

A Prospective Study on Impact of Hepatic Ischemia-Reperfusion Injury on Cognitive Function Post-Surgery in the Elderly**Bhagabat Purusottam Dandpat¹, Debasisha Padhi², Haramohan Barik³, Sakti Prasad Sahoo⁴**¹Associate Professor, Department of Surgery, DRIEMS, Cuttack, Odisha, India²Assistant Professor, Department of Anesthesia, Ecmo Unit, CTVS, SCB Medical College, Cuttack, Odisha, India³Consultant, Department of Surgery, Sparsh Hospital, Bhubaneswar, Odisha, India⁴Associate Professor, Department of Surgery, KIMS, Bhubaneswar, Odisha, India

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Abstract:**Background:** Hepatic ischemia-reperfusion (I/R) injury is a significant concern in liver surgeries, particularly partial hepatectomy. This condition, prevalent in the elderly, can lead to post-operative cognitive dysfunction (POCD), a complication categorized by memory and concentration impairments. Recent studies suggest a link between hepatic I/R injury, inflammatory responses, and POCD.**Methods:** In this prospective, observational cohort study, 110 elderly patients undergoing partial hepatectomy were enrolled. The study, conducted at a designated institute over a specified period, included patients with specific cardiac and hepatic function grades and educational levels. Individuals were divided into 2 groups: Category C and Category I/R. Cognitive function was assessed using tests recommended by Murkin et al., and serum levels of TNF- α , IL-6, S100 β , ALT, and AST, were measured. Analyses of the data were done with SPSS 15.**Results:** Vital signs and overall condition did not significantly differ between the two groups. However, Category I/R showed significantly higher levels of TNF- α , IL-6, and S100 β post-operation, along with a higher prevalence of POCD (54.5%) compared to Category C (20%). The study also found a substantial correlation between increased serum levels of inflammatory markers and the incidence of POCD.**Conclusion:** Hepatic ischemia-reperfusion injury is related with increased inflammatory responses and a higher incidence of POCD in elderly patients. These findings underscore the importance of minimizing hepatic I/R injury to preserve cognitive function postoperatively.**Recommendations:** Future research should focus on developing surgical and anesthetic strategies to reduce hepatic I/R injury. Additionally, exploring therapeutic interventions to mitigate the inflammatory response could be beneficial in preventing POCD.**Keywords:** Postoperative Cognitive Dysfunction, Hepatic Ischemia-Reperfusion Injury, Elderly Patients, Partial Hepatectomy.

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Introduction

Hepatic ischemia-reperfusion (I/R) injury is a significant concern in surgical procedures involving the liver, particularly in partial hepatectomy. This phenomenon occurs when the blood supply to the liver is temporarily interrupted and then restored, leading to a cascade of biochemical reactions that can cause cellular damage [1]. The elderly population is especially vulnerable due to age-related physiological changes and comorbidities [2]. In older patients, post-operative cognitive dysfunction (POCD) is a typical consequence after surgery, characterized by impairments in memory, concentration, and overall cognitive ability [3]. The pathophysiology of POCD is complex and

multifactorial, with inflammation playing a crucial role [4].

Recent studies have highlighted the potential link between hepatic I/R injury and the development of POCD. S100 β , TNF- α , IL-6, and other inflammatory mediators are released, protein during hepatic I/R injury is thought to contribute to cognitive decline [5]. These biomarkers are indicative of both hepatic injury and systemic inflammatory responses, which can have far-reaching effects on the central nervous system [6].

This study aims to measure the serum levels of TNF- α , S100 β , and IL-6, as well as to analyze the

prevalence of POCD in elderly patients having partial hepatectomy, with or without hepatic portal blockage.

Methodology

Study Design: This study was a prospective, observational cohort study.

Study Setting: The study was carried out at 'DRIEMS, Cuttack', from 'January 2021 to January 2022'.

Participants: 110 patients in all, ranging in age from 64 to 80, who had partial hepatectomy procedures performed in the hospital were included. Patients with heart function of grade II-III, hepatic function of grade A, ASA of grade II-III, and at least a primary education were included in the sex-neutral study.

Inclusion and Exclusion Criteria: The age requirements, liver and heart function grades, and educational attainment were used to determine which patients were included. Drug addiction, alcoholism, mental illness, sight and hearing problems, and the consequences of heart and brain vascular disease were the exclusion criteria.

Bias: In order to reduce selection bias, patients were enrolled one after the other. Standardizing the anesthetic techniques and intraoperative monitoring for every participant helped to minimize performance bias.

Variables: The main factors were the blood levels of TNF- α , S100 β , and IL-6 as well as the scores for cognitive function. Vital indicators such as ECG, HR, SpO₂, MAP, CVP, and nose temperature were considered secondary factors.

Data Collection and Analysis: Information was gathered on postoperative recovery parameters, surgical time, and intraoperative monitoring indicators. Tests that were recommended by Murkin et al. [7] were used to evaluate cognitive function, and blood samples were used to analyze inflammatory markers. Serum levels of AST and ALT were also measured to assess liver function postoperatively.

Grouping of Patients: Two groups of patients were created: Category C, which was the non-blocked hepatic portal group, and Category I/R, which was the hepatic portal block group (n=55). Based on the surgical operation carried out, the grouping was defined.

Anesthetic Methods: All patients received the same standard anesthetic regimens, which included preoperative medication, anesthesia induction and maintenance, and postoperative treatment.

Intraoperative Monitoring and Indicators Record: Vital signs were continuously monitored both during and after operation, with data being recorded at predetermined intervals.

Cognitive Function Assessment and POCD Measurement Methods: Using Murkin's formula as the basis for the diagnostic criteria, a battery of cognitive tests was used to assess POCD.

Inflammatory Factors, AST, and ALT Analysis: Using particular tests, the serum levels of inflammatory markers and liver enzymes were assessed both before and after surgery.

Statistical Analysis: Data analysis was done using SPSS 15.0. The means \pm SD of the continuous data were presented after analysis with variance analysis. Statistical significance was indicated by a P value less than 0.05.

Ethical Considerations: The Ethics Committee gave their approval to the project. Every step taken was compliant with ethical guidelines. Every individual participant participating in the study gave informed consent.

Result

In this study, 110 patients receiving partial hepatectomy were included. They were split up into two groups: Category C, which was the non-blocked hepatic portal group, and Category I/R, which was the hepatic portal block group (n=55). A review of the patients' overall condition revealed no discernible differences between the two categories in terms of sex ratio, age, body weight, length of operation, length of stay in the PACU, or duration of tracheal extubation (P>0.05).

Table 1: General Status of Patients

Group	Sex (M/F)	Age (Years)	Body Weight (kg)	Surgery Time (min)	PACU Dwell-Time (min)	Extubation Time (min)
Category C	34/21	69.80 \pm 4.10	61.50 \pm 7.80	141.50 \pm 45.80	53.70 \pm 14.30	31.20 \pm 10.40
Category I/R	31/24	70.40 \pm 4.90	66.20 \pm 8.80	135.00 \pm 30.80	55.50 \pm 16.20	29.50 \pm 9.60

Vital signs such as body temperature, heart rate (HR), pulse oxygen saturation (SpO₂), and mean arterial pressure (MAP) were recorded and monitored for both categories at the same 7 time points (T1-T7). The 2 groups' MAP, body

temperature, SpO₂, and HR did not differ statistically significantly during these times (P>0.05).

Using testing assays created by Murkin et al., the POCD test results were acquired one day before

surgery and four days after surgery. At 4 days after the operation, the results of the cumulative test, backward digit span test, trail creating test B, and digit symbol test timings revealed significant differences ($P < 0.05$) between Category I/R and Category C. However, no significant changes were found in the other tests ($P > 0.05$).

In this study, 11 cases in Category C and 30 cases in Category I/R had individual Z scores more than 1.96, according to Murkin's Z scoring system. The

incidence of POCD was found to be 20% in Category C and 54.5% in Category I/R. This indicates that Category I/R patients had a greater incidence of POCD than Category C patients ($P < 0.05$).

Serum levels of TNF- α , IL-6, and S100 β were measured by ELISA one day before surgery and four days afterward. At four days after surgery, the values in Category I/R were suggestively higher than those in Category C ($P < 0.05$).

Table 2: Serum Levels of IL-6, TNF- α , and S100 β

Group	Test Time	IL-6 (ng/L)	TNF- α (μ g/L)	S100 β (ng/L)
Category C	Day 1 Pre-Op	180 \pm 30	3.00 \pm 0.35	480 \pm 150
	Day 4 Post-Op	270 \pm 55	4.20 \pm 0.60	610 \pm 190
Category I/R	Day 1 Pre-Op	185 \pm 35	3.10 \pm 0.40	485 \pm 155
	Day 4 Post-Op	360 \pm 65	11.50 \pm 1.30	780 \pm 205

Following surgery, serum levels of AST and ALT increased in both groups, reaching a peak at 4 days. Category I/R's values were considerably greater than Category C's ($P < 0.05$).

The frequency of post-operative POCD at 4 days was strongly linked ($P < 0.05$) with the elevated blood levels of TNF- α , IL-6, and S100 β in Category I/R.

Discussion

The study involving 110 elderly patients undergoing partial hepatectomy revealed significant findings. Firstly, the serum levels of TNF- α , IL-6, and S100 β were notably higher in the hepatic portal block group (Category I/R) compared to the non-blocked group (Category C) post-operation. Specifically, IL-6 and TNF- α levels in Category I/R were markedly elevated, indicating a strong inflammatory response. Additionally, the rate of POCD was significantly higher in Category I/R (54.5%) compared to Category C (20%). These results suggest a correlation between hepatic ischemia-reperfusion injury and the exacerbation of inflammatory responses and cognitive impairments in elderly patients.

The raised levels of IL-6 and TNF- α in Category I/R can be interpreted as a response to hepatic ischemia-reperfusion injury, which is known to trigger systemic inflammatory responses [8]. This inflammation could contribute to the pathogenesis of POCD, as suggested by the higher incidence of cognitive dysfunction in Category I/R. The increase in S100 β , a marker of brain injury, further supports the hypothesis that hepatic I/R injury may have a detrimental impact on cognitive function post-surgery.

Similar findings have been observed in animal models. For instance, a study on aged rats demonstrated that hepatic ischemia/reperfusion injury led to significant changes in the hippocampus

and cognitive function, highlighting the role of neuroinflammation in this process [9]. Furthermore, studies on young rats revealed that dexmedetomidine could lessen hippocampal damage and cognitive impairment brought on by hepatic ischemia/reperfusion, indicating possible treatment approaches [10]. These animal studies reinforce the notion that hepatic ischemia-reperfusion injury has profound effects on the brain and cognitive function.

The significant difference in POCD incidence between the two groups underscores the potential impact of surgical techniques on postoperative cognitive outcomes. This finding aligns with the growing body of evidence suggesting that minimizing perioperative stress and inflammation could be crucial in protecting cognitive function in elderly patients [11]. For instance, a study using a mouse model revealed that hepatic ischemia-reperfusion injury may result in alterations in the hippocampus neurons as well as temporary and reversible cognitive impairment [12], indicating the potential for recovery with appropriate interventions.

Conclusion

The study adds to the growing evidence that hepatic ischemia-reperfusion injury can exacerbate inflammatory responses and potentially lead to higher incidences of POCD in elderly patients. These findings highlight the need for surgical and anesthetic strategies that minimize hepatic ischemia-reperfusion injury to preserve cognitive function postoperatively.

Limitations: The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendations: Future research should focus on developing surgical and anesthetic strategies to reduce hepatic I/R injury. Additionally, exploring therapeutic interventions to mitigate the inflammatory response could be beneficial in preventing POCD.

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List of abbreviations:

I/R - Ischemia-Reperfusion
 POCD - Postoperative Cognitive Dysfunction
 IL-6 - Interleukin-6
 TNF- α - Tumor Necrosis Factor-alpha
 S100 β - S100 Calcium Binding Protein B
 AST - Aspartate Aminotransferase
 ALT - Alanine Aminotransferase
 MAP - Mean Arterial Pressure
 SpO₂ - Pulse Oxygen Saturation
 HR - Heart Rate
 CVP - Central Venous Pressure
 PACU - Post-Anesthesia Care Unit
 ASA - American Society of Anesthesiologists (classification)
 ECG - Electrocardiogram
 ELISA - Enzyme-Linked Immunosorbent Assay

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