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REVIEW ARTICLE

The Assessment of Memory under Total Intravenous Anesthesia

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Abstract

Background and objectives: In this study, we aimed to assess implicit and explicit memory in patients who had abdominal surgery under total intravenous anesthesia (TIVA) with propofol and remifentanyl, in which anesthesia level was controlled by bispectral index (BIS) monitoring.

Method: Total intravenous anesthesia was administered to 60 adult patients, to obtain BIS levels of 40-60. Patients were randomly allocated to three groups according to tapes they listened to. Patients in the category group (CT) listened to a tape containing five animal names. Patients in the word recognition group (WM) listened to a tape containing five intermediate-frequency words, adapted into Turkish. Patients in the control group (CG) listened to sea sounds until the end of surgery. Two hours after surgery, tests were administered to each patient in the recovery room to assess memory.

Results: There was a difference between the CT and CG groups in their Mini-Mental State Examination scores, all values were > 20. The results of the category and word recognition tests that were applied to assess implicit memory were not statistically different among the groups. There was no evidence of implicit memory in any of the patients. One patient remembered hearing 'the sound of water' as a proof of explicit memory. Eleven patients said they had dreamt.

Conclusions: Although no evidence of implicit memory under adequate anesthesia with TIVA was found, one patient showed explicit memory. Although adequate depth of anesthesia provided by BIS monitoring supports our implicit memory results, it does not explain the explicit memory results.

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Introduction

The relation between anesthesia and memory has been attracting attention for a long time. This issue has been revived due to the increased number of malpractice lawsuits for awareness during surgery seen in recent years¹. Therefore, the relation between anesthesia and memory has been one of the most studied topics in recent years.

The effect of anesthesia on implicit memory is important because of post-traumatic stress disorder (PTSD) that develops as a result of negative side effects that can affect postoperative quality of life in patients, such as sleep disorders, nightmares and dreams, daily anxiety, fear that the same can happen if they need anesthesia again, doctor phobia, and the need for psychotherapy^{2,3}.

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As a result of symptoms such as pain, hearing speech during surgery, muscle weakness, desperation, anxiety, panic, and near-death experience, explicit memory developing under anesthesia is one of the most important reasons for decreased patient satisfaction¹⁻⁵.

In the literature review, we did not encounter any study in which implicit memory was studied by comparing memory tests, the depth of anesthesia was constantly controlled by BIS monitoring, or the difference between the group given total intravenous anesthesia (TIVA) with remifentanil-propofol base and the group solely listening to neutral voices was evaluated. The aim of this study was to assess memory in patients anesthetized with TIVA, when depth of anesthesia was controlled using bispectral index (BIS) monitoring.

Method

After approval from the local ethics committee and written informed consent from the patients, 60 ASA physical status I-II patients scheduled for elective abdominal surgery aged 18-80 with a minimum eight-year primary school education, were randomly and prospectively enrolled in the study. Patients with hearing disorders, with history of alcohol or drug abuse, who did not speak Turkish, or with Mini-Mental State Examination (MMSE) scores under 20 were excluded from this research.

Thirty minutes before surgery, the patients were transferred to the anesthesia preparation unit. Stait-Trait Anxiety (STAT) I-II tests were administered to assess preoperative and general stress response, and MMSE was performed for cognitive function assessment of the patients. An 18-gauge catheter was used to access an intravenous (i.v) line, and 5 mL kg⁻¹ of 0.9% sodium chloride was used for fluid loading. With no premedication, the patients' non-invasive systemic arterial pressure, ECG, pulse oximetry, and BIS were monitored in the operating room.

Anesthesia was induced with 0.5 mg i.v. atropine, followed by i.v. 0.5 µg kg⁻¹.min⁻¹ remifentanil infusion for one minute, and then 2 mg.kg⁻¹ i.v. propofol. Additional 20 mg i.v. propofol doses were administered at 30-second intervals in order to keep BIS values between 40 and 60. Two minutes after 0.1 mg.kg⁻¹ vecuronium i.v. was given, endotracheal intubation was performed. Anesthesia was maintained with 4-6 mg.kg⁻¹.h⁻¹ i.v. propofol, 0.1-2 µg.kg⁻¹.min⁻¹ i.v. remifentanil infusion, and 50% medical air/oxygen mixture to keep BIS values between 40 and 60. During anesthesia, maintenance 0.02 mg.kg⁻¹ i.v. vecuronium was administered when additional muscle relaxation was needed.

Right after intubation, headphones were placed on all patients and they were made to listen to a tape of sea sounds. The patients' BIS values were recorded during skin incision and every five minutes perioperatively. Five minutes after skin incision, the patients were divided into three groups according to the closed envelope method. The tape with sea sounds was replaced with a 7.5-minute recording in the experimental groups.

Category Test Group (CT group, n = 20)

The recording contained five medium-frequency animal names: dolphin, eagle, crocodile, giraffe, and monkey. These animal names were determined with a pilot study performed

on 60 volunteers in collaboration with the Psychiatry Department. Every word was pronounced in one second, and the interval between words was adjusted to 8 sec. After the 7.5-minute recording finished, during which every word was repeated 10 times, it was replaced with the natural sea sounds tape, to which the patient listened until the end of the surgery⁶.

Word Memory Test Group (WM group, n = 20)

The recording contained five medium-frequency words chosen from the Rey Auditory Verbal Learning Test list, adapted into the Turkish language (stove, button, curtain, gold, and carpet). Every word was pronounced in one second, and the interval between words was adjusted to 8 seconds. After the 7.5-minute recording finished, during which every word was repeated 10 times, it was replaced with the natural sea sounds tape, to which the patient listened until the end of the surgery⁶.

Control Group (CG group, n = 20)

The tapes were replaced in accordance with the other groups, but all the recordings that were played contained sea sounds.

During the closure of the fascia, all the patients received a 0.05 mg.kg⁻¹ loading dose of i.v. morphine via a patient-controlled analgesia (PCA) device. The infusion of remifentanil and propofol was stopped after skin closure. Neostigmine and atropine were administered for reversal of neuromuscular blockade, and the patients were extubated under conventional convenient conditions. During and five minutes after extubation, BIS values were recorded. In the recovery unit, the patients were supplied with oxygen aid for two hours and were watched for hemodynamic events.

In order to evaluate explicit memory two hours after surgery, the patients were asked the following two questions:

1. Do you remember anything between the beginning and the end of the surgery?
2. Did you have any dreams during the surgery?

After those questions, in order to evaluate implicit memory, the patients from the CT group were asked to name the first five animals that came to mind.

A list containing ten medium-frequency words chosen from the Rey Auditory Verbal Learning Test list and adapted into the Turkish language (stove, button, curtain, gold, carpet, garden, cloud, oven, mountain, and nose) and the five that had been played perioperatively for the patients were read to the WM patients. They were then asked to pick the words they had heard before.

Although the CG patients had not listened to anything but natural sounds during surgery, they were asked the same questions as both patient groups, by which basal values were acquired for comparison.

We evaluated whether the correct words or animal names that each of the two study groups and the control group remembered were of different frequency or not.

The sample sizes were calculated with the assumption of a possible difference in our study at least of 40% between any two groups. Therefore, 20 patients were allocated into each group in order to obtain an alpha error of 5% and statistical power of 80%.

Statistical Evaluation

Differences between the groups in independent variables such as age, gender, height, weight, length of surgery, and the surgery procedure were analyzed using Chi-square and t-test. After STAT I-II, MMSE, and BIS values were evaluated with a Test of Homogeneity, one-way ANOVA was used for analyzing the differences between the groups. The difference in distribution of correct recall in reference to independent variables was assessed using Chi-square and Fisher's exact tests. A p-value of less than 0.05 was considered significant.

Results

The distribution of groups by gender, age, weight, and height is shown in Table 1. No statistically significant differences between the groups were found in gender, age, weight, or height (Table 1).

There were no statistically significant differences between the groups in STAT I and STAT II questionnaire results (Table 2). MMSE test values were found significantly different between the CT and CG groups. Nevertheless, as all the obtained values were above 20, the patients' cognitive functions were accepted as adequate.

No statistically significant differences between the groups were found in terms of duration of surgery and surgical procedure (Table 3).

No statistically significant differences were found between the groups' basal BIS, intubation, skin incision, BIS values in the 5th minute after skin incision, extubation and 5th minute after extubation (Figure 1).

The implicit memory assessment by Category test conducted in the recovery room in the second hour after surgery showed no significant difference between groups. Patients in the CT and CG groups were asked to name the first five animals that came to mind; five patients in the CT group had one correct answer and two patients had two correct answers. Although the CG patients had not listened to anything but natural sounds during surgery, three patients had one correct answer (Table 4).

The implicit memory assessment by Word memory test conducted in the recovery room in the second hour after surgery showed no significant difference between the groups. The patients in the WM and CG groups were asked to identify five words they had been listening to during the surgery from a list of ten medium-frequency words by saying 'yes' when they recognized a word. Only two patients in the WM group confirmed correct words by saying 'yes'. However, four patients from the same group said they heard words they had not listened to during the surgery. Eight CG patients reported that they had heard one word (Table 5). No patient reported recalling more than one word. In the Word memory test, seven patients reported that they had heard a word or words. No significant difference between the groups was detected.

Table 1 Distribution of groups by gender, age, weight and height.

	Group WM (n = 20)	Group CT (n = 20)	Group CG (n = 20)	p
Female	19	19	18	0.776
Male	1	1	2	
Age (year)	38.25 ± 8.45	37.80 ± 7.30	40.30 ± 6.29	0.526
Height (cm)	163.5 ± 6.04	161.9 ± 6.02	162.45 ± 8.54	0.763
Weight (kg)	66.95 ± 12.74	72.05 ± 15.74	69.25 ± 12.43	0.504

*p < 0.05; means ± SD.

Table 2 STAT I, STAT II and MMSE tests results.

Tests	Group WM (n = 20)	Group CT (n = 20)	Group CG (n = 20)	p
STAT I	40.75 ± 6.36	42.35 ± 6.34	38.55 ± 4.33	0.121
STAT II	45.60 ± 5.13	47.60 ± 5.53	43.60 ± 3.98	0.440
MMSE	25.45 ± 2.35	23.95 ± 2.70	26.40 ± 2.04	0.007*

*p < 0.05; means ± SD.

Table 3 Distribution of groups by duration of surgery and surgical procedure.

	Group WM (n = 20)	Group CT (n = 20)	Group CG (n = 20)	p
Laparoscopic	13	13	12	0.931
Open abdomen surgery	7	7	8	
Duration of surgery (minute)	86.3 ± 47.05	102.5 ± 42.72	109.8 ± 46.74	0.270

*p < 0.05; means ± SD.

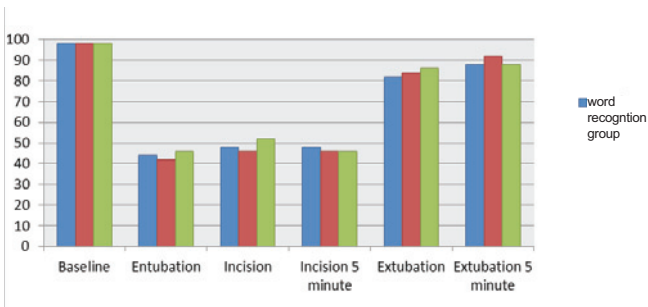


Figure 1 Basal, intubation and extubation BIS values.

The explicit memory assessment conducted in the recovery room in the second hour after surgery showed no significant differences between the groups. To the question ‘Do you remember anything between the beginning and the end of the surgery?’ only one patient in the WM group answered that she had heard ‘water sounds’ (Table 6). However, she pointed out that she did not feel pain or have any dreams during surgery. The patient who reported explicit memory had laparoscopic tubal ligation and curettage done. To the second question we asked, to evaluate explicit memory, ‘Did you have any dreams during the surgery?’ eleven patients gave positive answers. Four of them were in the WM group,

Table 4 The assessment of implicit memory by Category test.

The name of the first animal that comes to mind	Group CT (n=20) (%)	Group CG (n=20) (%)	p
0	13 (65.0)	17 (85.0)	0.219
1	5 (25.0)	3 (15.0)	
2	2 (10.0)	0 (0.0)	

*p < 0.05.

three in the CT group, and four in the CG group. In terms of having dreams during the surgery, no significant difference between the groups was found.

Discussion

For a long time, the connection between anesthesia and memory has remained a mystery. Is detected memory a part of awareness or is it a result of processing information during unconsciousness? There are still no answers to any of these questions^{7,8}. The first memory studies were performed on patients with organic amnesias; these patients have serious

Table 5 The assessment of implicit memory by the Word Memory test.

Word	Group WM		Group CG		P
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Stove	0 (0)	20 (100)	1 (5)	19 (95)	1.00
Button	0 (0)	20 (100)	1 (5)	19 (95)	1.00
Curtain	1 (5)	19 (95)	1 (5)	19 (95)	1.00
Gold	0 (0)	20 (100)	1 (5)	19 (95)	1.00
Carpet	1 (5)	19 (95)	0 (0)	20 (100)	1.00
Garden	2 (10)	18 (90)	2 (10)	18 (90)	1.00
Cloud	0 (0)	20 (100)	1 (5)	19 (95)	1.00
Oven	1 (5)	19 (95)	0 (0)	20 (100)	1.00
Mountain	0 (0)	20 (100)	1 (5)	19 (95)	1.00
Nose	1 (5)	19 (95)	0 (0)	20 (100)	1.00

*p < 0.05.

Table 6 The assessment of explicit memory.

	Group WM		Group CT		Group CG		P
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Dream	4 (20)	16 (80)	3 (15)	17 (85)	4 (20)	16 (80)	0.895
Remembering	1 (5)	19 (95)	0 (0)	20 (100)	0 (0)	2 (100)	0.362

*p < 0.05.

disability in learning new information and, therefore, show similarity to patients under anesthesia^{9,10}. This study was based on the following question: 'Is there implicit memory under adequate depth of anesthesia?'

Bispectral index, used during the maintenance of anesthesia, is the most specific and sensitive device for monitoring the depth of anesthesia¹¹⁻¹³ which prevents movement in response to surgical stimuli¹⁰ and, in particular, measures propofol-induced hypnotic effects¹². It has been shown that BIS decreased awareness around 77-82%, depending on the depth of anesthesia⁴. Lubke et al.⁸ showed that when BIS values were between 40 and 60, implicit memory was found in 11-43% of the patients. Haas et al.¹⁴ reported that when BIS values were in the 50-70 range, no implicit memory was observed. Our results support the findings of the study of Haas et al., as BIS values were in the 40-60 range and no implicit memory was observed.

We reported earlier that implicit memory was formed during cardiopulmonary bypass surgery, even though sevoflurane was given in 2% concentration and BIS value was 47¹⁵. One patient from our study expressed that she heard water sounds very clearly, which describes explicit memory, although she had BIS values between 40 and 60 during surgery and no implicit memory was observed. However, she did not mention the negative effects^{1,16} that patients in whom explicit memory is detected most often describe. We believe that our patient did not experience the negative emotions that can arise during explicit memory phase, as she listened to calming water sounds instead of hearing speech during the surgery while she was awake. These results are in contrast with the claim that explicit memory cannot be formed under adequate anesthesia. The clinical condition being inconsistent with the accepted BIS values may result from genetic factors, skull thickness, or neuronal activity differences¹⁷.

Sandin et al.¹⁸ found that gender does not affect memory; Sebel et al.⁴ showed that both gender and age have no influence on memory. In another study investigating ASA closed claim files, the authors show that level of awareness is not related to age; however, it was higher in females. In our study, the only patient with explicit memory was female. Due to the fact that remifentanyl has higher hemodynamic effects on patients over 50 years of age, we preferred to work with the 18-50 age group, in accordance with the studies of Jelacic et al.¹⁹ and Lequeux et al.⁷. While Jelacic et al. observed implicit memory in this age group, Lequeux et al. did not. In our study, implicit memory in this age group could not be detected.

The medications used for anesthesia have different effects on memory^{18,20-22}. In our study, patients were not premedicated, so that the results would not be affected.

Incidence of explicit memory in TIVA patients is believed to be higher compared to inhalation anesthesia²³. Andrade et al.⁶ could not find implicit or explicit memory in patients who received propofol-only infusion. In TIVA, propofol is often used together with an opioid. This combination significantly decreases the propofol dose required to achieve loss of consciousness⁷⁻²⁴⁻²⁵. Chaves et al.²⁶ showed that the addition of alfentanil to propofol or increasing alfentanil doses did not significantly affect the loss of consciousness or lack of recall. No evidence of implicit memory was detected

in our patients, on whom TIVA with remifentanyl-propofol was used. We believe that we decreased the risk of implicit memory by adjusting the medication dose in order to hold BIS values fixed.

Russel et al.^{20,27} did not find any evidence of explicit or implicit memory in patients with perioperative awareness where TIVA (propofol-alfentanil) was used to manage anesthesia. In a study of Munte et al.²¹, implicit memory was detected during anesthesia after alfentanil-propofol infusion with a reading speed task but not with a word stem completion task. Lequeux et al.⁷ did not determine implicit or explicit memory in remifentanyl-propofol TIVA patients. Unlike our study, tapes containing frequently used words were played to the patients preoperatively, when patients lost verbal response to commands and their median BIS value was 93 (80-98). In our study, tapes were played while BIS values were between 40 and 60 in both groups. Lequeux et al.⁷ could not determine implicit memory, although their study was conducted in the superficial anesthesia period and with frequently used words. It is thought that lack of implicit memory can be related to catecholamine release by anesthetized patients in response to a painful surgical stimulus. Negative results obtained in our study may result from depression of catecholamine discharge due to adequate depth of anesthesia, despite surgical stress.

It is believed that patients under anesthesia show better performance in perceptual tests^{1,5}. The number of presentation, frequency, and dominance of the words used in implicit memory tests are important as well. When patients are asked to say the first thing in their mind from any category, they will first recall frequently used and dominant words, which can affect test results. For this reason, we aimed to prevent false results by choosing words with medium frequency from the Rey Auditory Verbal Learning Test list, adapted into the Turkish language. Although two patients recalling two correct animal names in our study were from the CT group, which may indicate sensitivity, the results were statistically insignificant. The vast majority of our patients chose animals that we are used to seeing more often in our daily lives, such as cat, dog, or fish, as the first animal that came to mind. Perhaps, if we had used frequent animal names in the Category test, it would have seemed as if we had detected implicit memory. However, results that we would have obtained in that way would be far from accurate and would not reflect reality. Nevertheless, if we had conducted the pilot study on a larger number of volunteers instead of 60, we would have been more convinced of the accuracy of animal names used in the study.

Conducting the tests in the early postoperative stage may have positive effects on implicit memory²⁴. In a study of Sandin et al.¹⁸, awareness of some patients was detected on the postoperative seventh and 14th days, unlike the first examination conducted in the recovery room. Implicit memory could not be found in different postoperative periods, such as 6-8 h²¹, 24 h²⁸, 72 h²⁹, or two weeks. With the exception of Jelacic et al.¹⁹, who found evidence of implicit memory in tests performed two hours postoperative, other studies did not show the same results at the same times^{6,7,24,30}. According to these results, there is not a certain period of time when awareness of all patients can be determined.

Memory assessment interviews should be performed when patients have fully recovered from the effects of anesthesia on cognitive functions and before any priming effects of stimulus have dissipated. It can be between a few minutes and a few days, and it should be done before the patient leaves the hospital¹. In this study, we aimed to obtain better results by performing tests two hours after surgery in the recovery unit, because most of our patients were discharged from the hospital the same day and we thought communication problems might occur. However, while implicit memory was not detected in any patient, one patient showed evidence of explicit memory.

The incidence of dreaming under anesthesia is between 0.5 and 38%³⁰. While Sebel et al.⁴, reported this incidence as 6%, Liu et al.² found it as low as 0.2-0.9%. In our study, 11 out of 60 patients reported dreaming (18%). In our opinion, the reason for higher incidence in our study was the fact that our patients had not been premedicated and that they were all young, ASA I-II, and mostly females with elective surgeries. In a study of Leslie et al.³⁰, they detected intraoperative awareness in 4% of the patients who dreamt during surgery. In addition, they showed that BIS monitoring decreased the incidence of awareness related to dreaming. Our patient who reported awareness did not report dreaming. On the other hand, in our study, two implicit memory test groups were compared to the one control group, and BIS monitoring was used in order to ensure an adequate depth of anesthesia during the whole procedure. In this way, false positive results are reduced to a minimum.

In this remifentanyl-propofol TIVA study, no evidence of implicit memory and one case of explicit memory was observed by category and word memory tests. Although low stress levels of our patients and adequate depth of anesthesia provided by BIS monitoring support our implicit memory results, they do not explain the explicit memory results. We believe that further studies on the relation of anesthesia and memory should be conducted in larger patient groups.

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