



## Effect of General Anesthesia on Postoperative Cognitive Function in Patients Over 60 Years Old

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### Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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### ABSTRACT

**Background:** Postoperative cognitive dysfunction is one of the complications of surgery and general anesthesia (GA), causing short- and long-term mental and behavioral disabilities in patients. Such a disorder, especially in elderly patients, can lead to learning disabilities and memory impairment. Due to the importance of this subject, the present study aimed to assess the effects of GA on postoperative cognitive functions in patients over 60 years old who were candidates for surgery and anesthesia.

**Methods:** This descriptive-analytical clinical trial was performed on 45 patients over 60 years of age who were candidates for surgery under GA in Besat Hospital in Hamadan, Iran. Patients' memory function was measured by the Wechsler Memory Scale before the surgery and three days after the surgery. Finally, cognitive test scores pre- and post-anesthesia were compared, and the effect of different factors on them was evaluated.

**Results:** As evidenced by the results, the mean scores of general information, mental control, and word association subtests increased significantly after the surgery ( $P < 0.05$ ). Furthermore, the values related to the total score, the balanced score, and also the memory coefficient demonstrated a significant elevation after the surgery ( $P < 0.05$ ).

**Conclusion:** It seems that GA might exert neurotoxic or neuroprotective effects depending on the used dosage and the duration of the technique. Moreover, preoperative stress and disease severity may adversely affect patients' ability to answer memory questions.

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## 1. INTRODUCTION

General anesthesia (GA) is a drug-induced loss of consciousness accompanied by lack of pain and differs from normal sleep since the brain does not respond to painful stimuli, as well as tissue damage during surgery. The GA is performed by the administration of anesthetic drugs when the surgical or diagnostic process is lengthy, there is a possibility of bleeding, there is a need to lower the body temperature, or in such cases as chest or upper abdominal surgeries that affect the patient's breathing [1,2]. In adults, the GA is achieved using intravenous or inhaled (through a mask or intravenous airway) anesthetics. The anesthetic state is kept with anesthetics, analgesics, tranquilizers, sedatives, and skeletal muscle relaxant drugs.

During the operation, the patient's vital signs, such as cardiac and hemodynamic status, respiratory status, body temperature, as well as anesthesia and analgesia conditions, are carefully monitored by the anesthesia team to take immediate action in case of any problems. Therefore, the GA does not present any risk to most patients, although it may bring about some transient, mild, and harmless symptoms which pose no threat to patients' health. Nonetheless, some evidence suggests that anesthesia may have unintended short- and long-term side effects for the patient, especially the elderly. Cognitive complications from anesthesia, also known as "postoperative cognitive impairment," usually occur due to impaired mental function, impaired postoperative functional recovery, increased hospital stay, and incurred high medical costs [3-5].

By definition, cognitive disorders refer to a set of mental disorders that can be transient or permanent by causing inefficiencies in cognitive functions, namely complex attention, learning, memory, social cognition, as well as executive functions, such as problem-solving and logical thinking [6,7]. Cognitive impairments may be due to pathological changes in the structure of central nerve cells, such as the formation of fibrous plaques and masses of amyloid-beta protein, or as a result of reduced neurons, destruction of synapses, changes in nerve factors, or defective function of neural mediators. Nevertheless, the exact mechanism of cognitive impairment after surgery is not well understood; moreover, these disorders may even be improperly diagnosed

and considered a natural finding. Postoperative cognitive dysfunction includes disorders of mental processes that affect cognitive functions, such as memory, visual perception, speech perception, attention, or concentration [8,9].

The GA usually uses inhaled anesthetics, such as halothane, methoxyflurane, and nitric oxide, or intravenous anesthetics, namely propofol, barbiturates, benzodiazepines, and ketamine. However, these drugs are also regarded as risk factors for cognitive disorders due to their effects on the central nervous system. The life of nerve cells and their normal metabolism requires a constant supply of oxygen, glucose, and nutrients, as well as the excretion of waste products from metabolism. The proper performance of these processes requires the optimal maintenance of cerebral blood flow. Many general anesthetics, such as propofol and barbiturates, cause a decrease in nerve cell metabolism and sometimes postoperative cognitive complications by affecting cerebral blood flow and lowering body temperature. Barbiturates, for instance, reduce metabolism and brain function, which can be well detected by electroencephalography. Benzodiazepines also cause changes in blood flow to the brain and metabolism of nerve cells and may have such side effects as proximal forgetting. Among these, opioid derivatives have the least effect on blood flow and brain metabolism, compared to other anesthetics. On the other hand, halothane, which is an inhaled anesthetic, has the highest vasodilatory properties and the least change in brain metabolism; moreover, it increases the ratio of cerebral blood flow to cerebral metabolism [10-13].

In light of the aforementioned issues, the present study aimed to assess the effects of GA on postoperative cognitive dysfunction in order to help take appropriate measures to prevent the exacerbation of cognitive function, especially in patients above 60 years old undergoing surgery, and also select an appropriate method of anesthesia in these individuals.

## 2. MATERIALS AND METHODS

The present study was conducted in Besat Hospital in Hamadan, Iran.

### 2.1 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) age range of above 60 years, 2) candidate for

surgery under GA, 3) being in classes I or II of ASA classification, 4) ability to read and write, 5) and satisfaction to participate in the study. On the other hand, the exclusion criteria entailed: 1) dementia, 2) contraindications to GA (e.g., heart failure, severe renal failure, severe liver failure, respiratory failure, bleeding disorders, heart attack and stroke within the last six weeks, as well as progressive neurological disorders), 3) impaired level of consciousness after surgery for any reason (including Cerebrovascular accident), 4) a delay in waking up due to anesthesia complications) so that it is impossible to perform the relevant tests, 5) a history of alcohol use, 6) a history of drug use, 7) a history of taking sedatives, such as benzodiazepines and tricyclic antidepressants, 8) a history of anticonvulsant drug use, 9) a history of allergy to anesthetics, and 10) inability or unwillingness to participate in the study.

## 2.2 Study Design

This study was conducted on 45 patients over 60 years who were candidates for surgery under GA and were classified as Class I and II according to the American Society of Anesthesiologists (ASA) classification hospitalized in Besat Hospital in Hamadan from 2018 to 2019. The data collection tools were checklists and attached questionnaires. All demographic information, type of surgery, and variables related to the patient's vital signs during anesthesia were recorded in a researcher-made checklist. The Wechsler Memory Scale, the third edition, was also used to assess changes in cognitive function in patients. The sampling was performed using the convenience and non-probability methods.

At the preoperative visit, the demographic information of each patient was collected and recorded in a checklist designed by the researcher. Thereafter, the Wechsler Memory Scale, the third edition, was used for participants' cognitive functions, such as short- and long-term memory, as well as the ability to concentrate mentally before surgery (hospital day) and the third day after surgery. For the answers given to the questions of each sub-test, a raw score is considered, the sum of which gives the total score of the test. Following that, the raw scores of the sub-tests were converted into a single scale based on a table to calculate the balanced scores. The IQ was calculated based on another table from the sum of the total balanced scores. Finally, cognitive test scores before and after

anesthesia were compared, and the effect of different factors on them was evaluated.

During the procedure, electrocardiography, pulse oximetry, and a non-invasive sphygmomanometer were used to monitor the vital signs. The GA was performed in a standard manner by hospital anesthesiologists based on in-ward standards. Due to a large number of anesthesiologists and assistants working in the center and the relatively long time of the project, it was not possible to standardize the medications used in all cases, and the choice of drug was the responsibility of the relevant specialist. The types of surgeries performed included general surgery, orthopedics, ENT, neurosurgery, and maxillofacial surgery.

## 2.3 Statistical Analysis

Data were analyzed in SPSS software (version 16). All quantitative data with normal distribution were displayed as mean  $\pm$  standard deviation, while quantitative data with abnormal distribution were presented as a median and quadratic range. Qualitative variables were also expressed in the form of ratios and percentages. The quantitative data distribution method was determined using the Kolmogorov-Smirnov test. Thereafter, in patients with cognitive disorders, the variables were recorded before and after the surgery. Paired t-test was used when the data had an abnormal distribution, and the Wilcoxon test was applied when they had a normal distribution. The Chi-square test was also used to compare data related to qualitative variables. Moreover, in order to compare quantitative variables between the two groups with or without cognitive impairment, if they had a normal distribution an independent t-test was used, and if they had an abnormal distribution, Mann-Whitney test was used. In univariate analyzes to determine the effect of age, duration of surgery, and length of hospital stay on changes in postoperative cognitive test scores, the Pearson correlation coefficient was used, and the logistic regression test was applied in multivariate analyzes. A p-value less than 0.05 was considered statistically significant.

## 3. RESULTS

The present study included 45 patients undergoing GA with a mean age of  $66.1 \pm 6.8$  years (age range: 59-90). The majority of patients (66.7%; n=30) were male. Table 1 displays the demographic characteristics of the

patients, including marital status and education level.

Participants' memory performance was assessed by the Wechsler Memory Scale (Third Edition). It determines the general state of participants' memory by calculating the total score and coefficient of memory. Moreover, this scale consists of seven subtests, including general information about daily affairs, orientation (awareness of time and place), mental control, logic memory, repetition of digits (forward and reverse), visual memory, and word association, each of which can be used to assess the state of various components of memory.

This test was performed twice in total, once before the operation and once on the third day after the surgery. The average length of the test was 50 min. The data obtained from these tests were averaged after collection and the distribution of data was then determined by the Kolmogorov-Smirnov test. Finally, parametric and non-parametric data were compared using the paired t-test and Wilcox test, respectively. Among the data related to the Wechsler Memory Scale subtests before and after the surgery, only

the scores of the word association test had a normal distribution, and the data of other tests had an abnormal distribution both before and after the surgery ( $P < 0.05$ ). On the contrary, data on the overall test score, balanced score, and memory coefficient had a normal distribution both before and after the surgery. Probability values ( $P$ ) less than 0.05 reject the null hypothesis of the normality test, which is the normality of the data. In other words, if the p-value is less than 0.05, the data distribution is not normal, and if it is higher, it is normal.

After determining the distribution and normality of the data, the mean scores of the Wechsler Memory Scale subtests and the total test score, balanced score and the memory coefficient scores for possible changes were compared separately before and after the surgery and in pairs. For this purpose, data related to general information tests, orientation, mental control, logical memory, and repetition of digits, visual memory that had abnormally distributed by non-parametric Wilcoxon test, and data association test data that had a normal distribution were compared before and after the surgery by paired t-test.

**Table 1. Demographic characteristics of the patients**

Demographic Characteristics	Group	Frequency	Percent
Gender	Male	30	66.7
	Female	15	33.3
Education level	Illiterate	26	57.8
	Primary School	13	28.9
	Middle School	3	6.7
	Diploma	2	4.4
	Marital status	Married	45
	Single	0	0

**Table 2. Comparison between mean scores of sub-tests and total score of Wechsler memory scale before and after the surgery**

Subtest	Number	Before anesthesia			After anesthesia			Significance level
		The least	The most	Mean and standard deviation	The least	The most	Mean and standard deviation	
General information	45	2.0	6.0	4.16±1.22	2.0	6.0	4.42±1.14	0.011
Orientation	45	3.0	5.0	4.45±0.73	2.0	5.0	4.44±0.78	0.480
Mental control	45	0.0	6.0	4.04±1.52	0.0	7.0	4.42±1.66	0.017
Logical memory	45	0.0	7.5	3.31±1.78	0.0	12.5	3.47±2.28	0.904
Repetition of digits	45	0.0	11.0	3.49±2.25	0.0	11.0	3.91±2.40	0.075
Visual memory	45	0.0	9.0	3.18±2.69	0.0	9.0	3.38±2.95	0.337
Word association	45	0.0	14.0	5.17±3.08	0.0	15.5	6.82±3.17	0.006
Total score	45	11.0	47.5	28.37±8.37	5.0	48.0	30.87±9.77	0.007
Balanced score	45	59.0	95.5	76.32±8.43	53.0	96.0	78.82±9.79	0.007
Memory coefficient	45	30.0	96.0	69.64±11.10	50.0	97.0	74.16±12.08	0.008

As illustrated in Table 2, the mean scores of general information, mental control, and word association tests increased statistically significantly after the surgery ( $P < 0.05$ ). Nonetheless, there was no significant change in the mean scores of orientation tests, logical memory, repetition of digits, and visual memory, compared to before the surgery. On the other hand, comparing the mean of the total score, balanced score, and memory coefficient before and after the surgery using paired t-test displayed a significant increase in all three components after the surgery ( $P < 0.05$ ).

#### 4. DISCUSSION

The results of the present study pointed out that the mean scores of general information, mental control, and word association were significantly increased after the surgery, compared to preoperative scores. In addition, the values related to the total score, the balanced score, and also the memory coefficient demonstrated a significant increase after the surgery. As illustrated, these results are inconsistent with many previous findings on the attenuating effects of GA on cognitive function. It seems that in some cases, GA may be associated with metabolic and brain dysfunction. Numerous drugs used in GA reduce blood flow and decrease the metabolism of cells in the nervous system. The GA can also interfere with neurotransmitter pathways [14].

Studies on young animal specimens have pointed out that anesthetics can cause neuronal cell death, impaired learning and memory, altered dendritic morphology, and behavioral abnormalities. Although the duration of exposure and the doses administered to animals are not comparable to the doses prescribed to humans, the results of animal studies raise serious concern over the potential risk of anesthetic effects on the brain. Furthermore, the potentially harmful effects of anesthesia on the brain have been increasingly discussed in medical articles [15]. Therefore, growing evidence from animal and clinical studies suggested that anesthetics may exert neurotoxic effects on the brains of young and elderly people. It is noteworthy that postoperative cognitive impairment is more likely to occur in populations that are normally more at risk of cognitive impairment [16].

In accordance with the results of the present research, some other studies pointed to the neuroprotective effects of GA on the brain. In

their study on neurons in culture media, Kudo et al. detected that treatment with low concentrations of anesthetics reduced neurons' vulnerability to neurotoxic agents and have protective effects. The present study revealed that low concentrations of anesthetics reduced cell death due to the excitatory toxicity of glutamate, hypoxia, ischemia, as well as oxygen-glucose deprivation. For example, isoflurane, sevoflurane, and halothane were found to reduce the release of lactate dehydrogenase and the uptake of calcium ions into neurons and glial cells exposed to NMDA or glutamate at clinically used concentrations [17].

The short-term use of isoflurane has been also demonstrated to reduce cell death in cultured neurons of the rat hippocampus exposed to oxygen-glucose deprivation [18]. Isoflurane also increased the survival rate of rat cerebellar Purkinje neurons exposed to glutamate [19]. In explaining these findings, Gray et al. (2005) suggested that a moderate increase in the concentration of cytosolic calcium ions in the presence of isoflurane stimulates the signaling pathway of mitogen-activated protein kinases, including kinases regulated by extracellular signal, c-Jun NH<sub>2</sub>-terminal kinase, and protein kinase B, which are signaling proteins for cell survival [20].

Along the same lines, in their study on rat cortical neurons in a culture medium, Bickler and Fahlman found that isoflurane increased calcium ion-dependent signaling proteins by increasing the survival of hypoxic neurons [21]. The neutralization of all these effects by treatment with xestospongine C, which is an antagonist of inositol triphosphate receptors on the endoplasmic reticulum [22], as well as the ability of other inhaled anesthetics, such as sevoflurane and desflurane, or intravenous anesthetics, including propofol, to activate inositol triphosphate receptors, suggests that these anesthetics at low concentrations and in the short term may inhibit the activation of inositol triphosphate receptors, resulting in the gentle release of ions [23-25]. Calcium ions from the endoplasmic reticulum cause protective neuronal effects. In addition, isoflurane treatment has been displayed to be able to protect endothelial cells against damage caused by hypoxia through a mitochondrial-dependent mechanism [26].

Therefore, it seems that anesthetics, such as isoflurane, can exert both neuroprotective and

neurotoxic effects through differential activation of inositol triphosphate receptors and release of calcium ions from the endoplasmic reticulum. Inositol triphosphate and balanced release of calcium ions from the endoplasmic reticulum provide neuroprotection. On the other hand, anesthetics in high concentrations and in the long term act as long-term cerebral ischemia; moreover, as a stress factor, they cause overactivity of inositol triphosphate receptors, resulting in the excessive and abnormal release of calcium ions from the endoplasmic reticulum, which causes nerve damage. Accordingly, it is very important to notice the concentration and duration of treatment with general anesthetics in an attempt to maximize their beneficial effects and minimize their harmful effects, especially in elderly patients [27,28].

## 5. RESEARCH LIMITATIONS

One of the limitations of the present research is the relatively small sample size due to the large number of factors affecting cognitive impairment. The lack of comparison between spinal anesthesia and GA in cognitive impairment is the second limitation since the stress of surgery itself, regardless of the type of anesthesia, can cause cognitive impairment. Moreover, the surgeries of patient underwent and anaesthesia procedure are not same in this study, which should be same in order to make a correct comparison between patients.

## 6. CONCLUSION

As evidenced by the third version of the Wechsler Memory Scale test, the mean scores of general information, mental control, and word association were significantly increased after the surgery, compared to preoperative scores. Furthermore, it seemed that GA can exert neurotoxic or neuroprotective effects depending on the dose used and the duration of treatment. Moreover, preoperative stress and disease may adversely affect patients' ability to answer memory questions.

## ETHICAL APPROVAL AND CONSENT

All stages of this study were carried out in accordance with the principles of the Helsinki Declaration on medical research on humans and based on the instructions of the Ethics Committee of Hamadan University of Medical Sciences. This study has the code of ethics committee (IR.UMSHA.REC.1398.308) and IRCT

code (IRCT20190429043414N2). All patients entered the study after being informed of the research objectives and signing a written consent. Participants in the study were also assured that their information would be confidential and would not be used elsewhere except for this study. Patients participated in this study with their consent and were able to withdraw from the study at any time. This study did not interfere with the treatment process of patients and did not impose any additional costs on them.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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