Changes in NSE and S-100β during the perioperative period and effects on brain injury in infants with biliary atresia undergoing parent liver transplantation

**CURRENT STATUS:** POSTED

Hongli Yu  
Tianjin First Center Hospital

Wenli Yu  
Tianjin First Center Hospital

✉️ yuhongli1126@foxmail.com **Corresponding Author**

Min Zhu  
Tianjin First Center Hospital

Guicheng Zhang  
Tianjin First Center Hospital

Yiwei Shi  
Tianjin First Center Hospital

Ying Sun  
Tianjin First Center Hospital

**DOI:**  
10.21203/rs.2.21831/v1

**SUBJECT AREAS**  
Pediatrics

**KEYWORDS**  
*S100 calcium-binding protein β, neuron-specific enolase, liver transplantation, infant, brain injury, child development*
Abstract
Background: The S100 calcium-binding protein β (S-100β) and the neuron-specific enolase (NSE) can reflect brain injury, the value of the perioperative changes in S-100β and NSE levels in children with end-stage liver disease (ESLD) undergoing parent liver transplantation is unknown. This was to investigate the effects of parent liver transplantation on the changes of serum NSE and S-100β during the perioperative period, on brain injury, and on postoperative cognitive function.

Methods: This was a prospective observational study of infants with congenital biliary atresia who had to undergo selective liver transplantation in 2017 at Tianjin First Central Hospital. Blood samples were drawn before skin incision (T1), 30 min after anhepatic phase (T2), 1 h of neohepatic phase (T3), and 24 h after hepato-reperfusion (T4). S-100β and NSE were measured by ELISA. Children were assessed using the Bayley Scale of Infant Development (BSID) 1 day before and 3 months after surgery. The pediatric anesthesia emergence delirium (PAED) was used at 0.5, 2, and 4 h after extubation.

Results: Compared with T1, serum NSE and S100β were increased at T2, T3, and T4. Compared with T1, serum S-100β and NSE increased at T2 and peaked at T3 (all P<0.05). S-100β and NSE decreased at T4 (both P<0.05). Compared with 1 day before surgery, MDI and PDI were decreased at 3 months after surgery (MDI: from 87.7±8.4 to 84.5±8.5, P=0.015; PDI: from 82.9±8.7 to 79.6±8.8, P=0.016).

Conclusion: Liver transplantation causes a certain degree of brain injury in children, as revealed by serum NSE and S100β levels.

Background
End-stage liver disease (ESLD) is due to hepatic injury that led to an irreversible loss of liver function, change in architecture, and change in blood supply. The presenting symptoms vary widely from impaired synthesis of blood proteins to the loss of glucose or ammonia control and impaired bile acid production [1]. The incidence of ESLD in the pediatric population is low, but the condition is severe and requires tertiary care [1, 2]. Biliary atresia is the most common cause of pediatric ESLD (43.4%), followed by fulminant liver failure (15.0%), cirrhosis (9.1%), and metabolic diseases (8.0%) [3]. Liver transplant is the only curative treatment in many cases [4].

Parent liver transplantation has become the most effective treatment for children with ESLD [5], with
a postoperative five-year survival rate of 70–90% [6, 7]. Although great progress has been made regarding the procedure, perioperative injuries to vital organs such as heart, kidney, and brain still occur. The incidence of neurological complications can be as high as 46%, which severely affects the postoperative survival rate and quality of life [8]. The best operation timing of pediatric liver transplantation coincides with the peak time of cerebral development in children [9, 10]. Therefore, pediatric patients undergoing transplantation during this period are at high risk of neurological complications, imposing challenges to the anesthesiologist for the protection of the nervous system function or reducing neurological damage in the perioperative period.

Currently, the anesthetic drugs and surgical trauma have the potential to cause the death of neurons in development, leading to long-term injury to nerve function [11–14]. The S100 calcium-binding protein β (S-100β) is expressed by astrocytes, and the neuron-specific enolase (NSE) is expressed by ganglia cells [15, 16]. S-100β is secreted by astrocytes and can spill into circulation by injured astrocytes. Blood levels of S-100β increase during the acute phase of brain damage [17–19]. In the same manner, leakage of NSE into circulation indicates injured ganglia cells [20, 21]. A meta-analysis revealed that NSE had a moderate predictive value for brain injury in children [22]. High postoperative levels of S-100β and NSE are well known to be associated with brain injury in children who underwent major surgeries [23, 24], but the value of the perioperative changes in S-100β and NSE levels in children with ESLD undergoing parent liver transplantation is unknown.

Therefore, the present study investigated the effects of parent liver transplantation on the changes of serum NSE and S-100β during the perioperative period, on brain injury, and on postoperative cognitive function. The results could help improve the perioperative management of those children.

Methods

Study design and patients

This was a prospective study of infants with congenital biliary atresia who had to undergo selective liver transplantation from January to December 2017 at Tianjin First Central Hospital. This study was approved by the Medical Ethics Committee of the hospital (#2016N0039KY) and written informed consent was obtained from the infants’ guardians. The privacy rights of human subjects always be
observed. This study was registered at ClinicalTrials.gov (#NCT03024840).

The inclusion criteria were: 1) 4-12 months of age; 2) American Society of Anesthesiologists (ASA) physical status III or IV; and 3) scheduled to undergo elective pediatric living related donor liver transplantation. The exclusion criteria were: 1) known or suspected allergy to propofol, soy, or egg; 2) congenital heart disease, or impairment of renal or pulmonary function before liver transplantation; or 3) compound other site operation. All living donors were family members (father or mother). Every case of transplantation has passed ethical review and approval from Tianjin First Center Hospital.

**Anesthesia and intraoperative management**

All infants underwent combined intravenous and inhalation anesthesia. Preoperatively, routine fasting was performed (formula and milk were banned for 6 h before surgery; breast milk was not allowed for 4 h before surgery, and drinking was banned for 2 h before surgery). Atropine (0.01 mg/kg) was intramuscularly injected 30 min before anesthesia. After being transferred to the operating room, routine monitoring of pulse oxygen saturation (SpO₂) and electrocardiogram (ECG) was conducted. Peripheral venous access was opened. Rapid induction of anesthesia was performed using: methylprednisolone at 1 mg/kg, midazolam at 0.05 mg/kg, etomidate at 0.2 mg/kg, fentanyl at 2 µg/kg, and vecuronium bromide at 0.08 mg/kg. Auscultation of both lungs was performed after oral tracheal intubation to ensure clear breath sounds of both lungs. The ventilator was connected to mechanical ventilation to observe the normal waveform of the end-tidal carbon dioxide (PETCO₂).

Fraction of inspiration oxygen was 50%-60% (100% at the anhepatic phase), tidal volume was 8-10 ml/kg, respiratory rate was 20-26 breaths/min, and the inspiration and expiration ratio was 1.0:1.5-2.0. PETCO₂ partial pressure of 30-35 mmHg and airway pressure of 18-25 cmH₂O (1 cm H₂O=0.098 kPa) were maintained. After anesthesia induction was stable, the bispectral index (BIS) values were monitored. B-mode ultrasound-guided radial artery catheterization for invasive blood pressure monitoring and placement of triple-lumen central venous catheter through the right internal jugular vein for monitoring of central venous pressure (CVP) and intraoperative infusion were performed. Anesthesia maintenance was done using: continuous intravenous infusion of 1% propofol at 9-15
mg/kg/h, remifentanil at 0.1-0.2 µg/kg/min, and cisatracurium besylate at 0.12 mg/kg/h. Fentanyl at 1-3 µg/kg was added intermittently to maintain the depth of anesthesia. The intraoperative fluid infusion was warmed. Sodium lactate and glucose injection and albumin solution were intravenously infused. Body temperature was maintained at 36.0-37.5°C. According to the results of intraoperative blood gas analysis and coagulation function monitoring, the appropriate amount of concentrated red blood cells and fresh frozen plasma were infused. By adjusting the transfusion speed and continuous intravenous infusion of small doses of dopamine, mean arterial pressure (MAP) of 40-65 mmHg (1 mmHg=0.133 kPa), CVP of 6-8 mmHg, heart rate (HR) of 110-170 beats/min, SpO₂ of 95-100%, body temperature of 35.5-37.5°C, BIS of 40-60, PETCO₂ of 35-45 mmHg, hemoglobin (Hb) >80 g/L, and urine volume >1 ml/kg/h were maintained. According to the results of arterial blood gas analysis, the breathing parameters were adjusted in time. A heating blanket and infusion heating device were used to maintain the body temperature constant.

**Data collection and examination methods**

Central venous blood (1 mL) was collected into coagulation tubes at the beginning of skin incision after anesthesia (T1), 30 min after anhepatic phase (T2), 1 h after neohepatic phase (T3), and 24 h after neohepatic phase (T4). The samples were placed at room temperature for 10 min, centrifuged at 6000 rpm for 10 min, and stored at -80°C.

NSE and S-100β were detected with the use of enzyme-linked immunosorbent assay (ELISA) (Shanghai Biovol Technologies). HR, MAP, CVP, and BIS were recorded at each time point.

Two doctors independently conducted evaluations 1 day before surgery and 3 months after surgery. The Bayley Scales of Infant Development (BSID) is a standardized technique and measurement tool for evaluating the psychomotor behaviors of children aged from 2 months to 3 years [25]. BSID revised by the Hunan Medical University in 1990 was used to assess the psychomotor and behavior development conditions of all infants investigated [26]. According to the raw score, the corresponding mental development index (MDI) and psychomotor development index (PDI) were calculated to analyze the effect of liver transplantation on the neurocognitive behaviors of infants. All examinations
were carried out in a quiet environment. The MDI and PDI are standard scores obtained from conversion table based on the corresponding raw score of age and other values. The average number is 100, and the standard deviation is 16; ≥90 points indicate normal level, and < 90 indicate poor development. The postoperative delirium of infants was independently evaluated by two physicians at 30 min, 2 h, and 4 h after extubation using the pediatric anesthesia emergence delirium (PAED) scale [27].

**Statistical analysis**

Statistical analyses were performed using SPSS 20.0 (IBM, Armonk, NY, USA). Continuous data were tested with the Kolmogorov-Smirnov test and are presented as means ± standard deviation or medians (first and third quartiles), as appropriate; they were analyzed using repeated-measures ANOVA with the post hoc test across different time points. Categorical data are presented as numbers (percentage) and compared with the chi-square test. Pearson correlation was used to analyze the correlations among the NSE and S-100β at T3, PAED score at 30 min, MDI and PDI at 1 month after surgery. P values <0.05 were considered statistically significant.

**Results**

**Characteristics of the transplantations**

Living-related piggyback liver transplantation was performed. The left lateral lobe of the donor liver was used for transplantation, with a graft-to-recipient weight ratio (GRWR) of 0.83%-5.16%. The operation time was 8.2±1.2 h. The anhepatic phase was 45.5±12.4 min. The median warm ischemia time of the donor liver was 95.00 (64.00, 178.00) s. The average cold ischemia time was 160 min. The infusion of red blood cells was 2.00 (2.00, 3.68) U, The infusion of plasma was 400 (210, 400) ml. Details were shown in Table 1.

**Hemodynamic changes during surgery**

The hemodynamic changes in HR, MAP, CVP, and pH were significant during the anhepatic and hepato-reperfusion phases (all P<0.05 at all time points). After the inferior vena cava was blocked, arterial blood pressure and CVP decreased significantly. Arterial blood pressure and CVP gradually recovered during the hepato-reperfusion phase (Table 2).
**NSE and S100β**

Compared with T1, the NSE and S100β levels were increased significantly at T2, T3, and T4 (Table II). Compared with T1, serum S-100β and NSE levels gradually increased at T2 and peaked at T3 (all P<0.05). Then, S-100β and NSE levels decreased gradually at T4 (both P<0.05). Perioperative changes in S-100β and NSE concentrations are shown in Table 2.

**PAED**

The rate of delirium was 17.4% at 30 min after extubation. The incidence of delirium was low at 2 h (6.9%) and 4 h (3.4%) after extubation (both P<0.05 vs. 30 min) (Table 3).

**BSID**

Compared with 1 day before surgery, MDI and PDI were decreased at 3 months after surgery (MDI: from 87.7±8.4 to 84.5±8.5, P=0.015; PDI: from 82.9±8.7 to 79.6±8.8, P=0.016) (Table 4). These results suggest some degree of brain injury that occurred in infants during or after liver transplantation.

**Correlations**

NSE and S-100β were linearly correlated with MDI and PDI at 3 months after surgery. NSE was negatively correlated with postoperative MDI (r=-0.367, P=0.001) and PDI (r=-0.441, P<0.001). S-100β was negatively correlated with MDI (r=-0.254, P=0.018) and PDI (r=-0.312, P=0.003) at 3 months after surgery (Table 5). NSE was correlated with PAED at 30 min after surgery (r=0.251, P=0.020) (Table 6). These results suggest that elevated markers of neurological injury during or after surgery are correlated with delayed development.

**Discussion**

This study evaluated the effect of liver transplantation on the brain of infants according to the perioperative serum brain injury markers S-100β and NSE. The results suggest that hemodynamic fluctuations were significant during the anhepatic and hepato-reperfusion phases. The levels of brain injury markers S-100β and NSE increased and peaked at the ischemia-reperfusion phase, indicating that ischemia-reperfusion may affect the brains of the children to a certain degree. In addition, the incidence of delirium was the highest at 30 min after extubation. MDI and PDI were decreased at 3
months after surgery compared with 1 day before surgery. S-100β and NSE were negatively correlated with MDI and PDI, suggesting that elevated markers of neurological injury during or after surgery are correlated with delayed child development. The results strongly suggest that there is some degree of brain injury after parent liver transplantation in children with biliary atresia. Currently, it is generally believed that multiple factors are involved in perioperative brain injury during liver transplantation. The pathogenesis is that intraoperative liver ischemia/reperfusion leads to impaired autoregulation mechanism of cerebral blood flow, and intraoperative hemorrhage, infusion, and inferior vena cava blockage cause significant hemodynamic changes, resulting in drastic fluctuation of cerebral blood perfusion and oxygenation, especially in the neohepatic phase [28, 29]. Furthermore, the release of inflammatory factors results in large amounts of oxygen free radicals, leading to cerebral edema, delayed neuronal death, and other serious injuries [28, 29].

S-100β is a nervous tissue protein with a high concentration in the brain. After necrosis of nerve cells, S-100β protein is released into the cerebrospinal fluid and enters the bloodstream through the damaged blood-brain barrier [17-19]. The levels of S-100β protein in body fluids have been used to monitor perinatal asphyxia in infants and guide clinical treatment [15]. NSE is mainly present in neurons and neurosecretory cells and is also an important marker of brain injury [20, 21]. Its physical and chemical properties are quite stable, and changes in the external environments have little effect on its levels. NSE is closely related to neuronal injury and can be used as an important parameter to assess the severity of neuronal injury [22]. High postoperative levels of S-100β and NSE are well known to be associated with brain injury in children who underwent major surgeries [23, 24], but the changes in S-100β and NSE levels in children with biliary atresia undergoing parent liver transplantation is unknown. This study showed that the serum levels of S-100β and NSE in infants undergoing liver transplantation after anesthesia induction were significantly higher than the preoperative normal values. The possible mechanism was that preoperative abnormal liver function and liver failure led to internal environment and metabolic disorders. Preoperative brain functions in patients with end-stage diseases are usually manifested as serious abnormal infections. Moreover, it can also result in ischemia, sepsis, acid-base imbalance and electrolyte disturbance, which can cause
different degrees of damage to the central nervous system [16]. Parent liver transplantation is complicated. When anastomosing the inferior vena cava and donor hepatic vein, the inferior vena cava needs to be blocked. After entering the anhepatic phase, HR is increased, MAP and CVP are decreased, tissue hypoperfusion and hypoxic metabolism produce a large number of acidic metabolites. Ultimately, S-100β and NSE levels increase and peak after liver transplantation and reperfusion. Cardiac output does not recover rapidly in the early neohepatic phase; instead, it is decreased further, and numerous acidic metabolites, endotoxins, vasoactive substances, and inflammatory factors can cause damage to the nervous system in the early stage [28, 29]. If liver transplantation is successful, the new liver can gradually recover those imbalances, and there is a gradual reduction trend after surgery.

The use of elevated serological indicators for assessment of brain injury is uncertain. Therefore, this study further explored the neurobehavioral cognition and postoperative delirium in infants. BSID is a standardized technique and measurement tool for evaluating the psychomotor behaviors of children aged from 2 months to 3 years, which is used to evaluate the sensitivity, discriminability, and ability to respond to external things of sensory perception, learning and memorizing, and psychomotor abilities [25]. In the present study, BSID was applied to evaluate the psychomotor behavior conditions of infants before and after liver transplantation. The preoperative MDI and PDI scores were significantly lower than the normal levels, indicating that there was a certain neurocognitive dysfunction in infants with biliary atresia. The MDI and PDI scores at 3 months after liver transplantation were lower than those before surgery. The postoperative delirium conditions showed that the incidence of delirium was higher in a short time after extubation, which strongly suggest that liver transplantation could cause some level of brain injury in infants. Furthermore, the MDI and PDI scores were consistent with the S-100β and NSE results.

This study has limitations. This was a single-center study, and only included infants with simple biliary atresia undergoing parent liver transplantation. Only two markers of brain injury and hemodynamics were assessed, and systemic inflammation and oxidative stress were not measured. Therefore, multicenter studies involving other types of liver transplantation are needed to determine the
association of NSE and S-100β with brain injuries after other types of liver transplantation.

Conclusions

Brain injury is observed in the perioperative period in children during parent liver transplantation, as indicated by elevated serum NSE and S-100β levels. The anhepatic phase and ischemia-reperfusion can cause a certain degree of brain injury. The NSE and S-100β levels correlated with infant development scores. The detection of perioperative brain injury markers can determine and predict postoperative brain injury, thus providing guidance for clinical cerebral protection, which is of great significance for the prevention of postoperative neurological complications in infants after parent liver transplantation.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the hospital (#2016N0039KY) and written informed consent was obtained from the infants’ guardians. The privacy rights of human subjects always be observed. This study was registered at ClinicalTrials.gov (#NCT03024840).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by 2018 Tianjin Natural Science Foundation Project; and Tianjin Clinical Key Discipline Project (Anesthesiology); and College program of Tianjin first central hospital[CF201819]; and Tianjin health and family planning commission of science and technology research projects [16KG101]; and Tianjin health and family planning commission of Chinese and western medicine of traditional Chinese medicine combined with scientific research subject[2017056]; 2017 Tianjin natural
science fund project[17]CYBJC28000]. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

WY have made contributions to the conception; YS have made contributions to design of the work; GZ have made contributions to the acquisition, analysis; YS have made contributions to the conception; MZ have made contributions to interpretation of data; HY have drafted the work or substantively revised it. All authors read and approved the final manuscript

Acknowledgments

Not applicable

References

1. Sokal EM, Goldstein D, Ciocca M, Lewindon P, Ni YH, Silveira T, et al. End-stage liver disease and liver transplant: current situation and key issues. Journal of pediatric gastroenterology and nutrition. 2008;47:239-46. doi: 10.1097/MPG.0b013e318181b21c

2. Protheroe SM, Kelly DA. Cholestasis and end-stage liver disease. Bailliere's clinical gastroenterology. 1998;12:823-41. doi:

3. Group SR. Studies of Pediatric Liver Transplantation (SPLIT): year 2000 outcomes. Transplantation. 2001;72:463-76. doi: 10.1097/00007890-200108150-00018

4. Young S, Kwarta E, Azzam R, Sentongo T. Nutrition assessment and support in children with end-stage liver disease. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2013;28:317-29. doi: 10.1177/0884533612474043

5. Stanescu AL, Hryhorczuk AL, Chang PT, Lee EY, Phillips GS. Pediatric Abdominal
Organ Transplantation: Current Indications, Techniques, and Imaging Findings.
Radiologic clinics of North America. 2016;54:281-302. doi: 10.1016/j.rcl.2015.09.011

6. Tannuri AC, Gibelli NE, Ricardi LR, Silva MM, Santos MM, Pinho-Apezzato ML, et al. Orthotopic liver transplantation in biliary atresia: a single-center experience. Transplantation proceedings. 2011;43:181-3. doi: 10.1016/j.transproceed.2010.11.012

7. Colledan M, Torri E, Bertani A, Corno V, Guizzetti M, Lucianetti A, et al. Orthotopic liver transplantation for biliary atresia. Transplantation proceedings. 2005;37:1153-4. doi: 10.1016/j.transproceed.2004.11.031

8. Lee JY, Lim LT, Quak SH, Prabhakaran K, Aw M. Cholangitis in children with biliary atresia: health-care resource utilisation. Journal of paediatrics and child health. 2014;50:196-201. doi: 10.1111/jpc.12463

9. Nemati H, Kazemi K, Mokarram AT. Neurological Complications associated with Pediatric Liver Transplant in Namazi Hospital: One-Year Follow-Up. International journal of organ transplantation medicine. 2019;10:30-5. doi:

10. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology. 2014;60:362-98. doi: 10.1002/hep.27191

11. Schifilliti D, Mondello S, D'Arrigo MG, Chille G, Fodale V. Genotoxic effects of anesthetic agents: an update. Expert opinion on drug safety. 2011;10:891-9. doi: 10.1517/14740338.2011.586627

12. Istaphanous GK, Loepke AW. General anesthetics and the developing brain. Current opinion in anaesthesiology. 2009;22:368-73. doi:
13. Vutskits L. Anesthetic-related neurotoxicity and the developing brain: shall we change practice? Paediatric drugs. 2012;14:13-21. doi: 10.2165/11592840-000000000-00000

14. Stratmann G. Review article: Neurotoxicity of anesthetic drugs in the developing brain. Anesthesia and analgesia. 2011;113:1170-9. doi: 10.1213/ANE.0b013e318232066c

15. Wainwright MS, Craft JM, Griffin WS, Marks A, Pineda J, Padgett KR, et al. Increased susceptibility of S100B transgenic mice to perinatal hypoxia-ischemia. Annals of neurology. 2004;56:61-7. doi: 10.1002/ana.20142

16. Chiaretti A, Barone G, Riccardi R, Antonelli A, Pezzotti P, Genovese O, et al. NGF, DCX, and NSE upregulation correlates with severity and outcome of head trauma in children. Neurology. 2009;72:609-16. doi: 10.1212/01.wnl.0000342462.51073.06

17. Egea-Guerrero JJ, Revuelto-Rey J, Murillo-Cabezas F, Munoz-Sanchez MA, Vilches-Arenas A, Sanchez-Linares P, et al. Accuracy of the S100beta protein as a marker of brain damage in traumatic brain injury. Brain injury. 2012;26:76-82. doi: 10.3109/02699052.2011.635360

18. Yao B, Zhang LN, Ai YH, Liu ZY, Huang L. Serum S100beta is a better biomarker than neuron-specific enolase for sepsis-associated encephalopathy and determining its prognosis: a prospective and observational study. Neurochemical research. 2014;39:1263-9. doi: 10.1007/s11064-014-1308-0

19. Oris C, Pereira B, Durif J, Simon-Pimmel J, Castellani C, Manzano S, et al. The Biomarker S100B and Mild Traumatic Brain Injury: A Meta-analysis. Pediatrics. 2018;141. doi: 10.1542/peds.2018-0037

20. Thelin EP, Jeppsson E, Frostell A, Svensson M, Mondello S, Bellander BM, et al. Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels,
outcome, and extracranial injury severity. Critical care. 2016;20:285. doi: 10.1186/s13054-016-1450-y

21. Rech TH, Vieira SR, Nagel F, Brauner JS, Scalco R. Serum neuron-specific enolase as early predictor of outcome after in-hospital cardiac arrest: a cohort study. Critical care. 2006;10:R133. doi: 10.1186/cc5046

22. Nakhjavan-Shahraki B, Yousefifard M, Oraii A, Sarveazad A, Hosseini M. Meta-analysis of neuron specific enolase in predicting pediatric brain injury outcomes. EXCLI journal. 2017;16:995-1008. doi: 10.17179/excli2017-405

23. Schmitt B, Bauersfeld U, Schmid ER, Tuchschmid P, Molinari L, Fanconi S, et al. Serum and CSF levels of neuron-specific enolase (NSE) in cardiac surgery with cardiopulmonary bypass: a marker of brain injury? Brain & development. 1998;20:536-9. doi:

24. Liu Y, Xu Y, Li DZ, Shi Y, Ye M. Comparison of S100B and NSE between cardiac surgery and interventional therapy for children. Pediatric cardiology. 2009;30:893-7. doi: 10.1007/s00246-009-9454-x

25. Bayley N. Bayley scales of infant development. 2nd ed. San Antonio: Psychological Corporation; 1993.

26. Bai Y, Shang G, Wang L, Sun Y, Osborn A, Rozelle S. The relationship between birth season and early childhood development: Evidence from northwest rural China. PloS one. 2018;13:e0205281. doi: 10.1371/journal.pone.0205281

27. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138-45. doi: 10.1097/00000542-200405000-00015

28. Weiss N, Thabut D. Neurological Complications Occurring After Liver Transplantation: Role of Risk Factors, Hepatic Encephalopathy, and Acute (on Chronic) Brain Injury.
Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2019;25:469-87. doi: 10.1002/lt.25420

29. Singh S, Nasa V, Tandon M. Perioperative monitoring in liver transplant patients. Journal of clinical and experimental hepatology. 2012;2:271-8. doi: 10.1016/j.jceh.2012.06.003

Tables
Table 1. Basic data and indicators of operation
| Variables                                                                 | n=86                               |
|---------------------------------------------------------------------------|------------------------------------|
| Age (months)                                                              | 8.1 (6.6, 10.2)                    |
| Sex, male (%)                                                             | 51 (59.3%)                         |
| Weight (kg)                                                               | 7.6±1.7                            |
| Height (cm)                                                               | 66.3±7.2                           |
| ASA status                                                                |                                    |
| III                                                                       | 62 (72.1%)                         |
| IV                                                                        | 24 (27.9%)                         |
| PELD score                                                                | 16.6±2.2                           |
| Preoperative serum creatinine (µmol/L)                                    | 17.34±4.68                         |
| Preoperative ALT (U/L)                                                    | 114.46±48.25                       |
| Preoperative AST (U/L)                                                    | 206.80±85.26                       |
| γ-glutaryl transferase (U/L)                                               | 435.8±95.66                        |
| Total bilirubin (mg/dL)                                                   | 205.42±90.48                       |
| Anhepatic time (min)                                                      | 45.5±12.4                          |
| Operation time (h)                                                        | 8.2±1.2                            |
| Anesthesia duration (h)                                                   | 10.1±1.3                           |
| Bleeding volume (ml)                                                      | 127±30                             |
| Urine volume (ml)                                                         | 424±62                             |
| Intraoperative blood transfusions (U)                                      | 2.0 (2.0, 3.7)                     |
| Intraoperative frozen plasma transfusions (mL)                             | 400 (210, 400)                     |
| Graft cold ischaemia time (min)                                           | 95 (64, 178)                       |

PELD: pediatric end-stage liver disease. ALT: alanine aminotransferase; AST: aspartate aminotransferase.
Table 2. Changes in hemodynamics, serum pH, and biomarkers

| Indicator | T1         | T2                  | T3                 | T4                 |
|-----------|------------|---------------------|--------------------|--------------------|
| HR (beat/min) | 118.42±12.25<sup>a</sup> | 132.25±14.55<sup>b</sup> | 112.18±10.12<sup>c</sup> | 105.28±7.16<sup>d</sup> |
| MAP (mmHg) | 46.23±7.18<sup>a</sup> | 40.35±8.16<sup>b</sup> | 49.25±7.36<sup>c</sup> | 53.62±3.28<sup>d</sup> |
| CVP (cmH<sub>2</sub>O) | 4.36±1.42<sup>a</sup> | 2.84±1.06<sup>b</sup> | 6.42±1.91<sup>c</sup> | 7.42±2.23<sup>d</sup> |
| pH        | 7.45±0.46<sup>a</sup> | 7.32±0.44<sup>b</sup> | 7.39±0.65<sup>c</sup> | 7.42±0.51<sup>a</sup> |
| NSE (ng/ml) | 23.46±3.74<sup>a</sup> | 28.85±4.14<sup>b</sup> | 35.57±7.06<sup>c</sup> | 29.25±4.90<sup>b</sup> |
| S100-β (ng/ml) | 3.97±0.79<sup>a</sup> | 7.69±1.92<sup>b</sup> | 12.36±3.29<sup>c</sup> | 6.87±2.11<sup>b</sup> |

HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure; NSE: neuro-specific enolase.

T<sub>1</sub>: at the beginning of skin incision after anesthesia; T<sub>2</sub>: 30 min after anhepatic phase; T<sub>3</sub>: 1 h after neohepatic phase; T<sub>4</sub>: 24 h after neohepatic phase.

<sup>abcd</sup> Different letters indicate statistical significance.

Table 3. Comparison of delirium after extubation

| Indicator           | 30 min after extubation | 2 h after extubation | 4 h after extubation |
|---------------------|-------------------------|----------------------|----------------------|
| PAED score          | 9.6±2.4                 | 6.6±1.8<sup>a</sup>  | 4.0±1.1<sup>a</sup>  |
| Rate of delirium n (%) | 15 (17.4%)             | 6 (6.9%)<sup>a</sup> | 3 (3.4%)<sup>a</sup> |

<sup>a</sup>p<0.05 vs. 30 min after extubation. PAED: pediatric anesthesia emergence delirium.

Table 4. Changes in MDI and PDI before and after liver transplantation and comparisons

| Indicator | 1 d before surgery | 3 m after surgery | P   |
|-----------|--------------------|-------------------|-----|
| MDI       | 87.7±8.4           | 84.5±8.5          | 0.015 |
| PDI       | 82.9±8.7           | 79.6±8.8          | 0.016 |
MDI: mental development index; PDI: psychomotor development index.

**Table 5.** Analysis of the association of NSE and S-100β with MDI and PDI 3 m after surgery at T3

| Variables | MDI   | PDI   |
|-----------|-------|-------|
|           | r     | P     | r     | P     |
| NSE       | -0.367| 0.001 | -0.441| <0.001|
| S-100β    | -0.254| 0.018 | -0.312| 0.003 |

MDI: mental development index; PDI: psychomotor development index; NSE: neuro-specific enolase; S-100β: S100 calcium-binding protein β.

**Table 6.** Analysis of the association of NSE and S-100β with PAED at T3

| Variables | PAED                  |
|-----------|-----------------------|
|           | 30 min | 2 h   | 4 h   |
| NSE (r,p) | 0.251 (0.020) | 0.197 (0.069) | 0.141 (0.194) |
| S-100β (r,p) | 0.004 (0.970) | -0.067 (0.543) | -0.060 (0.581) |

PAED: pediatric anesthesia emergence delirium; NSE: neuro-specific enolase; S-100β: S100 calcium-binding protein β.