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Clinical Research

Cardiopulmonary Bypass Increases Plasma Glial Fibrillary Acidic Protein Only in First Stage Palliation of Hypoplastic Left Heart Syndrome

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ABSTRACT

Background: Univentricular congenital heart defects require open-heart surgery soon after birth, and are associated with risk of brain injury and poor neurologic outcome.

Methods: This is a prospective, observational study on children undergoing cardiac surgery. Plasma glial fibrillary acidic protein (GFAP), as an early marker of brain injury, was measured by ELISA at the end of anaesthesia induction, initiation of cardiopulmonary bypass (CPB), the end of cooling, the end of rewarming, the end of CPB, and after protamine administration. We recorded clinical and surgical parameters to assess which CPB phase and clinical parameters were associated with a GFAP increase.

Results: We studied 13 children less than 50 months of age: 8 underwent Norwood or Damus-Kaye-Stansel palliation (group 1) and 5 underwent Fontan procedure (group 2). A GFAP increase was only observed in group 1, with the highest median value at the end of rewarming. No quantifiable levels of GFAP were measured at pre-bypass and the start of CPB stages in all patients. End of cooling

RÉSUMÉ

Introduction : Les malformations cardiaques congénitales univentriculaires nécessitent une intervention chirurgicale à cœur ouvert peu après la naissance, et sont associées à un risque de lésions cérébrales et à un mauvais pronostic neurologique.

Méthodes : Ceci est une étude observationnelle prospective sur les enfants subissant une chirurgie cardiaque. La protéine acide fibrillaire gliale (PAFG), en tant que marqueur précoce d'une lésion cérébrale, a été mesurée par ELISA à la fin de l'induction d'une anesthésie, à l'initiation de la circulation extracorporelle (CEC), à la fin du refroidissement, à la fin du réchauffement, à la fin de la CEC et après l'administration de protamine. Nous avons enregistré les paramètres cliniques et chirurgicaux pour évaluer quelle phase de la CEC et quels paramètres cliniques étaient associés avec une augmentation de la PAFG.

Résultats : Nous avons étudié le cas de 13 enfants âgés de moins de 50 mois : 8 ont subi une chirurgie palliative de Norwood ou Damus-

Congenital heart defects (CHDs) affect nearly 1% of all births, and approximately 25% of patients have a critical CHD that needs a surgical intervention in the first year of life.[1,2] Cardiac anomalies with univentricular heart physiology, such as hypoplastic left heart syndrome, are among the most critical CHDs, and early surgery is the only way to grant survival, restoring blood oxygenation and hemodynamic balance between pulmonary and systemic flows.[3] Improved surgical techniques[4] and postoperative care in the last few decades have increased survival after surgery for CHDs, with an overall estimate of 3% early mortality.[5,6]

In this scenario, neurologic complications have emerged as a key issue in the long-term quality of life of children undergoing CHD surgery during infancy. Nearly 50% of children who had undergone surgery for a complex CHD requiring aortic cross-clamping or deep hypothermic circulatory arrest (DHCA) may show neurocognitive deficits at the

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and CPB-end GFAP, GFAP maximum value, and GFAP area under the curve all correlated with the CPB time spent at a cerebral regional saturation < 45% ($P = 0.021$, 0.028, 0.007, 0.021, respectively).
Conclusions: Children with univentricular heart defects exhibit a CPB plasma-GFAP increase only after stage 1 palliation. The maximum GFAP increase occurred at the end of rewarming. Further studies are needed to identify which clinical or surgical parameter(s) could reflect a GFAP increase during surgery for congenital heart defects, and whether GFAP levels correlate with the neurologic outcome.

Kaye-Stansel (groupe 1) et 5 ont subi une intervention de Fontan (groupe 2). Une augmentation de la PAFG a été observée uniquement dans le groupe 1, avec une valeur médiane la plus élevée lors de la fin du réchauffement. Aucun niveau quantifiable de PAFG n'a été mesuré avant dérivation et au début des étapes de la CEC pour tous les patients. La PAFG en fin de refroidissement et en fin de CEC, la valeur maximale de PAFG, et l'aire de PAFG sous la courbe sont toutes en corrélation avec le temps de CEC passé à une saturation cérébrale régionale <45 % ($P = 0,021$, 0,028, 0,007, 0,021, respectivement).
Conclusions : Les enfants atteints de malformations cardiaques univentriculaires présentent une augmentation de la PAFG plasmatique lors de la CEC seulement après l'étape 1 de la chirurgie palliative. L'augmentation maximale de la PAFG a eu lieu à la fin du réchauffement. D'autres études sont nécessaires pour déterminer quel(s) paramètre(s) clinique ou chirurgical pourrait refléter une augmentation de la PAFG pendant la chirurgie pour des malformations cardiaques congénitales, et si les niveaux de PAFG corrèlent avec l'évolution neurologique.

beginning of school age.[7] Several factors may contribute to these deficits, including prenatal lesions or technical issues during CHD surgery.[8]

Cerebral injury biomarkers[8-14] seem to be a promising tool to identify ongoing brain damage during or closely after surgery and thus may effectively act to prevent further exacerbation of central nervous system insults. The glial fibrillary acidic protein (GFAP) is the principal intermediate filament in mature astrocytes. GFAP seems to fully fit the requirements of specificity, readiness of release, and ease of assaying required by a diagnostic brain injury neuromarker; in fact, GFAP can be measured in the peripheral blood and quantified proportionally to the degree of the injury.[11,15]

In this study, we evaluated GFAP plasmatic level variations during the different phases of cardiopulmonary bypass (CPB) in a small selected group of patients with univentricular congenital heart defects undergoing surgery. The GFAP rise was correlated with time-correspondent clinical parameters to asses if readily measurable biological changes or specific surgery phases could be related to the increase of the GFAP plasmatic level.

Patients and Methods

Patients

This is a prospective, observational clinical study in children with univentricular congenital heart defects undergoing different stages of palliation. The study was approved by the local Institutional Review Board and Ethic Committee (Padova University Hospital). Inclusion criteria were as follows: children with complex univentricular heart defects; elective cardiac surgery (patient on spontaneous breath before cardiac surgery); CPB time > 60 minutes (with aortic cross-clamp > 20 minutes, when performed); hypothermia during CPB; stable hemodynamic conditions with constant inotropic support and constant volume loading for at least 3 hours before the study; and written informed consent. Exclusion criteria were as follows: age > 5 years; liver damage, factor V < 20% before surgery; kidney failure, with creatinine clearance < 30% before surgery; and preoperative diagnosis of chromosomal abnormalities (ie, Down or Di George syndromes).

According to the surgical procedure performed, patients could undergo aortic cross-clamp, DHCA, or selective regional cerebral perfusion. Neurologic risk time interval (NRTI) was defined as the period of time in which the patient was exposed at high risk of neurologic injury, that is, the time spent by the patient in selective regional cerebral perfusion plus the time of DHCA, whenever performed.

Patients were divided into 2 groups: patients who underwent an NRTI during surgery (group 1) and patients who did not require an NRTI during surgery (group 2).

Surgery and samples collection

After the induction of anaesthesia (fentanyl 5 μg/kg, thiopental 3 mg/kg or midazolam 0.2 mg/kg, and vecuronium bromide 0.1 mg/kg), infants were intubated and a central venous catheter was placed. General anaesthesia was obtained with fentanyl 50 μg/kg, cisatracurium besylate 3 mg/kg, and midazolam 3 mg/kg, infused at 1 mL/h or 2 mL/h, based on patient body weight (less or greater than 5 kg, respectively). After heparin 300 U/kg administration (activated clotting time [ACT] target = 480 s), arterial and venous cannulation were performed and CPB was initiated. Hematic prime was used to maintain hematocrit between 25% and 30%. Temperature was monitored with nasopharyngeal and rectal probes. Hypothermia during CPB was defined as mild (35°C-30.1°C), moderate (30°C-25.1°C), and deep (25°C-15.1°C).[16] Whenever required, hematic cardioplegia, aortic cross-clamp, and DHCA or selective regional cerebral perfusion were used; adequate CPB flows were calculated based on body surface area, cardiac index, and minimal body temperature reached. Surgical procedures were performed according to univentricular heart defects palliation techniques (Norwood-like palliation, bidirectional cavopulmonary anastomosis, or Fontan completion-extracardiac conduit).

Mixed venous saturation (SvO_2) was recorded every 5 minutes with CDI Blood Parameter Monitoring System 500 (Terumo, Tokyo, Japan). Transcranial cerebral regional oxygen saturation (rO_2) was measured with near infrared