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Yongpeng Zhou
Second XiangYa Hospital of Central South University
Jun Huang
The second XiangYa Hospital Central South University
Zhongzhou Si
The Second XiangYa Hospital of Central South University
Sumei Luo
The XiangYa Hospital of Central South University
Qin Zhou
Central South University Xiangya School of Medicine
Liwen Li (lilw1894@163.com)
the second xiangya hospital

Research article

Keywords: cognitive dysfunction、perioperatve、liver transplantation、transfusion、inflammatory cytokines

Posted Date: March 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17268/v1

Pathogenic factors of Cognitive Dysfunction after liver transplantation：An observational study

Yongpeng Zhou[1], Jun Huang[2], Zhongzhou Si[3], Sumei Luo[4], Qin Zhou[1], Liwen Li[1]

1. Department of Anaesthesiology, The Second Xiangya Hospital of Central South University, Changsha, P.R. China.

2. Department of Urology, The Second Xiangya Hospital of Central South University, Changsha, P.R. China.

3. Department of Liver Transplantation, The Second Xiangya Hospital of Central South University, Changsha, P.R. China.

4. Department of Anaesthesiology, The Xiangya Hospital of Central South University, Changsha, P.R. China.

Correspondance to Liwen Li, M.D Department of Anesthesiology, The Second Xiangya Hospital Of Central South University, #139 RenMing Middle Road, Hunan province, P.R.China

Tel: +86 13875854934; E-mail: lilw1894@163.com

Abstract

Background: Neurocognitive complications seriously affect long-term health-related quality of life in patients after liver transplantation, but what was it like during the transplant? There has been little related research， so it is very necessary to understand the changes in cognition during the perioperative period.

Methods：This observational study included patients with end-stage liver disease who are waiting for liver transplantation in our center. We performed the individual cognitive function investigation before and one week after successful surgery， then analyze the changes between them and further explore possible ones that cause perioperative cognitive dysfunction among several factors.

Results: From December 2018 to November 2019, there are 70 patients completed all the investgation. Compared with preoperative cognitive performance, 29 patients experienced deterioration, 14 patients showed significant improvement, and 27 patients remained unchanged. Multi-factor analysis results showed that, a mean arterial pressure <80 mmHg (p=0.035) during the reperfusion phase, sufentanil dosage <1.5 μg kg^{-1} (p=0.027), and blood transfusion volume ＞70 ml kg^{-1} (p=0.047) were closely related to early postoperative cognitive dysfunction.

Conclusions: The incidences of deterioration, maintenance, and improvement in cognitive function were 41.6%, 38.4%, and 20%,

respectively. Massive blood transfusion, hypotension during the reperfusion phase, insufficient intra-operative analgesia, and lower anesthesia depth may be the independent pathogenic factors for deteriorated cognitive function.

Trial registration: CHITR, ChiCTR1900027094. Registered 31 October 2019 - Retrospectively registered, http://www.chictr.org.cn/ChiCTR1900027094.

Key words：cognitive dysfunction；perioperatve；liver transplantation；transfusion；inflammatory cytokines

Background

Liver transplantation is the most effective method to resolve end-stage liver diseases such as hepatocellular carcinoma, viral cirrhosis, acute or chronic liver failure, and congenital biliary atresia. With the improvement of overall health service quality, both transplant success rate and the number of survivors have increased dramatically. However, how do these optimistic statistics reflect survivors' real health-related quality of life? Some literature suggested that it is not as good as expected.[1] Neuropsychiatric complications including memory deterioration, inattention, decreased executive function, chronic pain, and sleep disturbances,[2,3] account for a large part of the factors that affect their quality of life. There are many possible reasons for these neuropsychiatric complications, one of which is minimal HE (hepatic encephalopathy) or overt HE that exists before surgery. One study reported that the prevalence of minimal HE was high as 39.9% in hospitalized cirrhotic patients and proportionate to the degree of liver function.[4] These patients demonstrated not only affective symptoms, changes in behavioral patterns, bio-regulation disorders， but also significant cognition defects. Comprehensive neuropsychological testing has shown pronounced deficits in attention, visuo-constructive ability, and psychomotor function, in addition to less prominent deficits in other neuropsychological domains, such as memory and verbal ability.[6] Most of

these functional psychological capacities are restored to a large extent, but not completely, following successful liver transplants.[7] Some components may even accompany lifelong, leaving these patients unable to escape from endless suffering.[2] Moreover, post-traumatic stress response, anesthetics, inflammatory cytokines, and anti-rejection drugs may be culprits that damage patients' neuropsychiatric status. In summary, it is very necessary to assess perioperative cognition changes and actively explore the risk factors that cause this impairment. If possible， appropriate intervention to improve early and long-term cognitive performance will ultimately benefit the majority of survivors.

Patients and Methods

Subject Enrolment

The Ethical Committee of The Second Xiangya Hospital of Central South University reviewed and approved our clinical trial protocol. Eligible subjects were patients between the ages of 18 and 65 who were on the liver transplantation waiting list. Exclusion criteria were as follows: mental illness, history of central nervous system disease, drug dependence or general anesthesia in the last 3 months, severe language, visual, or hearing impairment, unwillingness to comply with the study protocol, complete hepatic encephalopathy, less than 3 years of education, have severe complications within 7 days after surgery. To eliminate the learning effect of using the same scale twice before and after surgery, we

also recruited 24 healthy volunteers as a control group, with educational level, age, and gender distribution similar to those of the subject group.

Perioperative Management

According to the clinical protocol， we recorded the following variables from all enrolled subjects before liver transplantation: demographic status, etiology, end-stage liver disease model, comorbidities, liver function index, inflammatory cytokines (C-reactive protein and procalcitonin), and number of episodes of overt HE. These data come from their electronic medical records. The donor organs included in our study all come from brain-dead donors and have no one from executed prisoners. All the procedures have subjected to rigorous ethical screening. Liver transplantation surgery performed under general anesthesia, which induced with midazolam, propofol, sufentanil, and vecuronium. We use propofol combined with remifentanil for anesthetic maintenance, adding cis-atracurium, sufentanil, and midazolam as needed. Other than that, we placed no restrictions on anesthetics, vasoactive agents, surgical approach, or blood transfusions, and these decisions determined entirely by the anesthesiologist(s) or surgeon(s). Patients were sent to the intensive care unit with intubation after successful liver transplantation. We checked daily to review their basic condition and evaluate whether they showed any signs for exclusion. At the same time,

determinating postoperative delirium according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). what worth mentioning is that all the subjects administered tacrolimus and mycophenolate mofetil as immunosuppression, and no one experienced acute or hyperacute rejection. We collected all the other necessary information and recorded it immediately. The sociodemographic, intraoperative, and postoperative data of all patients are listed in **Table 1**.

Neuropsychological Assessment

We selected the Chinese version of the Montreal Cognitive Assessment (MoCA), which is a brief and commonly used global cognitive screening tool. It has a higher sensitivity and specificity in patients with mild cognitive impairment.[8] MoCA covers several cognitive domains including visuospatial, multiple aspects of executive functions, naming, memory, attention, language, abstraction, delayed recall, and orientation. After an initial screening confirming that the subject exhibited no symptoms of complete hepatic encephalopathy, neuropsychological tests carried out in a quiet room with only the patient and investigator present. Investigators were trained to administer the tests developed by the psychologists who were responsible for the development of the test battery. If there were no events that met the exclusion criteria, we performed postoperative cognitive investigation on the 7th day after surgery. Meanwhile, we also assessed the pain and sleep

quality using the Visual Analogue Score (VAS) and the Pittsburgh Sleep Quality Index (PSQI), respectively.

Statistical Analysis

We used the same definition used in the ISPOCD1 study to determine the presence of postoperative cognitive dysfunction (POCD).[9] To quantify the practice effect, we compared the change in performance for control subjects in each age group (18–39 years, 40–59 years, and >60 years) between baseline and subsequent tests. For the transplant patient group, we compared preoperative scores with the one-week postoperative test results, subtracted the average practice effect from these changes, and divided the result by the SD of the control group to obtain a z-score for individual test outcome. Large positive z-scores indicated deterioration in cognitive function from the baseline compared with control subjects. We classified the patients as exhibiting POCD if their z-scores were 1.0 or greater, and individuals with z-scores less than -1.0 belonged to the improvement group, and all others belonged to the maintenance group. We used the chi-square or Fisher exact test for the bivariate analysis of categorical data, and Wilcoxon signed-rank tests or Kruskal-Wallis tests for the analysis of numerical data. Then we modeled the binary outcome of POCD in a logistic regression to determine which demographic and perioperative factors were associate with cognitive decline after adjusting for other factors. All factors that were significant in bivariate analysis

were included in the logistic regression model. A p-value < 0.05 was considered statistically significant. We use Stata/SE software version 15.1 (StataCorp, Texas, USA) for all statistical analyses.

Results

From December 2018 to November 2019, a total of 162 liver transplants performed at our center, of which 97 patients were enrolled in our study. In the end, 27 patients withdrew from this study, with a dropout rate of 27.8%. The detailed reasons for withdrawing are as follows: 15 patients did not have the transplant surgery; 2 patients refused our testing due to postoperative weakness; 9 patients had serious complications and could not complete cognitive testing (2 had heart failure, 1 had malignant arrhythmia, 1 had a myocardial infarction, 1 had gastrointestinal bleeding, 1 had a hepatic artery thrombosis, 1 had a severe pulmonary infection, 1 had mental disorder，and 1 had a perioperative hip fracture). We divided all patients into the POCD group or Non-POCD group according to the statistical results. The details of cognitive function scores and analysis have shown in **Figure 1**, **Table 2**, and **Table 3**. Of the 70 patients who completed all preoperative and postoperative tests, 29 (41.4%) patients experienced POCD, 27 (38.6%) patients maintained with preoperative levels, and 14 (20.0%) patients displayed significant improvement in cognitive function. Further analysis of the POCD group showed 5 (5/17), 8 (8/18), and 4 (4/5) patients in the 18-40 years, 41-60 years, and 60-65

years age groups, respectively. And did not show that POCD is closely related to age (p= 0.115). Analysis of the etiology and occurrence of POCD showed 18 (18/40) patients with liver cirrhosis, 3 (3/9) patients with alcoholic cirrhosis, 5 (5/13) patients with hepatic carcinoma, and 3 (3/8) patients with other etiologies. There were no significant differences between the etiologies (p=0.019). As defined, eleven (11/70) patients developed significant delirium, with an incidence of 15.7%, which was also unrelated to the presence of POCD (p=0.768). Logistic regression analysis showed that mean arterial pressure (MAP) <80 mmHg (p=0.035,OR=3.58) during the reperfusion phase, sufentanil dosage <1.5 μg kg^{-1} (p=0.027, OR=4.22), and blood transfusion volume >60 ml kg^{-1} (p=0.047,OR=3.65) were closely related to POCD, the value of the goodness-of-fit test is 0.775. **Table 4** lists the detailed logistic regression analysis results.

Discussion

Incidence of POCD

POCD is difficult to evaluate, as there are very large differences in methodology for analysis, such as the test batteries, the interval between sessions, the endpoints to be analyzed, how the analysis should be done statistically, and how neuropsychological deficits and POCD be defined.[10] A large number of factors can affect the neurocognitive function of patients with non-cardiac surgery, so the incidence of POCD reported in

previous studies varies, and may even be significantly different. The data of ISPOCD1 and ISPOCD2 studies show that it in the elderly (>60 years) and middle-aged (40-60 years) patients were 25.8% and 19.2%, respectively.[9,11] However, another study noted that at discharge it was 36.6% in young patients (18-40 years)， 30.4% in middle-aged patients (40-60 years), and 41.4% in elderly patients (>60 years).[12] We speculated that liver transplantation has unique risk factors for cognitive dysfunction compared to other non-cardiac surgery. For example, most patients have experienced mild or overt HE before surgery, have reperfusion syndrome during surgery, and have severed pulmonary inflammation or renal insufficiency after surgery. A review that analyzed all studies on the cognitive function of liver transplantation patients, but which have inconclusive results, reported that the incidence fluctuated from 0% to 50%.[13] In our study, our results showed that the overall incidence of POCD was 41.4%, which slightly higher than the widely recognized 20-40% for non-cardiac surgery, which is also in line with previous data and our expectations.

POCD and MAP during Reperfusion

Normal cerebral blood flow is kept relatively constant independent of MAP and $PaCO_2$, as long as the MAP is between the lower and higher limits of cerebral autoregulation, i.e. 60 to 150 mmHg. In patients with end-stage liver disease, the autoregulation of cerebral blood flow is

impaired. However， it can be restored soon after successful liver transplantation.[14] As a result, intraoperative cerebral perfusion is particularly dependent on MAP and $PaCO_2$. A slight decrease in MAP or $PaCO_2$ can lead to a significant decrease in cerebral blood flow.[14] Several reports have shown that by conducting transcranial ultrasound Doppler measurements, cerebral blood flow during the reperfusion period significantly increases to varying degrees compared with the prehepatic and anhepatic stages, some even report the values exceeding 100%.[14,15] And this increase is inconsistent with the degree of vasodilation, and can not be fully explained by changes in $PaCO_2$ or MAP, and also has nothing to do with the history of overt HE. Therefore, to ensure proper cerebral perfusion during reperfusion, factors known to decrease cerebral blood flow (e.g. hypotension or hypocapnia) and increase cerebral oxygen metabolism should be avoided, while sufficient depth of anesthesia and hypothermia may be especially important.[15]Our results suggest that it may be beneficial to maintain MAP above 80 mmHg during reperfusion to optimize or maintain neurocognitive status. Although this value is not necessarily applicable for every patient and still requires more rigorous analysis, it must be considered seriously.

POCD and Sufentanil

The surgical procedure characterized by complicated procedures, massive blood loss, and more time-consuming, so severe postoperative

pain and post-traumatic stress plagued most patients. Our results also confirmed this phenomenon, with an average VAS of 5.2±1.9 and 66.2% of patients suffering moderate to severe pain (VAS≥5). Sufentanil is commonly used to suppress intraoperative pain and nociceptive reflexes.[16] To a large extent, the dosage of sufentanil indirectly reflects the intensity of analgesia and the depth of anesthesia. Because we did not use any depth monitoring equipment, such as bispectral index and auditory evoked potential, and so far there are no suitable parameters to reflect the level of intraoperative analgesia. With increasing duration and bleeding, its plasma concentration decreases and may fall below the required level. Thus, long-acting anesthetics added timely and in a sufficient amount seems particularly important. Otherwise, the patients may experience some latent damage. To date, there have been few studies specifically evaluating the relationship between intraoperative analgesia or anesthesia depth and cognitive impairment, and the rare results are also controversial. Farag et al. showed that patients kept at lower Bispectral Index levels during the majority of the surgical procedure performed better in the information processing speed.[17] A study by Radtke et al. suggests that intraoperative neuromonitoring may reduce the incidence of postoperative delirium by reducing extremely low Bispectral Index.[18] An et al. found that deeper total intravenous anesthesia can decrease the incidence of cognitive dysfunction in the early postoperative period.[19]

It provides three possible protective mechanisms, the first of which is the decrease of cerebral metabolism and the assurance of adequate cerebral blood flow and oxygenation. The second is that deeper anesthesia might prevent a deleterious stress response. The last one is that deeper anesthesia inhibits implicit memory that has been shown to yield an immediate postanesthetic change in behavior or performance on a memory test.[20] In summary, although there is little definitive evidence to follow, it is extremely important to use anesthetics reasonably to maintain the most appropriate depth based on individual circumstances.

POCD and Blood Transfusion

End-stage liver disease results in reduced coagulation factors and platelet count, so patients in the waiting list tend to be hypocoagulable. Our data also confirmed this, with of preoperative mean International Normalized Ratio of 1.83±0.97, which is much greater than the normal range of 0.8-1.2. The process of liver transplantation involves hepatectomy， large vessel disconnection and anastomosis, usually accompanied by more bleeding. Combined with lower systemic vascular resistance, patients usually require more blood transfusions, including various blood components such as allogeneic red blood cells, plasma, platelets, and cryoprecipitate. Our results indicate an average transfusion volume of up to 56.0±27.1 ml kg^{-1}, which is not comparable with other non-cardiac surgeries. There have been many studies on the relationship

between blood transfusion and neurocognitive complications. Behrends et al. suggest that the administration of more than 1,000 ml of red blood cells was the strongest predictor of delirium on the first post-operative day.[21] One animal study has also shown that the infusion of red blood cells, which account for 20% of total volume, could induce neuroinflammation and impaired learning and memory.[22] Allogeneic red blood cell infusion contributes to a non-infectious inflammatory response by enhancing the inflammatory response or directly increase the plasma concentrations of inflammatory cytokines, such as bacterial permeability-increasing protein, interleukin-6, and C-reactive protein.[23,24] It is the inflammatory response that causes cognitive impairments such as decreased memory and psychomotor speed.[25,26] Another possible mechanism is that these inflammatory cytokines involved in silent brain infarctions or microvascular haemorrhage,[27,28,29] and that cognitive deterioration are the result of these lesions. Symptomatic cerebrovascular lesions are not uncommon after liver transplantation.[30]So it is reasonable to expect that asymptomatic stroke or cerebral haemorrhage may be more common, but we need more evidence from magnetic resonance imaging. These findings suggest that inflammation is involved in the pathophysiology of cognitive decline, although the possibility that both inflammatory activation and cognitive decline are the result of an underlying disease process cannot be excluded. Our results showed a

significant relationship between CRP concentration and transfusion volume (p=0.022), but not with cognitive impairment (p=0.327). We speculate that it is due to the dynamic changes in plasma CRP concentration. The concentration of CRP in patients without other complications peaks at 48 hours after surgery and drops to baseline at 7-10 days, but cerebrovascular lesions may have already existed. This is an extremely complex subject that needs more basic or clinical trials to provide rigorous and scientific proof for clarification.

Conclusions

Compared with preoperative results, most patients had neurocognitive function deteriorated or remained unchanged within one week after successful transplantation, and only a few patients improved rapidly. Massive blood transfusion, Cerebral insufficiency during reperfusion, insufficient intra-operative analgesia, and lower anesthesia depth may be the independent pathogenic factors for deteriorated cognitive function.

Limitations

Our clinical studies still have some limitations due to the complexity of the issue. Firstly, the sample size was relatively small. Available authoritative data on the incidence of POCD is limited, so the sample size is difficult to estimate accurately in advance. And because of

the particularity of the transplant surgery, a single-center may not be sufficient to meet the quantitative requirements. So we need large-scale multi-center clinical studies in the future to confirm our findings. Secondly, considering the clinical feasibility and acceptability, we used the Chinese version of MoCA. It is different from previous authoritative studies (such as the ISPOCD1 study) that used a series of neuropsychological tests. We think these tests may not be suitable for postoperative patients with extreme weakness and fatigue. Finally, due to the limitations of research conditions and personnel knowledge, we have ignored some indicators that should be paid attention to, including anxiety and depression state, depth of anesthesia, interleukin-6 and postoperative peak CRP levels, and cold ischemia time. These factors may lead to bias, and we hope to consider them in future research.

List of abbreviations

HE：Overt Hepatic Encephalopathy; OHE：Overt Hepatic Encephalopathy; DSM-IV： Diagnostic and Statistical Manual of Mental Disorders; MoCA：Montreal Cognitive Assessment; VAS：Visual Analogue Score; PSQI: Pittsburgh Sleep Quality Index; POCD： post-operative cognitive dysfunction; MELD: End-stage Liver Disease Model; MAP： mean arterial pressure; CRP： C-reactive protein; OLT: Orthotopic Liver Transplantation; PBLT: Piggyback Liver Transplantation.

Declarations

Ethics approval and consent to participate：The Ethical Committee of The Second Xiangya Hospital of Central South University reviewed and approved our clinical trial protocol（No. 2018-153）. The study was carried out according to the tenets of the Declaration of Helsinki, and all patients were provided with written informed consent.

Consent for publication：All authors of this study have read and agreed with the publication of this manuscript.

Availability of data and materials： We have saved all available information and data and can call it at any time.

Competing interests: none.

Funding： This study was supported by the HuNan Science and Technology Development Foundation（NO. wk3014）.

Authors' contributions: YPZ was involved in the design of study protocol and the collection of the vast majority of data. He was also a major contributor to statistical analysis and writing this manuscript. JH participated in language editing and submission. ZZS participated in obtaining subject's informed consent and interpreting the statistical results regarding liver transplantation. SML participated in statistical analysis of data. QZ participated in collection of some data. LWL, the corresponding

author, applied for financial support, designed the study protocol and provided guidance for manuscript writing.

Acknowledgements： The most grateful to all of the subjects, who provided us with invaluable data and support, even though they were already very vulnerable and exhausted. Wish them well soon.

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Figures

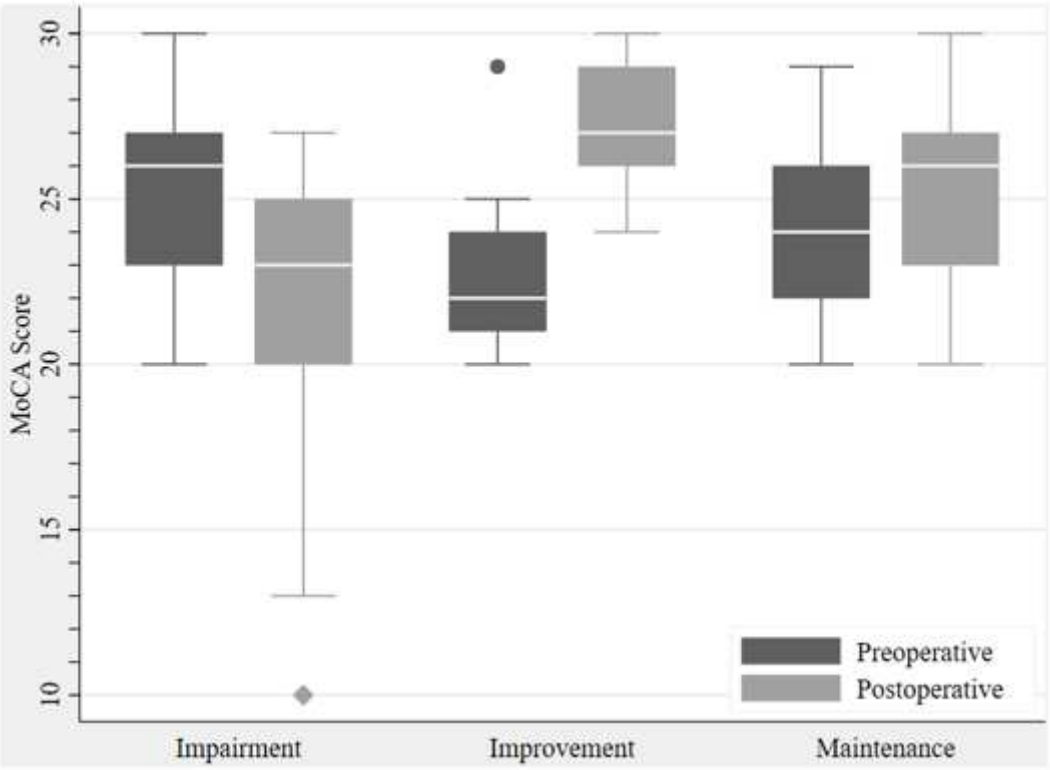

Figure 1

Preoperative and postoperative MoCA scores in all groups. Non-impairment group: Improement group + Maintenance group. The preoperative MoCA score was normal in the impairment group, but it was significantly lower in the non-impairment group. The postoperative situation was the opposite. Among them, the improvement group had the lowest preoperative score, but the highest after surgery.

Supplementary Files

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- Table2.docx
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