Göteborg, 2020

Neurochemical and cognitive aftermaths of surgery

Studies on short- and long-term effects of surgery and anesthesia

Akademisk avhandling

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av Mattias Danielson

Fakultetsopponent:
Professor Jonas Åkeson
Avd. för anestesiologi och intensivvård, Lunds Universitet

Avhandlingen baseras på följande delarbeten

I. Danielson M, Wiklund A, Granath F, Blennow K, Mkrtchian S, Nellgard B, Oras J, Jonsson Fagerlund M, Granstrom A, Schening A, Rasmussen LS, Erlandsson Harris H, Zetterberg H, Ricksten SE, Eriksson LI. *Neuroinflammatory markers associate with cognitive decline after major surgery: Findings of an explorative study.* Ann Neurol. 2020 Mar;87(3):370-382.

II. Danielson M, Wiklund A, Granath F, Blennow K, Mkrtchian S, Nellgard B, Oras J, Jonsson Fagerlund M, Granstrom A, Schening A, Rasmussen LS, Erlandsson Harris H, Zetterberg H, Ricksten SE, Eriksson LI. *The association between cerebrospinal fluid biomarkers of neuronal injury or brain amyloidosis and cognitive decline after major surgery.* Accepted for publication, Br J Anaesth 2020

III. Danielson M, Reinsfelt B, Westerlind A, Zetterberg H, Blennow K, Ricksten, SE. *Effects of methylprednisolone on blood-brain barrier and cerebral inflammation in cardiac surgery-a randomized trial.* J Neuroinflammation. 2018;15:283

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

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Mattias Danielson, Avdelningen för anestesiologi och intensivvård, Institutionen för kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige

Abstract

Background: Each year, around the world, more than 230 million patients have surgery. Improvements in healthcare have resulted in older and sicker patients undergoing surgical interventions. As a result, surgical safety has become a global public-health concern. Cognitive impairment has emerged as the most common postoperative complication in these older individuals. The etiology of this condition is unknown, although episodes of hypooxygenation/hypoperfusion, negative impacts of anesthetic drugs, cerebral microemboli from cardiopulmonary bypass, and neuroinflammation have been implicated.
Aims: To explore the mechanisms behind this postoperative cognitive dysfunction, we focused on the impacts of surgery on: 1) blood-brain barrier (BBB) function; 2) changes in the levels of systemic and neuroinflammatory biomarkers; and 3) biochemical evidence of perioperative neuronal damage. We also evaluated whether an unfavorable late neurocognitive postoperative outcome was associated with an enhanced neuroinflammatory response or cerebral biomarker evidence of neuronal injury. Finally, we investigated whether a single perioperative dose of methylprednisolone attenuates the postoperative BBB dysfunction and prevents neuroinflammation after cardiac surgery.
Methods: We conducted a prospective, observational, two-center study with patients who were undergoing elective major orthopedic surgery. Cognitive function was evaluated preoperatively, at discharge, and at 3 months postoperatively. Biochemical markers of inflammation, neuronal damage, brain amyloidosis, and BBB function were measured in cerebrospinal fluid (CSF) and blood samples during the initial 48 hours postoperatively. Furthermore, in a prospective, randomized, double-blinded, double-armed study, 30 patients who were undergoing elective open heart surgery were randomized to a single dose of either methylprednisolone or placebo. CSF and blood samples obtained preoperatively and at 24 hours after surgery were analyzed for biochemical markers of inflammation, neuronal damage, and BBB function.
Results: Disruption of BBB function, manifested as an increased CSF to serum albumin quotient, was detected after both cardiac and orthopedic surgeries. Both orthopedic and cardiac surgeries were associated with a pronounced increase in inflammatory biomarkers in the CSF and blood. The CSF inflammatory biomarkers were significantly associated with long-term cognitive decline 3 months after orthopedic surgery. Surgery resulted in increased levels of biomarkers of neuronal damage and brain amyloidosis in the CSF and blood, although there was no association between these biomarkers and postoperative cognitive decline. None of preoperative biomarkers were predictive of postoperative cognitive decline. Methylprednisolone attenuated the systemic inflammatory reaction but not the BBB dysfunction that followed cardiac surgery.
Conclusions: Surgery induces a profound systemic inflammatory reaction, followed by disruption of the BBB. Single-dose treatment with a potent corticosteroid did not attenuate the BBB disruption. The postoperative neuroinflammatory reaction, assessed as biomarker levels in the CSF, is significantly associated with long-term cognitive decline, whereas the increased postoperative markers of neuronal damage showed no such association

Keywords: Anesthesia, blood-brain barrier, brain amyloidosis, cardiac surgery, orthopedic surgery, inflammation, neuroinflammation, neuronal damage, cognitive decline, postoperative cognitive dysfunction

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