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SHORT COMMUNICATION

Early postoperative cognitive dysfunction is associated with higher cortisol levels in aged patients following hip fracture surgery

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Abstract This study aimed to evaluate the relationship between plasma cortisol levels and the occurrence of postoperative cognitive dysfunction (POCD) in aged patients following hip fracture surgery. A total of 175 patients, aged 65 years or older, who were scheduled for hip fracture surgery with spinal anesthesia were enrolled. Perioperative plasma levels of cortisol and neurocognitive tests were determined at 1 day preoperatively and 7 days postoperatively. Seventy-seven patients completed both blood sample collections and neurocognitive tests. POCD occurred in 29.9 % of patients at 7 days postoperatively. POCD patients presented significantly higher cortisol levels compared with non-POCD patients ($P < 0.05$). Furthermore, plasma cortisol levels were negatively correlated with mini-mental state examination (MMSE) scores at 7 days postoperatively ($P < 0.0001$). A specificity of 93 % and a sensitivity of 35 % were identified for the plasma cortisol measurement to discriminate POCD patients from non-POCD patients. The results suggest higher plasma cortisol levels are associated with POCD in aged patients following hip fracture surgery with spinal anesthesia.

Keywords Postoperative cognitive dysfunction · Cortisol · Plasma

Postoperative cognitive dysfunction (POCD) is a major complication, especially following major rather than minor surgery in the elderly [1–3], suggesting the extent of surgical trauma as a pivotal role in the pathogenesis of POCD. Surgical stimuli-induced hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis results in elevated cortisol levels, metabolic changes, and subsequent cognitive impairment [4, 5]. Hip fracture surgery is a common operation in the elderly, yet little is known about the significance of cortisol levels in this frail population with POCD. Therefore, this study aimed to evaluate a possible relationship between the plasma levels of cortisol and POCD occurrence in elderly patients following hip fracture surgery with spinal anesthesia.

This study was approved by the Ethics Committee of Jinling Hospital and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Inclusion criteria included ASA I or II, age 65 years or more, and scheduled for hip fracture surgery with spinal anesthesia. Exclusion criteria included preoperative mini-mental state examination (MMSE) scores <23, drug dependence, alcoholism, chronic glucocorticoid intake, psychiatric or neurological diseases, unwillingness to comply with the study protocol, or inability to understand the language used.

With the standard care, 1.2–1.4 ml 0.75 % bupivacaine diluted with 0.6–0.7 ml distilled water was administered into the spinal space to provide anesthesia. All the patients received postoperative patient-controlled analgesia with tramadol as previously described [2].

Venous blood samples were obtained at 9:00 a.m., and the neurocognitive tests were performed by a trained

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anesthesiologist in a quiet room with the Chinese version of MMSE at 9:30 a.m. on 1 day preoperatively and 7 days postoperatively. After centrifuging at 3,500 *g* for 10 min, the plasma samples were stored at −80 °C for further determination. The plasma cortisol levels were measured by radioimmunology at the Jiancheng Biologic Project Company, Nanjing, China. Cognitive function was assessed as previously described [2]. POCD was defined as a decline of more than 10 % in neuropsychological test results in this study. Thereafter, patients were divided into POCD and non-POCD groups according to whether POCD occurred at 7 days postoperatively.

Statistical analysis was performed by the SPSS Version 16.0 for Windows. Difference in the characteristics of patients with and without POCD was tested by *t* test or the Mann–Whitney test. The data for descriptive variables were analyzed by chi square tests. Bivariate relationship was evaluated by Spearman's correlation analysis. Receiver operating characteristic (ROC) curves were used to determine the optimal cutoff value of plasma cortisol for discriminating POCD patients from non-POCD patients. A $P < 0.05$ was considered to be statistically significant.

This study included 175 consecutive patients from January 2011 to June 2012. Of these, 59 patients withdrew voluntarily, 5 patients received general anesthesia because spinal anesthesia failed, and 34 patients were discharged before completing the cognitive tests at 7 days postoperatively, thus leaving 77 patients who completed the blood sample collection and neurocognitive tests. POCD occurred in 23 patients (29.9 %) at 7 days postoperatively.

There was no difference in age, gender, ASA classification, length of surgery, estimated blood loss, creatinine, alanine aminotransferase, albumin, hemoglobin, leukocytes, glucose, VAS scores, and type of surgery between POCD and non-POCD patients; however, a lower educational level was observed in POCD patients ($P = 0.002$). POCD patients presented higher plasma cortisol levels compared with non-POCD patients at 7 days postoperatively ($P < 0.05$; Fig. 1). Furthermore, plasma cortisol levels exhibited a negative correlation with MMSE scores at 7 days postoperatively ($P < 0.0001$, $r = -0.568$; Fig. 2). After setting the threshold of 232.5 ng/ml using ROC analysis, a specificity of 93 % and a sensitivity of 35 % were identified for the plasma cortisol measurement to discriminate POCD patients from non-POCD patients.

The reported prevalence of POCD varies widely in the literature [1]. One reason for this discrepancy might be different diagnosis criteria of POCD among studies [2]. The incidence of POCD observed in this study was comparable to a previous study showing a POCD incidence of 25.8 % at 1 week and 9.9 % at 3 months postoperatively in patients older than 60 years after major noncardiac surgery [1]. Although the pathogenesis of POCD remain unclear,

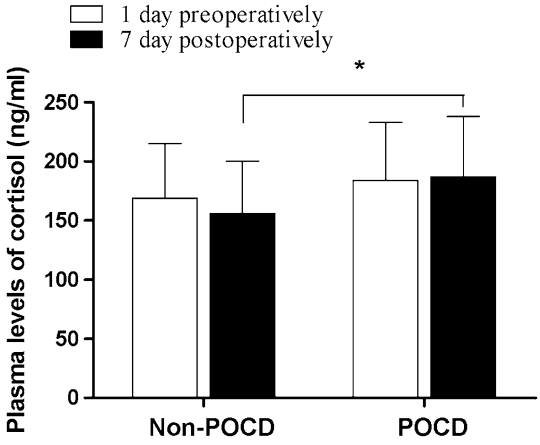

Fig. 1 Plasma levels of cortisol at 1 day preoperatively and 7 days postoperatively in postoperative cognitive dysfunction (POCD) and non-POCD patients. *POCD* postoperative cognitive dysfunction, *non-POCD* non-postoperative cognitive dysfunction. *$P < 0.05$ vs. non-POCD patients

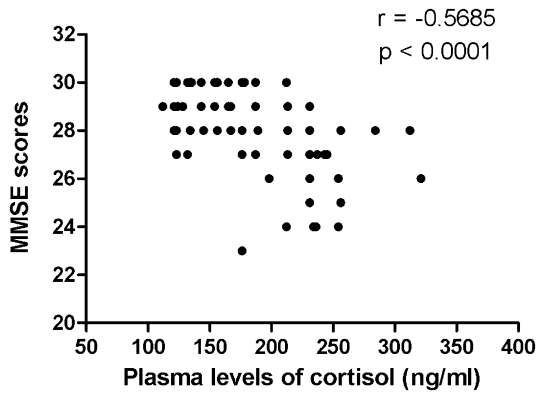

Fig. 2 Correlation between plasma cortisol levels and mini-mental state examination (MMSE) scores using Spearman's correlation analysis. Plasma cortisol levels exhibited a negative correlation with MMSE scores at 7 days postoperatively ($r = -0.569$, $P < 0.0001$)

risk factors such as older age, fewer years of education, prolonged duration of surgery, respiratory complications, and second operation have been identified [3]. In this study, we also demonstrated that POCD was associated with lower education levels.

Surgical trauma can result in increased levels of inflammatory cytokines in the peripheral and central nervous system and thus impair cognitive function [4]. In addition to inflammation, cortisol also increases after a stress reaction, which causes detrimental effects on the brain and is associated with many psychiatric diseases [5]. This realization was supported by the finding that hyperactivity of the HPA axis with higher cortisol levels is involved in the pathophysiology of delirium [5]. Although POCD and delirium are two different entities, they are often reported as part of the same continuum, with delirium

being transient, developing acutely, whereas POCD is long lasting and appears more subtle. Saczynski and collegues [6] have demonstrated that delirium is associated with a significant cognition decline during the first year after cardiac surgery. In this regard, delirium and POCD seem to share the same predisposing factors and pathophysiology mechanisms.

In this study, baseline plasma cortisol levels were similar in POCD and non-POCD groups, whereas plasma cortisol levels were higher in POCD patients compared with non-POCD patients at 7 days postoperatively. Moreover, the elevated plasma cortisol levels exhibited a negative correlation with the severity of postoperative cognitive function as assessed by the MMSE scores. The significant difference in plasma cortisol levels between patients with POCD and non-POCD suggests that plasma cortisol levels may have diagnostic value although the cutoff value only yields 93 % specificity and 35 % sensitivity in discriminating POCD and non-POCD.

In addition, it has been suggested that older patients presented higher cortisol levels after stress [4]. However, this confounding factor could be excluded in this study, because age was comparable between POCD and non-POCD patients. Moreover, postoperative medication as a reason for cognitive function was inconsequential in this study because all patients received the same analgesics.

However, some limitations should be considered in this study. First, this study has a relatively small sample size and short duration of follow-up. Second, POCD is a consequence of neuropathological processes in the brain and can be reflected in the cerebrospinal fluid. Therefore, assay of cerebrospinal fluid cortisol may illustrate results better than plasma measurement of the cortisol levels. Third, we did not detect serotonin and melatonin levels, which may be more closely related to cognitive function. In our future work, we will try to address these issues. Finally, as we did not perform multivariate analysis to assess risk factors for POCD, we therefore cannot exclude confounding factors such as age in the present study.

In summary, our findings suggest an association between higher plasma cortisol levels and POCD in aged patients following hip fracture surgery with spinal anesthesia. However, the value of cortisol as a diagnostic biomarker requires further evidence.

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Conflict of interest The authors have no potential conflicts of interest to disclose.

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