CRITICAL CARE

COMMENTARY

Is cortisol the key to the pathogenesis of delirium after coronary artery bypass graft surgery?

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See related research by Mu *et al.*, http://ccforum.com/content/14/6/R238

Abstract

Postoperative delirium is a serious complication of cardiac surgery. However, the pathophysiology of this mental syndrome is largely unknown. Recent findings suggest an association between elevated level of cortisol and postoperative delirium. Further studies should investigate the mechanisms responsible for excessive perioperative cortisol secretion.

More than 40 years after the first successful coronary artery bypass graft (CABG) surgery was performed, Chinese scientists report the association between high serum cortisol level and delirium, the latter of which is a serious complication of CABG [1]. Prior to 2010, the only study linking higher plasma cortisol and delirium after major surgery was published in 1985 [2]. New findings by Mu and colleagues [1], published in the previous issue of *Critical Care*, support the thesis that high serum cortisol level may play a significant role in the pathophysiology of early postoperative delirium.

Available studies revealed that postoperative delirium was associated with significant increases in patient mortality [3]. Furthermore, this neuropsychiatric complication of surgical procedures results in higher risks of sepsis, respiratory failure, sternum instability, and re-operation [4,5]. For these reasons, predictors of delirium following cardiac surgery have been intensively investigated, but very recent state-of-the-art studies have brought results that are more consistent (Table 1) [4,6,7]. However, the study by Mu and colleagues aimed to identify the mechanisms underlying factors associated with higher risk of delirium.

The authors hypothesize that the occurrence of postoperative delirium in patients undergoing CABG is associated with stress response and, therefore, with the elevated circulating cortisol level. Indeed, although cortisol is crucial for coping with stress, its excessive and prolonged secretion due to severe, acute stress (that is, major surgery) may contribute to delirium. As mentioned by the authors, high levels of circulating glucocorticoids might have harmful effects on hippocampal activity and thus can cause inattention and cognitive deficits [8]. Moreover, according to experimental studies, hippocampus plays an important role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and, as a result, in cortisol secretion. An increased level of cortisol may also be secondary to the dysregulation of the HPA axis in conditions such as depression, dementia, and aging, which are strong predictors of delirium after cardiac surgery (Table 1). Unfortunately, this study did not determine whether an increased level of cortisol is exclusively stress-related or induced by other factors, since screening tests for preoperative depression and cognitive impairment were not performed. The potential confounders like depression, dementia, or impaired executive functioning of the patients were not assessed or excluded from the study and therefore could interfere with the final results of the study. On the other hand, it has to be noticed that none of the available studies regarding higher cortisol level and delirium after major surgery entered psychiatric variables into the analysis.

Hypoxia and perioperative cortical hypoperfusion have been established recently as predictors of postoperative delirium and cognitive deficits [6,9] (Table 1). Moreover, in previous studies, an association between the duration of carotid artery cross-clamping and increased cortisol level was observed, suggesting a positive correlation between cerebral hypoperfusion and excessive cortisol secretion [10]. This interesting issue should be the subject of future investigation. It is worthwhile noticing that preoperative anxiety disorders, like post-traumatic stress disorder, were not associated with postoperative delirium in any of the previous studies [3], although surgery-related stress is postulated as contributing to delirium in the article by Mu and colleagues and in other articles. The putative explanation of this observation is that

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Table 1. Selected independent risk factors of delirium after cardiac surgery according to existing studies [4,6,7]

Factors related to mental state	Factors related to physical condition	Factors related to anesthetic and surgical procedures
Major depression[a]	Atrial fibrillation[a]	Prolonged intubation[b]
Cognitive impairment[a] (MMSE score of less than 25)	Anemia[a]	Valvular surgery[c]
Dementia[a]	Hypoalbuminemia[a]	Extracorporeal circulation[c]
Disturbed executive functions[a]	Peripheral vascular disease[a]	
	Hypoxia[b]	

[a]Preoperative factors; [b]postoperative factors; [c]less well-documented factors. MMSE, mini-mental state examination.

chronic stress, contrary to acute trauma, is associated with hypocortisolism that is due to hypothalamic supersensitivity to glucocorticoids [11]. Thus, the deleterious effect of increased cortisol plasma concentration is avoided. Recently, Plaschke and colleagues [12] reported that, besides cortisol, an increased level of interleukin-6 is associated with delirium among individuals after open-heart surgery. However, that study was conducted in a smaller (n = 114) and more heterogeneous population (patients referred for different types of cardiac surgery). Several studies suggest the association between delirium and the apolipoprotein E4 allele in older patients, but the results are inconsistent and depend on the methodology used by the researchers [13]. Moreover, variations in the *SLC6A3* gene and possibly the *DRD2* gene were found to provide protection from delirium in a mixed population of surgery and non-surgery patients [14].

The baseline concentration of plasma cortisol was not measured in the study by Mu and colleagues or in the two other studies investigating the association between high cortisol level and postoperative delirium [12,15]. This limitation prevented Mu and colleagues from drawing a more detailed conclusion regarding the causative role of cortisol in delirium development. Still, it should be noted that their study was well designed and was conducted in a large and homogenous population. The novel and reasonable endeavor was the use of Richmond Agitation Sedation Scale to detect deeply sedated or unarousable subjects before the final assessment of delirium was performed.

An elevated level of cortisol seems to play an important role in the pathophysiology of delirium after CABG. However, the mechanisms responsible for excessive perioperative cortisol secretion are unclear. Future studies should investigate these mechanisms and the role of factors such as cerebral hypoperfusion, gene polymorphism, and cytokines.

Abbreviations

CABG, coronary artery bypass graft; HPA, hypothalamic-pituitary-adrenal.

Competing interests

The authors declare that they have no competing interests.

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