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Research Article

Relationship between Depth of Anesthesia and Interleukin-6 with the Incidence of Postoperative Delirium (POD) in Geriatric Patients Undergoing General Anesthesia

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ABSTRACT

Background: The incidence of postoperative delirium (POD) in geriatric patients is aged 3-61%. The combined effects of inflammatory factors and depth of anesthesia can affect neurotransmitters and receptors in the central nervous system that affect POD. To analyze the relationship between depth of anesthesia and IL-6 with the incidence of POD in geriatric patients undergoing general anesthesia.
Methods: A prospective cohort study was conducted in geriatric patients undergoing general anesthesia. Patients were divided into two groups based on the bispectral index (BIS): BIS 40-45 and BIS 51-60. POD was measured using the Confusion Assessment Method (CAM) and Mini-Mental State Exam (MMSE) 24 hours postoperatively. Serum IL-6 measurements were also performed before and 24 hours postoperatively.
Results: A total of 22 patients were collected with the results that the MMSE score decreased insignificantly at 24 hours postoperatively, and there was no difference in MMSE scores based on BIS ($p > 0.05$). The depth of anesthesia was significantly associated with CAM ($p < 0.05$). Delirium incidence was more frequent in BIS 40-45. IL-6 levels increased significantly at 24 hours postoperatively ($p < 0.05$). IL-6 levels were not significantly associated with MMSE and CAM scores ($p > 0.05$).
Conclusion: BIS 40-45 has the potential to be a predictor of POD in geriatric patients with general anesthesia.

Introduction

General anesthesia is the induction and maintenance of a state of unconsciousness without the sensation of pain, often performed in major surgery. [1-2]. Globally, many patients receive general anesthesia to safely undergo surgical procedures. Most general anesthesia patients are geriatric patients aged 65 years or older [2]. General anesthesia causes side effects such as dry mouth, nausea and vomiting, chills, confusion, sore throat or hoarseness, muscle pain, bladder problems, dizziness, and itching. In geriatrics, general anesthesia can cause cognitive disorders [3]. Based on the onset of the disease, the mental disorder consists of postoperative delirium (POD) for onset 24–72 hours after surgery with a reversible course and postoperative cognitive dysfunction (POCD) for onset several weeks after surgery and persisting for a more extended period.

POD is a post-operative mental disorder such as memory impairment, cognitive impairment, anxiety, mental confusion, and personality changes [4]. The short-term effects of POD are that it can worsen other

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postoperative complications and increase the duration of hospitalization and costs. The long-term impact of POD is that it prolongs recovery, decreases the quality of life, and even increases the postoperative mortality ratio [5].

The incidence of POD most often occurs in geriatric patients over 65 years of age, and the incidence of POD in geriatrics reaches 3-61% [4-5]. Most cases of POD are reversible but can progress from a chronic disease to long-term cognitive impairment. As many as 10–15% of POD cases progress to dementia each year [6]. Therefore, perioperative screening to identify risk factors in geriatric patients is necessary so that timely intervention can be carried out to prevent and treat POD effectively [5].

One of the modifiable risk factors for POD that anesthesia techniques can control is the depth of anesthesia [7]. Differences in the effects of anesthesia depth affect cerebral blood flow, cerebral metabolic rate, inflammatory factors, and synaptic plasticity. Increasing the depth of general anesthesia significantly decreases cerebral blood flow and cerebral metabolic rate and causes abnormalities in neurotransmitters and receptors in the central nervous system (CNS). This condition causes disruption in the process of forming, storing, releasing, and inactivating neurotransmitters so that synaptic plasticity changes and encourages the release of inflammatory factors that cause POD [8].

The pathogenesis of POD is related to central nervous system inflammation [9]. POD develops as a result of surgical trauma, thus affecting the inflammatory cascade of the central nervous system. Surgical trauma causes damage-associated molecular patterns (DAMPs) to bind to pattern recognition receptors (PRRs). The formation and release of proinflammatory cytokines by NF-κB in monocytes can occur as an immune response that can eventually damage the blood-brain barrier (BBB). The breakdown of the BBB allows the chemokine MCP-1 to attract bone marrow macrophages (BM-DM) expressing CCR2 into the hippocampus. Activated macrophages then release proinflammatory cytokines and kill neurons, causing impaired learning and memory and ultimately cognitive impairment [4].

In a previous study, Wan et al. found in experimental animals that levels of inflammatory factors such as IL-1, IL-6, and TNF-α were increased in the central nervous system (CNS) and positively correlated with levels of inflammatory factors in peripheral blood in non-craniocerebral surgery. These results support the hypothesis of central nervous system inflammation for POD [10]. Meanwhile, Shu et al. compared the depth of anesthesia on postoperative cognitive function in laparoscopic patients with a combination of intravenous-inhalation anesthesia. The results showed that the depth of anesthesia BIS 41-50 obtained a milder effect on postoperative cognitive function than BIS 31-40 and BIS 51-60 [8]. Inflammatory factors and depth of anesthesia can produce combined effects that affect neurotransmitters and receptors in the CNS [8]. Previous studies have never conducted research on the depth of anesthesia and IL-6 levels on the incidence of DPB in geriatric patients. Therefore, this study is interested in analyzing the relationship between the depth of anesthesia and IL-6 with the incidence of DPB in geriatric patients undergoing general anesthesia.

Methods

This study used a prospective cohort design conducted at Dr. Wahidin Sudirohusodo General Hospital and network hospitals in Makassar City from April 2024 until the minimum sample size was met. The study population included geriatric patients undergoing general anesthesia, with samples selected by consecutive sampling based on the order of the surgical schedule. Inclusion criteria included patients aged >65, ASA II physical status, and willingness to sign an informed consent. Patients with comorbidities such as diabetes mellitus, uncontrolled hypertension, preoperative cognitive impairment, or certain neurological conditions were excluded from the study. Patients who met the criteria were observed prospectively, starting from the initial examination, venous blood sampling for IL-6 levels, monitoring the depth of anesthesia using BIS during surgery, and postoperative observation for 24 hours. Patients were randomly divided into two groups based on the bispectral index (BIS): the group with BIS 40-45 and BIS 51-60. BPB was measured using the Confusion Assessment Method (CAM) and Mini-Mental State Exam (MMSE) 24 hours postoperatively. MMSE was also measured before surgery. Serum IL-6 measurements were performed before and 24 hours postoperatively. Data were analyzed using SPSS 27 with the Mann-Whitney test, Kruskal-Wallis test, Wilcoxon test, Spearman correlation, and chi-square test. The study was conducted after obtaining a research permit from the Hasanuddin University Makassar Ethics Committee number 1052/UN4.6.4.5.31/PP36/2024.

Results

This study involved 22 geriatric patients undergoing general anesthesia at Wahidin Sudirohusodo General Hospital and network hospitals in Makassar City, who were randomly divided into two groups based on the depth of anesthesia (BIS 51–60 and BIS 40–45), each consisting of 11 patients. The majority of subjects were male with normal body mass index. Analysis of characteristics based on BIS categories showed no statistically significant differences in terms of age, gender, and BMI ($p > 0.05$) (Table 1). Delirium in this study was assessed using MMSE before and 24 hours after surgery. The results in (Table 2) show a non-significant decrease in MMSE scores postoperatively (p

> 0.05. Despite the decline, the mean MMSE scores preoperatively and postoperatively remained within the normal category. IL-6 levels increased significantly postoperatively, both overall and in each BIS group ($p < 0.05$) (Table 2). Analysis in (Table 3) shows that there is no significant relationship between the depth of anesthesia and the preoperative MMSE score or its changes ($p > 0.05$) but significant postoperatively ($p < 0.05$). Patients with deep anesthesia (BIS 40–45) tend to have lower MMSE scores than other groups. Based on the postoperative CAM evaluation, there was a significant relationship between the depth of anesthesia and the incidence of delirium ($p < 0.05$), with the highest incidence in patients with BIS 40–45 (Table 4). The results in (Table 5) show no significant relationship between IL-6 levels, both preoperative and postoperative, and postoperative MMSE scores in geriatric patients undergoing general anesthesia ($p > 0.05$). Meanwhile, there is no significant relationship between preoperative IL-6 levels and postoperative IL-6 levels with the incidence of postoperative delirium with a P value > 0.05 (Table 6). The results in (Table 7) show no significant relationship between the depth of anesthesia and preoperative or postoperative IL-6 levels or changes in IL-6 levels ($p > 0.05$). However, there is a tendency for IL-6 levels and their increase at 24 hours postoperatively to be lower in the deeper anesthesia group (BIS 40–45) compared to BIS 46–50 and BIS 51–60 (Figure 1).

Table 1- Characteristics of research subjects

Characteristics	BIS 40-45 (n= 11)	BIS 51-60 (n= 11)	P value
Age (years)[a]	67 (65-73)	69 (63-76)	0.790
Gender[b]			0.881
Male	6 (54.5)	7 (63.6)	
Female	5 (45.5)	4 (36.4)	
BMI (kg/m2)[c]	22.43 ± 3.25	22.58 ± 3.95	0.667

[a]Numerical data is displayed with median (minimum value-maximum value) tested using the Mann Whitney test.; [b]Categorical data is displayed with the number (n) and percentage (%) tested using the Chi-square test.; [c]Numerical data are displayed as mean ± standard deviation (SD), tested using the independent sample t-test.

Table 2- Comparison of MMSE scores and IL-6 between preoperative and postoperative

Parameter	Preoperative	Pascaoperative	P value
	Median (min-max)	Median (min-max)	
MMSE score			
BIS 40-45	25 (24-28)	24 (24-25)	0.066
BIS 51-60	25 (24-27)	25 (24-27)	0.785
Total	25 (24-28)	25 (24-27)	0.061
IL-6 levels (pg/mL)			
BIS 40-45	2.17 (0.79-26.87)	17.99 (2.46-100.89)	0.016*
BIS 51-60	3.09 (1.41-37.50)	35.49 (2.32-133.00)	0.008*
Total	2.62 (0.75-37.50)	30.65 (2.32-133.0)	< 0.001**

Numerical data are displayed with median (minimum value-maximum value). Data were tested using the Wilcoxon test, P value <0.05 is considered significant; *significant. MMSE: Mini-Mental State Examination, BIS: Bispectral Index

Table 3- Relationship between depth of anesthesia and postoperative delirium (POD)

Depth of anesthesia	Skor MMSE					
	Preoperatuve		Pascaoperative		Delta pre-pascaoperative	
	Median (min-max)	P value	Median (min-max)	P value	Median (min-max)	P value
BIS 40-45	25 (24-28)	0.847	24 (24-25)	0.034	0 (-4-0)	0.300
BIS 51-60	25 (24-27)		25 (24-27)		0 (-2-3)	

Numeric data is displayed with median (minimum value-maximum value), Data is tested with Mann Whitney test, MMSE: Mini-Mental State Examination, BIS: Bispectral Index.

Table 4- Relationship between anesthesia depth and CAM

Depth of anesthesia	CAM postoperative		P value
	Delirium	No delirium	
	n (%)	n (%)	
BIS 40-45	6 (54.5)	5 (45.5)	0.040*
BIS 51-60	1 (9.1)	10 (90.9)	

Categorical data are displayed with number (n) and percentage (%). Data were tested using the Chi-square test. A P value <0.05 is considered significant; * significant, CAM: Confusion Assessment Method, BIS: Bispectral Index

Table 5- Relationship between IL-6 levels and postoperative MMSE scores

IL-6 levels	MMSE	
	r	P value
Preoperative	0.271	0.127
Pascaoperative	-0.041	0.820

Data numerik dengan uji korelasi Spearman.

Table 6- Relationship between IL-6 levels and postoperative CAM

IL-6 levels (ng/mL)	Delirium (n= 9)	No delirium (n= 24)	P value
Preoperative	2.13 (0.79-37.50)	2.62 (0.75-28.00)	0.766
Pascaoperative	50.62 (2.46-116.06)	35.09 (2.32-133.00)	0.309

Numeric data is displayed with median (minimum value-maximum value) and is tested using the Mann-Whitney test.

Table 7- Relationship between IL-6 levels and depth of anesthesia

IL-6 levels (pg/mL)	BIS 40-45	BIS 51-60	P value
Preoperative	2.17 (0.79-26.87)	3.09 (1.41-37.50)	0.300
Pascaoperative	17.99 (2.46-100.89)	35.49 (2.32-133.00)	0.332
Delta pre-postoperative	15.86 (-21.60-99.22)	30.38(-5.89-130.17)	0.652

Numeric data is displayed with median (minimum value-maximum value) and is tested using the Mann-Whitney test.

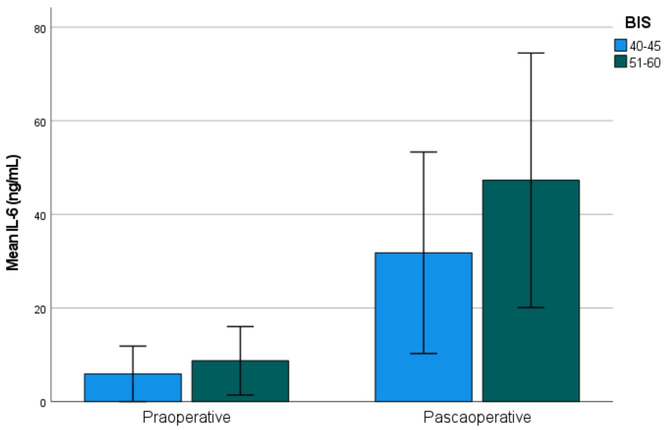

Figure 1- Comparison of IL-6 levels based on depth of anesthesia preoperatively and postoperatively

Discussion

In this study, the results showed that there was a tendency for increased delirium at 24 hours post-surgery in geriatric patients who received more profound general anesthesia, but not significantly. The results align with Quan et al.'s research that the depth of anesthesia did not affect POD at 3 months post-surgery [11]. A meta-analysis study by Lu et al. also stated that POD did not differ significantly between low and high BIS groups [12]. Similar results in a meta-analysis study by Ling et al. showed no significant difference in MMSE and POD scores at 7 days post-surgery between high BIS and low BIS [7].

Different results from this study were reported by Quan et al. There was a significant relationship between the depth of anesthesia and the incidence of POD 7 days after surgery, where the BIS 45–60 group resulted in a greater incidence of POD than the BIS 30-45 group [11]. Hou et al.'s study on 66 patients aged ≥ 60 years who underwent total knee replacement surgery under general anesthesia stated that POD at 24 hours postoperatively in the BIS 40-50 group was 20% and only 3.3% in the BIS 55-65 group [13]. The difference in results with this study may be caused by differences in monitoring POD time and BIS category. In contrast, in this study, POD monitoring was carried out 24 hours post-surgery. The BIS categories studied were BIS 51-60 and BIS 40-45.

In this study, there was a tendency for increased neurocognitive disorders at 24 hours postoperatively in geriatric patients. However, it was insignificant, and the MMSE score was still within the normal category range. These results indicate that general anesthesia in geriatric patients does not cause delirium at 24 hours postoperatively because BIS monitored the range of this study at 40-60. This result is supported by the study by Lee et al., which stated that general anesthesia maintained with 5-6 vol% desflurane targeting BIS 40-60 resulted in a significant decrease in the incidence of GNPB [14].

The results of CAM showed that there was a significant relationship between the depth of anesthesia and the incidence of delirium at 24 hours postoperatively. The incidence of delirium mainly occurred at BIS 40-45. This result is in line with the research of Evered et al., which found that the incidence of postoperative delirium in the BIS 50 group was lower than in the BIS 35 group [15]. Similar results were reported in a meta-analysis study by Long et al. that anesthesia increased postoperative delirium in cardiac and non-cardiac surgery [16].

The effects of general anesthesia on POD can be explained because general anesthetics have some common receptors in the central nervous system, including the inhibitory NMDA receptor or the reinforcing gamma-aminobutyric acid type A (GABAA) receptor that affects memory. Cognitive deficits due to anesthesia can also occur due to disturbances in calcium homeostasis and neuroinflammation [17].

This study showed that IL-6 levels increased significantly at 24 hours post-surgery in overall IL-6 and IL-6 levels based on the entire BIS group. These results are explained in previous studies that the neuroinflammatory response peaked 24 hours after surgery [18]. Surgical trauma also significantly increased levels of the proinflammatory cytokine IL-6 in the hippocampus at 6 and 24 hours after surgery [19]. Increased production of IL-6 cytokines reflects the high level of tissue trauma. In major surgery, IL-6 concentrations increase at 30–60 minutes after the start of surgery and increase significantly after 2–4 hours postoperatively and peak at 24 hours and remain elevated for 48–72 hours postoperatively [20].

In this study, preoperative and 24-hour postoperative IL-6 levels were not significantly associated with MMSE, which are measures of 24-hour postoperative POD. These results indicate that IL-6 is not a predictor or indicator of 24-hour postoperative BPD in geriatric patients with general anesthesia. These results are consistent with the study of Zhao et al. in rats, where hippocampal IL-6 increased 6 hours after surgery. At 6-24 hours after surgery, microglia were highly active in the hippocampus, but the behavior of the rats did not change significantly. These results indicate that neuroinflammation due to trauma and anesthesia during surgery is not enough to disrupt the spatial reference memory of rats [21].

The difference between these results and previous studies can be explained by the difference in the trend of increasing IL-6 levels based on the time of postoperative measurement. The study by Sharipova et al. compared patients with or without POCD at 7 days postoperatively, showing a significant increase in IL-6 levels in patients who showed POD at the end of surgery and 24 hours postoperatively. In patients with POD, IL-6 increased drastically at 6 hours postoperatively, decreasing at 24 hours postoperatively [22]. In addition, it was reported in the study by Zhang et al. that patients with IL-6 ≥ 830.50 pg/mL at 6 hours postoperatively had a 5-fold higher risk of experiencing POD [23]. Chen et al.'s study reported that IL-6 levels ≥ 583 pg/mL at 18 hours postoperatively can serve as a strong predictor of postoperative delirium in coronary artery bypass graft patients [24]. In this study, no patients experienced delirium 24 hours after surgery, which can be explained because, in this study, the average preoperative IL-6 level pg/mL was 7.34 pg/mL, which increased only to 39.33 pg/mL.

In contrast to these results, a randomized, prospective, controlled study by Kristek et al. in patients aged 65 years and older scheduled for femoral fracture fixation also reported that the predictor of POD at 5 days postoperatively in all patients was IL-6 levels at 72 hours postoperatively [20]. These results illustrate the role of IL-6 as a predictor of POD. The difference in results is because this study measured IL-6 levels at 24 hours post-surgery and measured POD at 24 hours post-surgery, so in this study, it was found that IL-6 was not a marker of POD at 24 hours post-surgery.

In this study, the absence of a relationship between POD and IL-6 levels can be explained because various other molecules can also increase and decrease in the hippocampus with specific kinetics after surgery that also affect POD [17]. In addition, the acute impact of surgery on cognition is not caused by a single cytokine or chemokine in isolation. Still, it potentially involves multiple secreted factors working together, such as IL-1b, TNF-α, S-100B, and IGF-1, which also influence POD [17,19]. This study showed that IL-6 levels tended to be lower in deep anesthesia (BIS 40-45) than in BIS 51-60 but were insignificant. Similar results were reported in a study by Li et al. in 60 patients undergoing elective laparoscopic colorectal cancer surgery that IL-6 levels and numeric rating scale (NRS) scores in the BIS 55 group were significantly higher than those in the BIS 35 group at 24 hours postoperatively [25]. Quan et al.'s study also stated that IL-6 levels in the BIS 55 group were significantly higher than those in the BIS 35 group at 24 hours after surgery [11]. Lv et al. studied the effects of different depths of anesthesia on inflammatory factors in 80 elderly patients aged over 65 years undergoing laparoscopic radical gastrectomy in which the depth of anesthesia was maintained using a closed-loop target-controlled infusion system: the EEG bispectral index was set to BIS 55 and BIS 45. Compared with the BIS 45 group, the plasma concentration of IL-6 in the BIS 55 group was significantly increased at 6 hours postoperatively. The plasma concentration of IL-6 was higher in both groups at 6, 24, and 72 hours postoperatively than preoperatively [26]. These results can be explained because the proinflammatory cytokine IL-6 is closely related to the response and intensity of surgical stress and is positively related to pain intensity. Pain is also a trigger for immunosuppression [25]. These results are similar to the results of Hou et al.'s study, which showed that there was a decrease in the release of inflammatory factors in patients with anesthesia and sedation depth at BIS 45. These results can explained by the fact that the mean arterial pressure, blood catecholamine concentration, and heart rate of patients during light anesthesia are higher so that the body's stress response is greater and the inflammatory response is stronger than during deep anesthesia. In addition, BIS 45 produces a significantly greater amount of propofol than BIS 55 during surgery [27]. Propofol plays a role in inhibiting the inflammatory response through the NF-κB pathway [26]. This study examined the relationship between the depth of anesthesia as a predictor of POD and IL-6 as a marker of POD at 24 hours postoperatively, which was the first to be conducted in Indonesia. The limitations of this study were the small sample size and only a 24-hour follow-up postoperatively.

Conclusion

Based on the results of the study, there was a tendency for an increased incidence of postoperative delirium (POD) in geriatric patients undergoing general anesthesia with an anesthesia depth of BIS 40–45 compared to the BIS 46–50 and BIS 51–60 groups, although the difference was not significant. Likewise, IL-6 levels 24 hours after surgery tended to be lower in the BIS 40–45 group but without a substantial relationship to the incidence of POD. These results imply that BIS 40–45 has the potential to be a predictor of POD in the geriatric population. Further research can be conducted with a larger sample size and a more extended observation period, up to three months after surgery, to obtain a more comprehensive understanding of the relationship between anesthesia depth, inflammatory response, and postoperative delirium.

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