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EDITORIAL

Serum biomarkers of brain injury: S100B protein, cognitive dysfunction, and major non-cardiac surgery

Biomarcadores séricos de lesão cerebral: proteína S100B, disfunção cognitiva e cirurgia não cardíaca de grande porte

Short- and long-term cognitive decline are adverse outcomes after major surgery associated with an increased risk for mortality and morbidity.[1] Cognitive dysfunction related to surgery, namely Postoperative Cognitive Dysfunction (POCD), is highly prevalent in humans, affecting more than 50% of patients submitted to cardiac surgery at hospital discharge and approximately 40% at five years after surgery.[2] POCD is a common situation that may occur after any sort of surgery and defined by a reduction in cognitive performance on a set of neuropsychological tests before and after anesthesia and surgery.[3] Notably, POCD may compromise a wide range of cognitive functions, including working and long-term memory, information processing, attention and cognitive flexibility, consequently affecting quality of life.[4] Although the pathogenesis of cognitive decline after surgery is not completely understood, there is growing evidence on experimental and translational research pointing to a critical role for neuroinflammation as a relevant mechanism underlying this condition.[5]

Inflammation of the Central Nervous System (CNS) may trigger neural cell dysfunction or death, leading to increased blood concentrations of biochemical markers of brain injury.[6] More recently, several serum biochemical markers of brain injury have been investigated both in animals and humans, especially the S100B protein.[6–13] S100B is an acidic calcium-binding protein mostly found in astrocytes and Schwann cells.[14,15] After CNS damage, glial cells may be activated, and S100B is released into blood circulation. Increased serum concentrations of S100B may reflect either glial damage or reactive astrogliosis, events that could be related to beneficial or detrimental effects.[9] Notably, serum concentrations of S100B protein may be increased following cardiac and non-cardiac surgery.[6–10] Altogether these findings point to the S100B protein as a potential serum biochemical marker of CNS injury.

In this issue of the *Brazilian Journal of Anesthesiology*, an interesting study provides new insights into the association between Postoperative Cognitive Dysfunction (POCD) and increased serum concentrations of S100B protein in patients undergoing Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP).[16] In this study, authors enrolled 82 consecutive patients undergoing RALRP and determined the serum concentrations of S100B protein preoperatively, after anesthesia induction, and at 30 minutes and 24 hours postoperatively. Additionally, authors applied a neuropsychological test battery in order to evaluate the cognitive function preoperatively, and at 7 days and 3 months postoperatively. Approximately 30% of patients displayed POCD 7 days postoperatively, and around 10% at 3 months after surgery. Serum S100B protein concentrations were significantly increased 30 minutes and 24 hours after surgery in patients displaying POCD. Interestingly, this study has demonstrated that the length of anesthesia was also significantly longer in patients displaying POCD up to 3 months after surgery compared with those without POCD, and a similar finding was observed for the duration of Trendelenburg position in patients undergoing RALRP. Hence, authors concluded that S100B protein serum levels were increased after RALRP, a finding strongly associated with POCD development in this population.[16]

Surgery and anesthesia can induce a strong systemic inflammatory response and activation of the immune system.[5,17] Local inflammation related to surgical trauma is paralleled by an increase in systemic inflammatory mediators.[17] Several of these compounds cause inflamma-

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tory processes in the CNS, leading to the activation of glial cells and immune response in the brain.[6] When excessive CNS inflammation occurs, cytokine release can cause dysfunction of synaptic connections, neural toxicity, and cognitive dysfunction.[17] There is considerable evidence indicating that an inflammatory response may be involved in the occurrence of POCD.[5,18] Considering that neuroinflammation has been associated with cognitive impairment, we may hypothesize that this mechanism is underlying POCD. Consequently, the quantification of serum levels of S100B protein and other biochemical markers of CNS damage may potentially identify patients displaying surgery- and/or anesthesia-related cognitive dysfunction.

In the past few years, the widespread use of robotic-assisted surgery has revolutionized the traditional laparoscopic urology. Although there is a remarkable success of the technique due to the increase in number of cases being performed every year, the debate about the benefits and risks of robotic prostatectomy is still ongoing.[19] In order to perform the procedure, the patient must be placed in a steep Trendelenburg position, in some cases for an extended period of time. Additionally, the insufflation of CO_2 to generate pneumoperitoneum increases the intracranial pressure (ICP)[19] and the anesthesiologist should be vigilant when placing patients in those conditions for an extended period of time. Fortunately, there is previous evidence indicating that cerebral oxygenation and cerebral perfusion pressure are maintained above normal levels in patients undergoing RALRP.[19]

In their manuscript, Ozturk et al.[16] have performed some interesting insights into the potential risks of RALRP. The combination of pneumoperitoneum along with the steep Trendelenburg position during RALRP may affect cerebrovascular, respiratory, and hemodynamic parameters. Consequently, authors claim that an association between POCD and markers of CNS injury in patients undergoing RALRP is not surprising. The development of POCD after RALRP may be due to a combination of several factors, including patient positioning and procedure duration, increased ICP, advanced age, duration of surgery, and anesthesia. Therefore, strategies designed to minimize the effects of those factors should be considered and attempted by anesthesiologists. These strategies may include advanced neurological and hemodynamic monitoring during surgery, aiming a close control and maintenance of regional cerebral oxygenation, cardiovascular and pulmonary parameters within physiological limits.

Besides the incidence of POCD after RALRP, Ozturk et al.[16] performed a robust statistical analysis on the potential application of serum S100B protein as a marker of brain injury and POCD in this population. Their findings corroborated previous research, demonstrating that S100B can accurately predict POCD following cardiac and non-cardiac surgery.[20] In fact, authors observed a five-fold increase in S100B protein 30 minutes after surgery in patients displaying POCD. Although some reports indicate that the elevation of S100B levels is somewhat short-lived with peak serum concentrates occurring in the first minutes to hours after surgery,[14] Ozturk et al.[16] found that serum S100B levels were still increased up to 24 hours following RALRP. Notably, authors performed Receiver Operating Characteristic (ROC) curve analysis, addressing some potential cut-off or thresholds values for S100B as a predictor of POCD. In summary, authors showed that a cut-off value of 1.35 $ng.mL^{-1}$ for S100B at 30 minutes after surgery had sensitivity of 94.4% and specificity of 86.4% in the prediction of POCD on day 7. A cut-off value of 1.55 $ng.mL^{-1}$ for S100B at 30 minutes after surgery had sensitivity and specificity of 85.7% and 87.3%, respectively, for POCD at 3 months.

The present study certainly displays some relevant limitations, including some controversy related to the criteria for POCD diagnosis and cognitive function assessment up to 3 months, a relatively short-term follow-up in POCD studies. However, this interesting study added new insights into the growing evidence regarding S100B as a marker of CNS damage and its accuracy to detect POCD following cardiac and non-cardiac surgery. Notably, authors demonstrated that the serum concentration of S100B protein could also be used as a biochemical marker of POCD in patients undergoing robotic surgery. Despite many studies investigating the role of S100B as a biomarker of brain injury or CNS dysfunction, some controversy about its regular application into the clinical practice still remains. Importantly, early recognition of patients who are at increased risk for POCD is pivotal for a timely intervention to minimize CNS damage both during and after surgery. Therefore, future studies and guidelines should focus on a better definition of the S100B protein concentration cut-off points for different clinical scenarios in order to implement evidence-based recommendations on its use into the surgical setting.

Conflicts of interest

The authors declare no conflicts of interest.

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