Int J Clin Exp Pathol 2016;9(11):11911-11916
www.ijcep.com /ISSN:1936-2625/IJCEP0037769

Original Article

Baseline S100B protein as a potential predicator for postoperative cognitive dysfunction in elderly patients after hip joint replacement surgery

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Received August 12, 2016; Accepted September 27, 2016; Epub November 1, 2016; Published November 15, 2016

Abstract: Background: Postoperative cognitive dysfunction (POCD) is well described as a permanent decline of cognition after both cardiac and non-cardiac surgery without a defined etiology. This present study sought to investigate potential predicators for POCD at day 7 after hip joint replacement surgery. Methods: 171 patients who scheduled to undergo elective total hip replacement for osteoarthritis were finally enrolled in this single-center, prospective observational study. The presence status of POCD was assessed before the surgery (baseline) and at day 7 after the surgery with neuropsychological tests. Multiple logistic regression and receiver operating characteristic (ROC) curve analysis were used for the analysis of predicators for POCD. Results: The incidence of POCD at day 7 after the surgery was 19.3% (33/171) in this study. Serum S100B protein expression at baseline was an independent risk factor for POCD (OR: 2.21, 95% CI: 1.32-5.43, P=0.013) by multiple logistic regression analysis. The area under the curve (AUC) of S100B protein for POCD was 0.685, with 95% CI of 0.576-0.795, the sensitivity of 62.77% and specificity of 72.73% respectively (P<0.001) by ROC analysis. Conclusions: Our results suggested that baseline S100B protein as a potential predicator for POCD in elderly patients after hip joint replacement surgery.

Keywords: Postoperative cognitive dysfunction, S100B protein, biomarker, elderly patients

Introduction

Postoperative cognitive dysfunction (POCD), distinct from postoperative delirium, is well described as a permanent decline of cognition after both cardiac and non-cardiac surgery [1, 2]. The incidence of POCD in old patients (>60 years) undergoing non-cardiac surgery is reported to be as high as 25.8 at 1 week and 9.9% at 3 months by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) [3]. While another study conducted by Monk et al. found an incidence of 41.4% at discharge and 12.7% at 3 months in old patients with non-cardiac surgery [4]. While POCD may prominently prolong the length of hospital stay, interfere the postoperative recovery [5], affect the quality of life [6] and increase the mortality [7]. Although POCD has been studied for several decades, the mechanisms of POCD still remain abstruse and a key issue about potential predicators for POCD requires being resolved. Previous studies have revealed that several factors (including postoperative pain, hypoperfusion, thrombosis, inflammatory status and anesthetic factors, etc.) might be involved in the mechanisms of POCD [8]. Potential predicative factors for POCD will be greatly helpful in the etiology investigation and risk evaluation after the surgery. Recent reports have revealed that S100B protein may be closely associated with POCD [9], however whether it can be used as a valid clinical indicator for POCD still remains unclear. This research was designed to verify whether S100B protein could predict POCD in patients undergoing hip joint replacement surgery.

Material and methods

Patients

This study protocol was approved by the Medical Institutional Ethics Committee of Jiangsu province. This single-center, prospective observa-

tional study was conducted in the Department of anesthesiology, Taizhou People's Hospital from July 2012 to July 2015. The eligible elderly patients (≥60 years) who scheduled to undergo elective total hip replacement for osteoarthritis were consecutively enrolled. All the participants were required to offer the written informed consent. The exclusion criteria were described as follows: patients with preexisting neurological or neurovascular disease; MMSE score <24 or with history of dementia; patients with the history of surgery or cerebrovascular accidents within 6 months; those with low compliance, blindness or deafness; those with subsequent loss to follow-up.

Neuropsychological testing and POCD assessment

The enrolled patients were assessed with neuropsychological tests which were commonly used and recommended by the consensus statement before the surgery (baseline) and at day 7 after surgery [10]. The test battery was comprised with the widely described tests including Mini-mental state examination (MMSE), Digit span test, Trail making test (part A), Verbal fluency test, Word recognition memory tests and Symbol digit test [5]. By using test results and the baseline levels, a Z score was then individually calculated according to the description by International Study of Postoperative Cognitive Dysfunction (ISPOCD1 and ISPOCD2) [3, 11]. POCD was defined while the Z scores on at least two tests ≥1.96 [12].

Biochemical parameters

Fasting blood sample were obtained from all the enrolled patients before the anesthesia as the baseline levels with anticoagulant tubes. The collected samples were centrifuged (820 rpm, 10 min, 4°C) and then the supernatant was stored at -80°C for further detections. The biochemical parameters including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), S100B protein were all measured by enzyme-linked immuno sorbent assay (ELISA) according to the manufacturer's instructions using ELISA kits (R&D Systems, Minneapolis, MN, USA). An electrochemiluminescent assay was used for the neuron-specific enolase (NSE) measurement using an anti-NSE antibody (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Data was analyzed by using GraphPad Prism 5.0 (GraphPad Inc., CA, USA) and SPSS 19.0 (SPSS, Inc., IA, USA). Continuous data was presented as mean and standard error (S.E.M) while categorical data as number (n) and percentage (%). Continuous variables were compared with Mann-Whitney U test or t test, whereas categorical data analyzed by Chi-square test or Fisher exact test. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of S100B protein in the discrimination of POCD and non-POCD. Multivariate logistic regression analyses were used for determining independent risk factors for POCD. All statistical tests were bilateral probability and $P<0.05$ was considered significant.

Results

Patient cohort

This prospective study has recruited 226 patients according to the inclusion criteria. 55 of them were excluded due to the various reasons (30 data not completed, 7 MMSE <24, 10 refused to cooperate, 8 with financial problems), and consequently, 171 were enrolled into the final study analysis. A diagnosis of POCD at day 7 after the surgery was observed in 33 patients (33/171, 19.3%). The demographics, baseline characteristics and operation-related data of patients with or without POCD were presented in **Table 1**. Our results exhibited a close correlation between the advancing age and POCD occurrence ($P<0.05$). The patients in POCD group showed significantly increased blood loss as compared to those in non-POCD group ($P<0.05$). Those with longer duration of anesthesia and surgery were more likely to develop POCD ($P<0.05$).

Biochemical tests

As listed in **Table 2**, there were no statistical differences in the serum expressions of IL-6, creatinine, urea and NSE at baseline between two groups ($P>0.05$). Compared with non-POCD group, CRP, TNF-α and S100B protein were all observably elevated among POCD group ($P<0.05$).

Neuropsychological tests at baseline

Table 3 summarized the neuropsychological tests at baseline between the POCD and non-

Table 1. Characteristics of patients with or without POCD

	POCD (n=33)	Non-POCD (n=138)	*P*-value
Age (year)	70.4±6.9	67.7±6.4	0.033*
Gender			
Male	13 (39.4%)	57 (41.3%)	
Female	20 (60.6%)	81 (58.7%)	0.841
BMI (kg/m^2)	23.5±3.7	23.1±4.3	0.623
ASA physical status			
II	19 (57.6%)	84 (60.9%)	
III	14 (42.4%)	54 (39.1%)	0.728
Preoperative comorbidity and complication			
Diabetes	5 (15.2%)	13 (9.4%)	0.335
Hypertension	20 (60.6%)	71 (51.4%)	0.344
Peripheral vascular disease	2 (6.1%)	10 (7.2%)	0.811
Hypercholesterolemia	16 (48.5%)	52 (37.7%)	0.255
History of myocardial infarct	4 (12.1%)	10 (7.2%)	0.359
History of smoking	16 (48.5%)	55 (39.9%)	0.366
Duration of surgery (min)	114.2±37.3	100.8±31.1	0.034*
Duration of anesthesia (min)	161.3±40.1	146.3±33.9	0.029*
Recovery time (min)	41.3±11.3	40.5±12.2	0.732
Estimated blood loss (ml)	751.3±154.7	684.1±135.1	0.014*
Preoperative medications			
ACE inhibitors	7 (21.2%)	24 (17.4%)	0.609
β-blockers	5 (15.2%)	23 (16.7%)	0.833
Statins	12 (36.4%)	41 (29.7%)	0.458
Antidepressants	5 (15.2%)	26 (18.9%)	0.621

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; ACE, angiotensin-converting enzyme; POCD, Postoperative Cognitive Dysfunction. *P*-values were calculated by Chi-square test, Fisher exact test, Mann-Whitney U-test or t test. **P* value <0.05.

Table 2. Baseline biochemical levels of patients with or without POCD

Baseline	POCD (n=33)	Non-POCD (n=138)	*P*-value
CRP (mg/L)	14.1±5.7	12.2±4.5	0.041*
IL-6 (pg/mL)	18.3±9.7	17.8±8.8	0.774
TNF-α (nmol/L)	8.3±1.9	7.6±1.5	0.024*
Creatinine (mmol/L)	87.2±23.3	84.8±30.2	0.670
Urea (mmol/L)	6.8±2.2	6.5±3.1	0.601
S100B (ng/mL)	0.37±0.11	0.31±0.08	<0.001*
NSE (ng/mL)	10.4±1.2	10.7±1.4	0.258

POCD, Postoperative Cognitive Dysfunction; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; NSE, neuron-specific enolase. *P*-values were calculated by Mann-Whitney U-test or t test. **P* value <0.05.

POCD groups. Patients in POCD group had significantly poor preoperative levels of MMSE and verbal fluency test than those in non-POCD group (P<0.05). And the other neuropsychological tests results did not differ significantly between the two groups (P>0.05).

Independent risk factors for POCD

All the possible risk factors for POCD mentioned above were forced into a multivariate logistic regression model. The results from **Table 4** revealed that serum S100B protein expression was an independent risk factor for POCD (OR: 2.21, 95% CI: 1.32-5.43, P= 0.013).

Predicative value of S100B protein for POCD

As displayed in **Figure 1**, ROC curve analysis was utilized for the predicative value analysis of S100B protein for POCD. The area under the curve (AUC) of S100B protein for POCD was 0.685, with 95% CI of 0.576-0.795, the sensitivity of 62.77% and specificity of 72.73% respectively (P< 0.001).

Discussion

Despite the great steps in anesthetic and surgical techniques during the past decades, the brain injury or cognitive decline after the surgery still remains highly prevalent [13]. This prospective study revealed that POCD was seen in approximately 19.3% of elderly patients who scheduled to undergo elective total hip replacement, which was relatively close to previous reports [3, 11]. POCD has been widely observed in patients at any age with major surgery, especially in those elderly patients [4]. The age has been repeatedly verified as an important risk factor for the development of neurological disorder [14]. The decline in memory and learning

Table 3. Neuropsychological test results at baseline of patients with or without POCD

Neuropsychological test (Baseline)	POCD (n=33)	Non-POCD (n=138)	*P*-value
MMSE	28.6±1.1	29.0±0.9	0.030*
Digit span test			
Correct order	8.5±0.8	8.3±0.7	0.154
Reverse order	4.6±1.2	4.3±1.3	0.229
Trail making test A (s)	19.4±10.6	17.7±12.6	0.475
Verbal fluency test	14.6±3.2	16.5±3.7	0.007*
Word Recognition memory tests	1.4±1.0	1.4±1.1	1.000
Symbol digit test	31.1±11.8	32.8±12.0	0.464

MMSE, Mini-Mental State Examination; POCD, Postoperative Cognitive Dysfunction; *P*-values were calculated by Mann-Whitney U-test or t test. **P* value <0.05.

Table 4. Multiple logistic regression analysis for POCD

	POCD		
Parameter	OR	95% CI	*P* value
Age	1.56	0.91-3.82	0.128
Duration of surgery	2.21	0.73-7.44	0.153
Duration of anesthesia	3.31	0.82-8.23	0.211
Estimated blood loss	2.03	0.62-5.21	0.198
CRP	2.73	0.81-6.15	0.142
TNF-α	2.01	0.78-5.13	0.138
S100B	2.21	1.32-5.43	0.013*
MMSE	2.01	0.33-14.31	0.453
Verbal fluency test	5.71	2.21-11.33	0.112

POCD, Postoperative Cognitive Dysfunction; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; MMSE, Mini-Mental State Examination; CI: Confidence Interval; OR, Odds Ratio. **P* value <0.05.

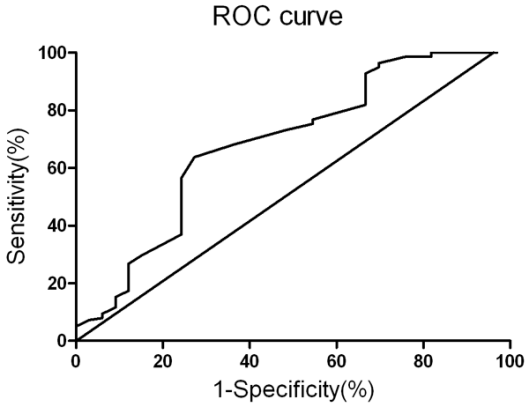

Figure 1. Predicative value of S100B protein for POCD by receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) of S100B protein for POCD was 0.685, with 95% CI of 0.576-0.795, the sensitivity of 62.77% and specificity of 72.73% respectively (P<0.001).

ability associated with advanced age is commonly observed in both humans and animal models due to the susceptibility to neuroinflammation. Our results also showed a close relationship between age and POCD. However, the multivariate logistic regression analysis didn't support the predicative value of age for POCD, which were not quite corresponding with previous investigations. The pathogenesis of POCD is considered multifactorial and it still remains unclear until now.

Previous studies have shown that the surgical trauma can influence the magnitude of postoperative inflammation [15]. The studies conducted in aged rats reveal that the performing of partial hepatectomy will result in a cognitive decline [16]. Many studies in aged animals suggest that surgery of greater magnitude would potentially induce more remarkable neuroinflammation and result in significant cognitive deficiency [17].

NSE has been suggested as a valid biochemical marker for postoperative dysfunction [18], however, no solid association was found in our study between baseline NSE levels and POCD. Our results from the multivariate logistic regression analysis suggested that baseline S100B protein expression was an independent risk factor for POCD. ROC curve analysis also demonstrated the significant predicative value of serum S100B for POCD at day 7. Although it still remains controversy, several studies have also demonstrated the close correlation between S100B protein and cognitive dysfunction [19, 20], which is in consistence with our findings.

As a member of the S100 protein family, S100B is mainly expressed by astrocytes [15]. It has been reported that enhanced S100B exerts critical actions in learning capabilities and spatial memory by previous studies conducted in animal models [21]. Data have reported that elevated S100B can upregulate cyclooxygenase-2 expressions through the receptor for advanced glycation end product (RAGE) pathway in microglia [22, 23]. In addition, cyclooxygenase-2 inhibitor can ameliorate the cognitive function in patients with Alzheimer disease by inhibiting neuroinflammation [24]. S100B pro-

tein can also could also promote the activation of nuclear factor-kappa B (NF-κB) pathway by binding to RAGE and up-regulate proinflammatory mediators including IL-1β [25]. In contrast, the IL-1β secretion can also impact the S100B expression through NF-κB pathway modulation [26]. This may be one of the explanations why serum S100B protein can serve as a predicator for POCD in this present study. Investigations have indicated that overexpressed S100B can promote Aβ generation from amyloid precursor protein [27]. In addition, the increased Aβ and amyloid precursor protein after the surgical procedure is closely associated with cognition decline [28]. This may provide a possible involved mechanism supporting the critical role of S100B in predicating POCD.

This study has some limitations. First, this is a relative small single-center cohort with no follow-up design. Moreover, the involved mechanisms why S100B acts as a predicative role for POCD remains unclear. Furthermore, a larger scale study should be designed to compensate for the inadequacies.

Disclosure of conflict of interest

None.

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