 ± 3.81	41.00 ± 4.90	0.8726	0.8863
Creatinine (μmol/liter)	86.20 ± 13.88	88.94 ± 18.20	0.4375	91.11 ± 15.99	89.00 ± 12.03	0.6197	0.5179
Blood sugar(mg/liter)	5.07 ± 0.56	5.06 ± 0.75	0.9426	4.87 ± 0.44	5.52 ± 0.78	0.0025	0.1292
Operation time(h)	9.29 ± 1.47	9.57 ± 1.36	0.3366	9.58 ± 1.90	10.19 ± 1.63	0.2613	0.0851
MMSE ¹	27.17 ± 1.92	28.30 ± 1.36	0.0009	27.44 ± 2.17	28.62 ± 1.53	0.0416	0.472
IGF-1 ¹				114.37 ± 9.41	136.08 ± 10.41	<0.0001	
IGFBP7 ¹				26.03 ± 4.11	26.48 ± 3.18	0.6833	

Data are shown as mean ± SD or number (percentage). MMSE1: the score of MMSE on the day before operation. IGF-11: the circulating IGF-1 level on the day before operation. IGFBP71: the circulating IGFBP7 level on the day before operation. ΔMMSE1: the D-value of MMSE1 and MMSE2. p1: the p value compared between the total patients and patients completing collection of all four blood samples.

inhibiting IGFBP7 function in mice that develop AD-like memory impairment reinstates associative learning behavior.

However, none of these studies has shown the influence of general anesthesia on circulating IGFBP7 level and the relationship between the circulating IGFBP7 level and POCD. The present study was designed to assess the relationship between circulating IGFBP7 level and POCD.

2. Materials and methods

2.1. Patient population

The study was performed in patients scheduled for elective head and neck carcinoma surgery under general anesthesia in the past several months. The study was approved by the Institutional Ethical Committee (Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China), and written informed consent was obtained. It was also registered as a clinical trial (<http://www.chictr.org/cn/reg.aspx>, identifier: ChiCTR-RCH-14004914). Patients, ≥60 years old, without neuropsychopathic disorders, were included. All patients underwent a standardized clinical evaluation that included medical history and cognitive function assessment (Mini-Mental State Examination; MMSE) [17]. Patients whose MMSE < 23 and operation time < 8 h were excluded.

2.2. Anesthesia and surgery

Patients received routine monitoring in the operating room, including five-lead electrocardiography, blood pressure, continuous cardiac output measurement, pulse oximetry, capnography, and temperature monitoring. Fiberoptic intubation was performed in all patients and the induction medicine included fentanyl, midazolam, propofol and cisatracurium. Anesthesia was maintained with a remifentanyl continuous infusion of 0.1 μg/(kg min), a target-controlled infusion (TCI) of propofol at 2 mg/ml, 2–3% sevoflurane, intermittently infusion of cisatracurium. ETCO₂ was maintained between 35–45 mm Hg via adjusting the tidal volume and respiratory frequency. The blood pressure and heart rate were maintained

relatively stabilization (±20% baseline) via adjusting the anesthesia depth, infusion of crystalloid solution, colloidal solution or blood production, and cardiovascular agents when it was necessary.

2.2.1. Assays

On the day before the operation and postoperative 1, 3 and 7 days, MMSE test was performed by the same doctor in the afternoon (recorded as MMSE¹, MMSE², MMSE³ and MMSE⁴) and blood samples were collected at 08:00 after overnight fasting in lithium heparin on ice, centrifuged at 4 °C at 4000 × g for 20 min, and the plasma samples were stored at –80 °C until analysis. Circulating IGF-1 level (recorded as IGF-1¹, IGF-1², IGF-1³ and IGF-1⁴) and IGFBP7 (recorded as IGFBP7 [1], IGFBP7², IGFBP7³ and IGFBP7⁴) were measured by Enzyme-linked immunosorbent assay kits (R&D Systems, Oxford, UK). According to the manufacturer's data sheets, the detection range for the IGF-1 assay was 10–200 μg/l and for the IGFBP7 assay was 1.3–40 μg/l.

Statistical analysis

All statistical analyses were performed using Stata12.0 and a $P \leq 0.05$ was considered to be statistically significant. Normal data were presented as mean and standard difference of the mean. The paired or unpaired *t*-test was used to compare mean values of normally distributed data. Differences in categorical data (expressed as percentages) were assessed using the χ^2 test. Correlation analysis was used to illustrate the relationship of different parameters. Logistic regression analysis was used to investigate factors contributing to the risk of POCD.

3. Results

3.1. Patient characteristics and POCD correlation factors

A total 102 patients completed all four MMSE tests, and were divided into two groups: POCD and non-POCD according to ΔMMSE¹ > 2 (the D-value of MMSE¹ and MMSE²) (Table 1). The

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