

## Original Research Article

### Effect of General Anesthesia on Postoperative Cognitive Function in Patients

#### Over 60 Years Old

#### 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.

24 **Keywords:** Cognitive dysfunction, General anesthesia, Memory, Surgery, Wechsler Scale

25 **Introduction**

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

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

43 By definition, cognitive disorders refer to a set of mental disorders that can be transient or permanent by  
44 causing inefficiencies in cognitive functions, namely complex attention, learning, memory, social  
45 cognition, as well as executive functions, such as problem-solving and logical thinking (6, 7). Cognitive  
46 impairments may be due to pathological changes in the structure of central nerve cells, such as the  
47 formation of fibrous plaques and masses of amyloid-beta protein, or as a result of reduced neurons,

48 destruction of synapses, changes in nerve factors, or defective function of neural mediators. Nevertheless,  
49 the exact mechanism of cognitive impairment after surgery is not well understood; moreover, these  
50 disorders may even be improperly diagnosed and considered a natural finding. Postoperative cognitive  
51 dysfunction includes disorders of mental processes that affect cognitive functions, such as memory, visual  
52 perception, speech perception, attention, or concentration (8, 9).

53 The GA usually uses inhaled anesthetics, such as halothane, methoxyflurane, and nitric oxide, or  
54 intravenous anesthetics, namely propofol, barbiturates, benzodiazepines, and ketamine. However, these  
55 drugs are also regarded as risk factors for cognitive disorders due to their effects on the central nervous  
56 system. The life of nerve cells and their normal metabolism requires a constant supply of oxygen,  
57 glucose, and nutrients, as well as the excretion of waste products from metabolism. The proper  
58 performance of these processes requires the optimal maintenance of cerebral blood flow. Many general  
59 anesthetics, such as propofol and barbiturates, cause a decrease in nerve cell metabolism and sometimes  
60 postoperative cognitive complications by affecting cerebral blood flow and lowering body temperature.  
61 Barbiturates, for instance, reduce metabolism and brain function, which can be well detected by  
62 electroencephalography. Benzodiazepines also cause changes in blood flow to the brain and metabolism  
63 of nerve cells and may have such side effects as proximal forgetting. Among these, opioid derivatives  
64 have the least effect on blood flow and brain metabolism, compared to other anesthetics. On the other  
65 hand, halothane, which is an inhaled anesthetic, has the highest vasodilatory properties and the least  
66 change in brain metabolism; moreover, it increases the ratio of cerebral blood flow to cerebral metabolism  
67 (10-13).

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

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## 74 **Material and Methods**

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

### 76 **2.1 Inclusion and Exclusion Criteria**

77 The inclusion criteria were as follows: 1) age range of above 60 years, 2) candidate for surgery under  
78 GA, 3) being in classes I or II of ASA classification, 4) ability to read and write, 5) and satisfaction to  
79 participate in the study. On the other hand, the exclusion criteria entailed: 1) dementia, 2) contraindications  
80 to GA (e.g., heart failure, severe renal failure, severe liver failure, respiratory failure, bleeding disorders,  
81 heart attack and stroke within the last six weeks, as well as progressive neurological disorders), 3)  
82 impaired level of consciousness after surgery for any reason (including Cerebrovascular accident), 4) a  
83 delay in waking up due to anesthesia complications) so that it is impossible to perform the relevant tests,  
84 5) a history of alcohol use, 6) a history of drug use, 7) a history of taking sedatives, such as  
85 benzodiazepines and tricyclic antidepressants, 8) a history of anticonvulsant drug use, 9) a history of  
86 allergy to anesthetics, and 10) inability or unwillingness to participate in the study.

### 87 **2.2 Study Design**

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

**Comment [Z1]:** Why study population above 60 years considered to look for cognitive disorder after GA?

**Comment [Z2]:** Dementia is very common in age group above 60 and how you excluded? Mention in Methods

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

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

### 110 **2.3 Statistical Analysis**

111 Data were analyzed in SPSS software (version 16). All quantitative data with normal distribution were  
112 displayed as mean±standard deviation, while quantitative data with abnormal distribution were presented  
113 as a median and quadratic range. Qualitative variables were also expressed in the form of ratios and  
114 percentages. The quantitative data distribution method was determined using the Kolmogorov-Smirnov  
115 test. Thereafter, in patients with cognitive disorders, the variables were recorded before and after the  
116 surgery. Paired t-test was used when the data had an abnormal distribution, and the Wilcoxon test was  
117 applied when they had a normal distribution. The Chi-square test was also used to compare data related to  
118 qualitative variables. Moreover, in order to compare quantitative variables between the two groups with  
119 or without cognitive impairment, if they had a normal distribution an independent t-test was used, and if

120 they had an abnormal distribution, Mann-Whitney test was used. In univariate analyzes to determine the  
121 effect of age, duration of surgery, and length of hospital stay on changes in postoperative cognitive test  
122 scores, the Pearson correlation coefficient was used, and the logistic regression test was applied in  
123 multivariate analyzes. A p-value less than 0.05 was considered statistically significant.

#### 124 **Ethical Considerations**

125 All stages of this study were carried out in accordance with the principles of the Helsinki Declaration on  
126 medical research on humans and based on the instructions of the Ethics Committee of Hamadan  
127 University of Medical Sciences. This study has the code of ethics committee (   
128 IR.UMSHA.REC.1398.308) and IRCT code (IRCT20190429043414N2). All patients entered the study  
129 after being informed of the research objectives and signing a written consent. Participants in the study  
130 were also assured that their information would be confidential and would not be used elsewhere except  
131 for this study. Patients participated in this study with their consent and were able to withdraw from the  
132 study at any time. This study did not interfere with the treatment process of patients and did not impose  
133 any additional costs on them.

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#### 135 **Results**

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

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

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**Comment [Z3]:** Include Age- It will give Idea most particepants were from which age group.

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	100
	Single	0	0

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

149 This test was performed twice in total, once before the operation and once on the third day after the  
150 surgery. The average length of the test was 50 min. The data obtained from these tests were averaged after  
151 collection and the distribution of data was then determined by the Kolmogorov-Smirnov test. Finally,  
152 parametric and non-parametric data were compared using the paired t-test and Wilcoxon test, respectively.  
153 Among the data related to the Wechsler Memory Scale subtests before and after the surgery, only the  
154 scores of the word association test had a normal distribution, and the data of other tests had an abnormal  
155 distribution both before and after the surgery ( $P < 0.05$ ). On the contrary, data on the overall test score,  
156 balanced score, and memory coefficient had a normal distribution both before and after the surgery .  
157 Probability values (P) less than 0.05 reject the null hypothesis of the normality test, which is the normality

158 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  
159 higher, it is normal.

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

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

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183 Table 2. Comparison between mean scores of sub-tests and total score of Wechsler memory scale before

184 and after the surgery

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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	1.22±4.16	2.0	6.0	1.14±4.42	0.011
Orientation	45	3.0	5.0	0.73±4.45	2.0	5.0	0.78±4.44	0.480
Mental control	45	0.0	6.0	1.52±4.04	0.0	7.0	1.66±4.42	0.017
Logical memory	45	0.0	7.5	1.78±3.31	0.0	12.5	2.28±3.47	0.904

Repetition of digits	45	0.0	11.0	2.25±3.49	0.0	11.0	2.40±3.91	0.075
Visual memory	45	0.0	9.0	2.69±3.18	0.0	9.0	2.95±3.38	0.337
Word association	45	0.0	14.0	3.08±5.17	0.0	15.5	3.17±6.820	0.006
Total score	45	11.0	47.5	8.37±28.37	5.0	48.0	9.77±30.87	0.007
Balanced score	45	59.0	95.5	8.43±76.32	53.0	96.0	9.79±78.82	0.007
Memory coefficient	45	30.0	96.0	11.10±69.64	50.0	97.0	12.08±74.16	0.008

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191 **Discussion**

192 The results of the present study pointed out that the mean scores of general information, mental  
193 control, and word association were significantly increased after the surgery, compared to  
194 preoperative scores. In addition, the values related to the total score, the balanced score, and also  
195 the memory coefficient demonstrated a significant increase after the surgery. As illustrated, these  
196 results are inconsistent with many previous findings on the attenuating effects of GA on  
197 cognitive function. It seems that in some cases, GA may be associated with metabolic and brain

198 dysfunction. Numerous drugs used in GA reduce blood flow and decrease the metabolism of  
199 cells in the nervous system. The GA can also interfere with neurotransmitter pathways (14).

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

209 In accordance with the results of the present research, some other studies pointed to the neuroprotective  
210 effects of GA on the brain. In their study on neurons in culture media, Kudo et al. detected that treatment  
211 with low concentrations of anesthetics reduced neurons' vulnerability to neurotoxic agents and have  
212 protective effects. The present study revealed that low concentrations of anesthetics reduced cell death  
213 due to the excitatory toxicity of glutamate, hypoxia, ischemia, as well as oxygen-glucose deprivation. For  
214 example, isoflurane, sevoflurane, and halothane were found to reduce the release of lactate dehydrogenase  
215 and the uptake of calcium ions into neurons and glial cells exposed to NMDA or glutamate at clinically  
216 used concentrations (17).

217 The short-term use of isoflurane has been also demonstrated to reduce cell death in cultured neurons of  
218 the rat hippocampus exposed to oxygen-glucose deprivation (18). Isoflurane also increased the survival  
219 rate of rat cerebellar Purkinje neurons exposed to glutamate (19). In explaining these findings, Gray et al.  
220 (2005) suggested that a moderate increase in the concentration of cytosolic calcium ions in the presence  
221 of isoflurane stimulates the signaling pathway of mitogen-activated protein kinases, including kinases

222 regulated by extracellular signal, c-Jun NH2-terminal kinase, and protein kinase B, which are signaling  
223 proteins for cell survival (20).

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

234 Therefore, it seems that anesthetics, such as isoflurane, can exert both neuroprotective and neurotoxic  
235 effects through differential activation of inositol triphosphate receptors and release of calcium ions from  
236 the endoplasmic reticulum. Inositol triphosphate and balanced release of calcium ions from the  
237 endoplasmic reticulum provide neuroprotection. On the other hand, anesthetics in high concentrations and  
238 in the long term act as long-term cerebral ischemia; moreover, as a stress factor, they cause overactivity  
239 of inositol triphosphate receptors, resulting in the excessive and abnormal release of calcium ions from  
240 the endoplasmic reticulum, which causes nerve damage. Accordingly, it is very important to notice the  
241 concentration and duration of treatment with general anesthetics in an attempt to maximize their  
242 beneficial effects and minimize their harmful effects, especially in elderly patients (27, 28).

### 243 **Research Limitations**

244 One of the limitations of the present research is the relatively small sample size due to the large number  
245 of factors affecting cognitive impairment. The lack of comparison between spinal anesthesia and GA in

246 cognitive impairment is the second limitation since the stress of surgery itself, regardless of the type of  
247 anesthesia, can cause cognitive impairment. Moreover, the surgeries of patient underwent and anaesthesia  
248 procedure are not same in this study, which should be same in order to make a correct  
249 comparison between patients.

## 250 **Conclusion**

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

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