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Research Article

Comparative study of implicit memory during bispectral index guided total intravenous anesthesia versus sevoflurane inhalation anesthesia

Ahmed M. Elbadawy [a,*], Ahmed M. Khidr [b], Alia Adel Saleh [a]

[a] *Cairo University, Egypt*
[b] *Zagazig University, Egypt*

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Abstract *Background:* Several studies that investigate the implicit memory under general anesthesia revealed conflicting results. Limitations may be due to failure to control depth of anesthesia. This prospective randomized study was designed to compare the implicit memory during total intravenous versus inhalational anesthesia.
Method: Fourty patients ASA I and II undergoing orthopedic procedures under BIS-guided (40–60) general anesthesia were tested for implicit memory of previously introduced auditory material. Patients were divided into two groups (each group 20 patient). Group I, anesthesia was induced with propofol and maintained with propofol, fentanyl and cis-atracurium. Group II, anesthesia was induced with propofol and maintained with sevoflurane, fentanyl and cis-atracurium. Explicit memory was evaluated by asking four standard questions regarding intra-operative awareness. Free recall and recognition tests for implicit memory testing were carried out 30 min and 120 min after recovery.
Results: No participant manifested explicit recall according to the 4-question interview. None of the patients gave a free recall of the presented items during anesthesia in the immediate and delayed tests of memory. In the recognition tests, immediate test (5%) and (0%) of the patients indicated correctly the presented words in TIVA and sevoflurane group respectively, in delayed test (10%) in TIVA group and (5%) in sevoflurane group. These results are not significant for implicit memory.
Conclusion: There was no significant evidence of implicit memory in the two groups. BIS – controlled anesthesia appears to abolish implicit memory.

1. Introduction

There is a difference between the two words awareness and memory or recall. Awareness is the state of being conscious

* Corresponding author. Address: Faculty of medicine, Cairo university, 5 Heliopolis rock compound-Sheraton Heliopolis, Cairo, Egypt. Tel.: +20 1064249076.
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or aware. The term memory usually includes the acquisition of new information, its storage and subsequent retrieval. There are two distinct forms of memory: explicit memory which is the deliberate recollection of an experience and implicit (also called none declarative memory), which is the influencing of a response by memory of a previous experience without the person knowing that he or she is being influenced [1,2]. Formation of explicit memories during general anesthesia is associated with intra-operative awareness. It is measured by recall and recognition tests which require conscious and deliberate retrieval of information [3].

Implicit memory during anesthesia has been recognized more recently. Because there is no conscious recollection of implicit memories, they can only be demonstrated by facilitation of completion or identification tests following prior exposure to target materials. Presenting a list of spoken words (priming) under anesthesia and subsequent administration of a recognition test after emergence from anesthesia is a common used method [1,4].

There is a recent continuing interest in the depth of anesthesia monitor such as the Bispectral Index (BIS) which is being increasingly used in clinical practice as well as in memory studies.

BIS is a patient monitor that quantifies the depth of the hypnotic component of anesthesia. It uses electro encephalogram recorded over the forehead and computes a number (ranging from 0 to 99) using an algorithm. This number is displayed on the monitor and helps the anesthesiologist to titrate the anesthetic agents. A BIS range of 40–60 has been generally accepted to represent ideal anesthetic depth where explicit recall is extremely unlikely [5].

The aim of this work was to study comparatively the recovery from the effects of total intravenous anesthesia (TIVA) and inhalation anesthesia using sevoflurane on implicit memory. The latter was studied by testing the post-operative recall and recognition of presented auditory material during anesthesia.

2. Patients and methods

Following approval of ethics committee and after obtaining written informed consent, 40 ASA I & II male and female patients aged 25–40 years undergoing moderate orthopedic procedures (60–90 min) were included in our comparative study, which was done in orthopedic theater in ELkasr EL Ainy Hospital. Specific exclusion criteria included history of drug abuse, antipsychotic medication treatment, head trauma, central nervous system disorders (e.g. epilepsy) or allergy to any of the used drugs.

In the preparation room IV cannula was inserted using lidocaine infiltration. No premedication was given (benzodiazepines were not used). In the operation room Standard anesthesia monitors included ECG, non-invasive blood pressure, pulse oximetry, temperature and end-tidal gas monitoring after tracheal intubation were applied. Bispectral index (S/5 BIS module, DSC XP, Datex – Ohmeda, Helsinki, Finland) was monitored in all patients starting from before the induction of anesthesia until the end of the operative procedure.

A bolus of fentanyl (2 $\mu g\ kg^{-1}$) was given intravenously. After preoxygenation for 2 min, anesthesia was induced with propofol (1.5–2 $mg\ kg^{-1}$) to abolish the eyelash reflex. Cis-atracurium (0.15 $mg\ kg^{-1}$) was given to facilitate tracheal intubation. Ventilation was controlled artificially to attain an end-tidal partial pressure of carbon dioxide of 33–38 mmHg.

Immediately following tracheal intubation, patients were randomly assigned into one of two groups according to maintenance of anesthesia:

Group I (20 patients): anesthesia was maintained with propofol (6–12 $mg\ kg^{-1}\ h^{-1}$) fentanyl (0.3 $\mu g\ kg^{-1}$) and cis-atracurium (0.15 $mg\ kg^{-1}\ h^{-1}$).

Group II (20 patients): anesthesia was maintained with sevoflurane (end-tidal concentration of 1.5–2%) and cis-atracurium (0.15 $mg\ kg^{-1}\ h^{-1}$).

Auditory presentation began after the target BIS level was achieved (range: 40–60) and within 5 min of the beginning of the surgical instrumentation of bone. The duration of the surgical procedure ranged 60–90 min.

The following parameters were measured:

(1) The recovery time: defined as the interval between termination of the anesthetic and the patient's correct recall of his/her name and address.
(2) The choice reaction time to optical stimuli (red or green light): which was used as parameter for attention and psychomotor functions.
(3) Category production task: was used to measure the verbal memory. This task included an exposure phase (word priming) and a test phase. The exposure phase comprised auditory presentation of a list of five words. Words were emotionally bland (e.g. sister, planet, color, number, and name) and were presented via closed headphones running on a notebook computer with a randomly selected auditory file during anesthesia. Each auditory file was 3 s. in length separated by short period of silence (2 s). Exposure phase was about 40 min. as the sequence was repeated to enhance audibility and understanding.

A coder blinded to the study hypotheses as well as to which words a particular patient had heard while under anesthesia was assigned to do the tests. The test phase started by asking the patient four free response questions to exclude explicit recollection of intraoperative events: "What is the last thing you remember before falling asleep? What is the first thing you remember about waking up? Do you remember anything in-between? Did you dream?" The questions were similar to those used in previous studies [2,6]. Testing was done through post-operative interviews 30 min (immediate test) and 120 min (delayed test) carried out to assess cognitive functions as follows:

Free recall: the patient was reminded that he/she was read some words during surgery and was asked to recall any remembered words.

Recognition: The target words were read in distractors and the patient was asked to indicate those that were presented during surgery.

3. Statistical analysis

Data were statistically described in terms of mean ± (SD) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t*-test

Table 1 Demographic data and intra-operative clinical variables.

Variable	Group I (n = 20)	Group II (n = 20)
Age (years)	38 ± 3.0	36 ± 4.5
Weight (kg)	76.8 ± 4.3	77.2 ± 2.1
Gender (male/female)	13/7	11/9
Elapsed time in surgery (min)	70 ± 15	75 ± 10
Heart rate (beat min^{-1})	70 ± 5	78 ± 6
Mean B.P (mmHg.)	87 ± 6	94 ± 5
BIS during word presentation	47.1 ± 6	45.8 ± 7

Values are mean ± SD.

for independent variable and paired *t*-test to compare the choice reaction time. A Fisher's exact test used to compare the cognitive functions between the two groups. A *p*-value of < 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

4. Results

The two groups were comparable in age and weight, duration of operation and intra-operative clinical variables (Table 1).

A statistical comparative study of the recovery and choice reaction times is shown in (Tables 2 and 3).

Implicit memory testing is made through a study of the cognitive functions (free recall, and recognition tests) 30 min and 120 min post-operatively (Table 4).

5. Discussion

This study demonstrated that, during both sevoflurane and TIVA-maintained anesthesia with controlled depth of anesthesia (BIS 40–60), no explicit recall according to the 4-question interview, also none of the patients gave a free recall of the presented items during anesthesia in the immediate and delayed tests of memory. The results of immediate and delayed recognition tests (the number of the patients indicated correctly the presented words), are not significant for implicit memory.

In both groups the cardiovascular variables (Table 1) were within normal limits. Blood pressure and pulse rate values in the propofol group were less than in the sevoflurane anesthetized patients but the differences were not statistically significant. Recovery time in the sevoflurane group was significantly greater than in the propofol group ($P < 0.001$) (Table 2). Similar comparative studies on total intravenous anesthesia versus enflurane [7] and isoflurane anesthesia indicated a significantly faster recovery in the TIVA group [8].

Psycomotor function and attention were tested by the choice reaction time to optical stimuli (red or green) light. In the present study, it was found that the latter was significantly increased 30 min after recovery from anesthesia in both groups ($P < 0.05$). In the propofol group they returned to normal value after 120 min while in the sevoflurane group a significant increase in the choice reaction time was still observed 120 min after recovery from the anesthetic ($P < 0.05$) (Table 3). Similar studies on psychomotor performance showed a significant faster return of mental and motor functions in TIVA group patients compared to inhalational anesthetized patients [8–10].

In the verbal memory for category production task, none of the patients gave a free recall of the presented items during anesthesia in the immediate and delayed tests of memory (30 min and 120 min post operatively consequently) (Table 4).

In the recognition tests, when the cue – target items were read, one patient (5%) in the TIVA group indicated correctly the presented words in the immediate test and the number increased to two patients (10%) in the delayed test. In group II, one patient (5%) recognized them in the delayed test (Table 4). These results are not significant for implicit memory for the presented auditory material.

Although the patients were completely oriented when interviewed, yet they were not completely recovered from anesthesia 30 min post-operatively and this might explain the suppression of their task performance on the immediate trial and its improvement on the delayed one (Table 4).

In the current study, there was uniformity of surgical stimulus and depth of anesthesia at the time of word presentation. For all patients, presentation of words started 2–3 min of bone instrumentation and lasted for 40 min. Depth of anesthesia was achieved before word presentation was started and maintained for the duration of priming. It is possible that when the hypnotic state of patients is controlled with BIS guidance of anesthesia depth (40–60), this might prevent implicit learning.

In another study Stonell et al. [11], titrated anesthetics to BIS guided range of 55–60 and found implicit memory for word series. The authors also confirmed lack of evidence for memory function below BIS 40 as noted by other studies as well [12].

Similarly, Hadzidiakos et al. used a word stem completion test and found no implicit memory effect in patients with median BIS value of 32.5 which corresponded to an anesthetic depth where implicit memory can be abolished [13].

On the other hand, Kerssens et al. also studied implicit memory in a group of patients where BIS was only recorded but did not guide drug administration. Instead, standard clinical signs such as heart rate and blood pressure guided anesthetic management (standard practice). They observed implicit memory alongside a wider range of BIS values [14].

It was found that elderly subjects and subjects under the influence of benzodiazepines, scopolamine and sub anesthetic concentrations (30%) of nitrous oxide have impaired explicit memory [15]. It is known that benzodiazepines have profound effects on memory as they have antero-grade amnestic properties thus they were avoided in the present study as well as nitrous oxide [16].

Dobrunz et al. showed no superior memory effect for repeated presentation of words given to patients. The reason they gave was that the patients were constantly protected against pain using a continuous infusion of remifentanyl. In addition, desflurane was used as the inhalational anesthetic. This combination may have impairing effects on the unconscious information processing [17].

Table 2 Recovery time after anesthesia (mean ± SD).

Parameter	Group I (n = 20)	Group II (n = 20)
Recovery time (min)	8 ± 2.4	14 ± 5.2*

* Statistically significant in group II compared to group I ($P < 0.05$).

Table 3 Choice reaction time before and after anesthesia.

Choice reaction time (s)	Pre-operative	Immediate test (30 min. post-op.)	Delayed test (120 min. post-op.)
Group I (n = 20)	8 ± 3.34	45 ± 11.6*	8 ± 1.8
Group II (n = 20)	9 ± 3.5	88 ± 29*	17 ± 1.3*

Values are mean ± SD.
* Statistically significant in group I and II postoperatively compared to preoperative values ($P < 0.05$).

Table 4 Cognitive functions in patients following anesthesia.

Parameter	% Number of patients	
	Group I (n = 20)	Group II (n = 20)
Free recall:		
Immediate test	0	0
Delayed test	0	0
Recognition:		
Immediate test	5	0
Delayed test	10	5

Immediate test: 30 min post-operative.
Delayed test: 120 min post-operative.

There are two practical implications of implicit memory under anesthesia. One of them is that unfavorable comments may be retained by the unconscious person and this might have deleterious effects on the post-operative outcome.

The suppression of auditory awareness depends on the pharmacological degree of sedation in relation to the surgical stimulation. The present results as well as the results of similar Work [7–10] indicate that TIVA is accompanied by faster recovery of motor and mental functions and better recall of presented auditory material. Total intravenous anesthesia might thus bear the risk of consciousness and recall, this risk could be reduced by the use of computer technology [14,17] to design and control variable rate infusion schemes so that stable drug concentrations can be achieved and proportional changes in the concentrations can be made with equal rapidity according to patient's requirements. It can also be reduced by premedicating the patient with amnesic drugs as benzodiazepines or scopolamine [16].

Furthermore, maintaining the BIS below 60 may be an adequate strategy to prevent the formation of implicit as well as explicit memories [2]. Nevertheless, it may be reasonable to caution anesthesiologist, nurses and surgeons to restrain their conversations as some of them may be retained by the unconscious patients [14].

As a minimum standard, the patients should be at least protected from noises in the operating theater by introducing closed head-phones and audio players presenting, example, relaxation music.

The second implication of implicit memory is the possibility of influencing a patient's post-operative course favorably.

In the emergence phase and especially in some surgery indications (e.g. open heart surgery), phases of light anesthesia or even consciousness may not be prevented. During these phases, the anesthetists should communicate with the patients and reassure that everything is under control. It has been shown that some patients responded positively to therapeutic suggestions administered during anesthesia [18,19]. If this technique could be developed, it might reduce the common post-operative side effects as the emergence phenomena and nausea. Pain management and over all outcome may as well be improved.

6. Conclusion

According to this study no significant evidence of implicit memory in sevoflurane or TIVA maintained anesthesia with BIS-guided depth of anesthesia (40–60). Further studies may be needed to verify this impact.

Conflict of Interest

No conflict of interest.

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