REVIEW ARTICLE

Awareness during anesthesia: how sure can we be that the patient is sleeping indeed?

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Abstract

Awareness during surgery is a very serious problem for the anesthetist and the patient as well. Such incidents are the cause for 2% of the legal claims against anesthetists while patients with intraoperative awareness experience describe it as the worst thing they have ever suffered from. Pain, anxiety and inability to react due to muscle paralysis often lead to the situation called posttraumatic stress disorder which demands psychiatric support. The fact that there are patients who report intraoperative experience, even several days after surgery, raises questions about the way the anesthetic drugs interfere with the mechanisms of memory and consciousness while, in bibliography, there are studies proving that even deeply anesthetized patients can be influenced by auditory stimuli without being able to recall them. Intraoperative monitoring of the anesthesia depth is important for the prevention of this problem. From all the available devices only the Bispectral Index Monitoring (BIS) has been proven to be effective for this purpose but the high cost per person and the low specificity in preventing awareness episodes do not allow its everyday use. The surgeon and especially the anesthesiologist must be aware of the risk factors, the prevention measures and the actions that must be taken after an awareness incident in order to minimize the unfortunate complications for both the patient and the doctors. Hippokratia 2009; 13 (2): 83-89

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The application of general anesthesia in 1845 by Horace Wells and 1846 by William TG Morton, with the use of nitrous oxide and ether respectively, was a revolution and is still considered as one of the greatest evolutions in medicine.

Since then, the discovery and use of new, safer anesthetics and the rapid progression of monitoring but mainly the major advances in anesthesiology have significantly contributed to the safe administration of anesthesia daily to millions of patients in the world. According to Fleisher, deaths that occur only because of anesthesia are about 1 in 200,000 anesthetic actions[1]. Despite that, the toxic actions of anesthetics, especially on patients with major health problems and elder patients, continue to be under constant research[2].

General anesthesia is defined as the condition of pharmacogenic loss of consciousness so that the patient is unresponsive to painful surgical stimuli[3]. Despite the fact that anesthesia and loss of consciousness are synonymous, there are many cases where patients recall various experiences during the operation[3-10]. This fact raises questions about the way surgical anesthetics act on the mechanisms of memory and consciousness and the possible consequences of intraanesthetic awareness on their life after the operation. Also, the ability of monitoring anesthesia depth in order to identify and prevent intraoperative awareness, is another important issue and the actions that an anesthesiologist and a surgeon must take if awareness occurs as well.

Awareness during general anesthesia was observed even at the first patients who were anesthetized. Morton himself reported that his anesthetized patients were "half asleep" and that they were feeling pain during surgery[4,6]. The first case report was done by Winterbottom in 1950[11], while in 1961 Meyer and Blatcher[12] observed that the patients who were waking up after cardiac operations presented, after a few days, some kind of neurosis and psychological disorders which were later characterized as the "invisible scars of the surgery"[7].

The use of neuromuscular blocking agents and the increase of one day operations have increased the danger of awareness during surgery[9,13]. According to a large multicenter study in the USA in 2004, the frequency of intra-anesthetic awareness is about 0.13%, which means almost 2,000 cases every year[10]. Despite the relatively low frequency, the problem is serious if we consider that 50% - 54% of the patients are afraid that they will wake up during surgery[14,15], while 2% of the legal claims against anesthesiologists involve cases of awareness[16].

Intraoperative patient experiences and post operative symptoms

Patients with anesthetic awareness report various intraoperative experiences[5,17] (Table 1). In most cases they

Table 1: Usual experiences of intraoperative awareness.

1)	Conversations of the surgery stuff
2)	Various images and pictures
3)	Dream-like events
4)	Pain
5)	Paralysis
6)	Anxiety
7)	Helplessness
8)	Posttraumatic stress disorder:
	I. nightmares, irritating dreams, sleep disorders
	II. irritating thoughts
	III. excitability
	IV. avoidance of medical care

report that they were hearing conversations between the stuff without feeling anything else. But there are many cases where they report pain, paralysis and anxiety because of the fact that they feel helpless. An intubated patient who feels pain, although he wants to react, he is unable to do so because of the neuromuscular blocking agent that has been usually administered and has paralyzed him. Some patients describe this situation as the worst experience they ever had in a hospital[17]. All the above symptoms are very lively described by an anesthesiologist, who was an awareness victim during an urologic operation, in the article of Peduto et al[18].

The recalling of these experiences can be done immediately after surgery, in the recovery room, or several days later[17], while there has been reported a case of a patient who recalled a specific detail 5 years after the operation[4]. According to Osterman and van der Konk[4], after a case of awareness many patients have a posttraumatic stress disorder.

The main characteristics of this disorder are: 1) reexperience of the intraanesthetic experiences 2) avoidance of any situation that can remind the intraoperative experiences and 3) excitability when recalling occurs. The major symptoms are insomnia, nightmares or frequent disturbing dreams, irritating thoughts and excitability. Patients report that they feel anxiety, fear, and paralysis every time they fall to sleep and this is the main reason that they avoid sleeping. Others describe feelings of pain every time they try to sleep or that they see images or shapes resembling their surgical trauma. Also, there have been cases where patients felt significant fear, or had recalls and disturbing thoughts after seeing blue or green color (the usual color of the surgical stuff's suit), watching television shows with medical subjects or hospitals or even after smelling alcohol. Finally, it is important that 2/3 of the patients with anesthetic awareness, when asked to return to the hospital for an interview, had symptoms of panic and refused to go to the hospital[4]. The fact that these patients try to avoid anything that might cause the recalling of unpleasant experiences causes their withdrawal from every kind of psychological and psychiatric support, which are absolutely necessary.

The main cause of posttraumatic stress disorder is dissociation, which is an unconscious defensive mechanism where one or more groups of mental functions dissociate from natural consciousness[19]. Dissociation is caused by the inability of the paralyzed patient to take action in order to end the unpleasant situation (fight or flight reaction) and acts by organizing memory as a sensory barrier with the form of emotional conditions (stress) and making the patient unable even to narrate his experience.

Apart from these cases there is a category of patients who report faded memories and recall images which can or cannot be related to intraoperative facts, and patients who describe dream-like experiences that can be connected with conversations of the surgical stuff during the operation[20]. The fact that several patients describe awareness experiences even days after the operation[9,20], and the indications of unconscious memory during surgery[5], raises many questions about the effect of anesthesia on the mechanisms of memory and consciousness.

Consciousness – Memory – Anesthesia

Consciousness and memory are complex brain functions whose mechanisms, although under constant research by neurophysiology, are not yet fully understood. Anesthesia has contributed significantly to the ongoing experimental results.

Anesthetic drugs act on the central nervous system in many ways (Table 2). The main mechanism of action is by interfering with the neurotransmission systems and especially with ion gates which regulate the secre-

Table 2: Action of anesthetic drugs on the brain.

1)	Affection of neurotransmission via action on receptors ($GABA_A$, NMDA, nACH)
2)	Action on the receptors of G proteins (acetylcholine, noradrenalin, dopamine, adenosine, opioid)
3)	Action on the ion gates K_{2P}
4)	Reduction of cerebral blood flow
5)	Reduction of glucose metabolism from the nervous cell

tion of stimulating and inhibiting neurotransmitters like $GABA_A$ (Gama-Amino-Butiric-Acid) receptors, NMDA (N-Methyl-D-Aspartate) receptors and nicotinic receptors of the central nervous system (nACh)[15,21]. Beside ion gates, anesthetic drugs also act on G protein receptor (g protein coupled receptors or GPCRs) which are related to the function of the receptors of acetylcholine, norepinephrine, dopamine, adenosine and opioids. This action is responsible for the multiple adverse reactions of these drugs. During the last years, the action of anesthetic drugs on newer types of potassium receptors (K_{2p} or background potassium channels), which regulate the excitability of the nerve cells by providing backup electrical currents[15], has been discovered. Anesthetics alter the sensitivity of the nerve cells to electrical stimuli via K_{2p} gates.

These are the main ways anesthesia affects consciousness and memory. Consciousness is the state where someone can evaluate and process the information he/she gets from the environment. The available data indicate that there are many central nervous system structures that participate in this function like the brain stem, the hypothalamus and parts of the cerebral cortex while the reticular formation has an important role in the waking up process. Mainly by interfering with the thalamocortical neurons, anesthesia causes loss of consciousness while other mechanisms include decrease of brain hematosis and glucose metabolism by the nervous cells[22].

As far as memory is concerned, there are two categories, the short term and the long term memory. According to Bailey and Jones[5], the short term memory involves storage and processing of information connected with learning, taking decisions and recalling memories which are stored in long term memory. The storage of information is done either phonetically (an "inner voice" repeats the information) or visually (the information is stored as a picture). The mode of storage is regulated by a central processing system. The hippocampus and the medial temporal lobe seem to play the most important role in this procedure. Long term memory includes facts which are stored immediately in memory and are recalled after effort (a car crash for example or somebody's name) and are called explicit memory, and procedures and skills that are gradually learned but are recalled without conscious effort (learning how to drive, writing) and affect behaviour and habits and are called implicit memory. Long term memory is related to activity in various areas of the central nervous system like the hippocampus, amygdala, neostriatum, cerebellum and the cortex which are connected via multiple neuronic circuits in order to perform complicated brain functions. Anesthetic drugs seem to affect these circuits and deregulate the coding of the stimuli and their storage in long term memory[22].

Jones described four stages of general anesthesia's implication in memory and consciousness (Table 3) : 1) perception and explicit memory, where the patient recalls intraoperative facts and feelings without necessarily feeling pain (if large doses of opioids were administered to them) and having psychological disorders, 2) perception without explicit memory, where the patient can follow instructions and perform movements without being able to recall hearing them, 3) no perception and implicit memory and 4) no perception and no memory. From all the above categories the third one is the most interesting and is the cause of scientific controversy. There are some studies which indicate that even during deep anesthesia, learning, processing of information and storing it in long term memory is possible[5,24]. There are anesthetized patients who were continuously hearing four kind of fruits and four colours via headphones and, although they could not recall hearing them, when they were asked postoperatively to say the first three colours and fruits that they could think of, they were saying those they were hearing during the operation (with statistically significant difference compared with those that were not hearing anything)[25]. A similar study, where patients were asked to fill unfinished words, had the same results: the patients were filling the gaps with the words they were hearing intraoperatively without being able to recall hearing them. Even more impressive is the fact that researchers who were transmitting positive messages via headphones to patients who were being operated under general anesthesia (like "you will get up early" or "you will not feel pain after surgery") had significant results in reducing the duration of postsurgical hospital stay and the need for opioid analgesics[26-28]. Even discontinuation of smoking has been observed at patients who were ordered to stop smoking during general anesthesia. Finally, it has been found that in patients under deep anesthesia, auditory and somatosensory stimuli can cause cortical electrical activity[22].

Table 3: Anesthesia stages according to Jones[23].

1)	Perception and explicit memory
2)	Perception and no expicit memory
3)	No perception and implicit memory
4)	No perception and no memory

On the other side, there are researchers that did not have the same results after similar studies[5]. The subject of intraoperative storage of information and postoperative recalling remains controversial. There are some specific risk factors which increase the possibility of intra-anesthetic awareness.

Risk Factors

The main risk factors of awareness during anesthesia are, according to Ghoneim and Weiskopf (Table 4): 1) insufficient anesthetic medication, 2) different anesthetic requirements by some categories of patients and 3) malfunction of the anesthesia machine[8].

The first category includes operations where the anesthesiologist can not administer large doses of anesthetics due to the hemodynamic instability which for same

Table 4: Risk factors of intraoperative awareness.

1)	Insufficient drug administration
	I. Cardiothoracic surgeries
	II. Trauma
	III. Emergency operations
	IV. Cesarean section
	V. ASA 4-5
2)	Patients with different anesthetic requirements
	I. Chronic use of benzodiazepines or opioids
	II. Alcoholics
	III. Severely anxious patients
	IV. Difficult airway
	V. Previous awareness experience
3)	Anesthesia machine malfunction
	I. Disorder
	II. Incomplete check

reason can be caused and might prove dangerous for patient's life. These are mainly cardiothoracic operations, surgeries to multitrauma patients and generally emergency cases, cesarean sections and operations on ASA 4 or 5 patients according to ASA (American Society of Anesthesiologists) categorization[3]. The use of neuromuscular blocking agents is an extra risk factor[3,6,9] because it makes the patient unable to react by moving.

The second category includes patients who have greater need for anesthetic drugs, like those who take benzodiazepines or opioids chronically, alcoholic patients, patients who are very anxious preoperatively, patients with predicted difficult intubation who might have to be intubated awake and finally patients with previous awareness experience[3,7,24].

The last category includes cases due to device malfunction, incorrect use or improper checking of the anesthesia device, so that the needed amount of anesthetics is not administered to the patient[3,7].

Intraoperative monitoring of anesthesia depth

The available options for intraoperative monitoring of anesthesia depth are limited and the methods used are not very reliable (Table 5). This fact makes diagnosis and prevention of awareness even more difficult.

Tunstall in 1977[29] was the first who tried to estimate the anesthesia depth of his patients by applying the isolated forearm technique. Before the administration of the neuromuscular blocking agents he was inflating a cuff at the patient's hand and was estimating the depth of anesthesia by the movement of the hand after giving orders via microphone and headphones[24]. The danger of hand ischemia limited the time that this method could be applied.

The anesthetic drugs have actions like analgesia, causing paralysis of the striated muscles, amnesia and blockade of the autonomic and harmonic response to painful stimuli. This is why the estimation of anesthesia depth can not be based on the changes of the patient's cardiac and respiratory rhythm, blood pressure, the production of sweat and tears or the pupil size[3].

Measurement of the contractions of the lower esophageal sphincter with the use of a special manometer has been applied in the past. Although the response of the esophagus to stimuli is related to the depth of anesthesia, it can not be considered a safe method of intraoperative anesthesia monitoring[5]. The electroencephalogram of the frontalis muscle, which is the least sensitive to neuromuscular blockers, is another available but unreliable method[5].

The continuous progress in medical technology has created some new devices that can analyse the electrical activity of the brain and can be used intraoperatively in order to monitor anesthesia depth. The three most often used devices are the AEP (Auditory Evoked Potentials) monitor, the Narcotrend and the BIS (Bispectral Index Monitoring).

The AEP monitor records the electrical activity of the brain stem, and cortex after auditory stimuli that are delivered to the patients with the use of headphones. The signal is processed mathematically and is finally shown on the screen of the device as a number from 0 to 100. The lower the number on the screen, the greater the depth of anesthesia is.

In contrast to AEP, which records brain response after stimulation, the Narcotrend records brain activity without the application of any stimulus. This monitor analyses the signal of the encephalogram and categorizes anesthesia depth in a system of 6 letters. It also

Table 5: Methods of intraoperative estimation of anesthesia depth.

1)	Isolated forearm technique
2)	Observation of the vital signs and sympathetic reactions
3)	Measurement of lower esophageal sphincter contractions
4)	Electroencephalogram of the frontalis muscle
5)	Monitoring of brain electrical activity
	I. AEP
	II. Narcotrend
	III. BIS

produces a number from 0 to 100 (Narcotrend index). The stages are: A= awake, B_{0-2}= sedation, C_{0-2}= light anesthesia, D_{0-2}= general anesthesia, E_{0-2}= general anesthesia with deep hypnosis, F_{0-1}= general anesthesia with heavy depression of reaction to painful stimuli[30,31]. Although the beginning of its use was very promising, the clinical data shows that it is unable to estimate reliably the depth of anesthesia and prevent cases of awareness[28,32].

The only reliable anesthesia depth monitor is the BIS. BIS works like the Narcotrend. It records the electroencephalogram from 3 electrodes and after processing it with mathematic algorithms it generates a number from 0 to 100. When the BIS value is lower than 40, the patient is in deep anesthesia state, when the value is over 80, the patient is under light sedation[33]. A number of studies have shown that the use of BIS reduces the need for anesthetic drugs and the time of stay at the post-anesthesia care unit[34,35] and, mainly, the cases of intraoperative awareness[36]. Myles et al came to the same conclusion (reduction of the awareness cases) in a large multicenter retrospective study with 2463 patients, which also raised the big problem of cost effectiveness if BIS is applied to all the surgical patients. Two thousand and two hundred dollars are required in order to prevent one case of awareness. Also the BIS monitor must be applied to 138 patients in order to prevent one case of awareness (numbers needed to treat 138)[17] which means that this monitor has a low specificity in preventing intraanaesthetic awareness. The meta-analysis by Liu had the same results too. Despite the financial benefits from the reduction of anesthetic drug use due to BIS application, of the stay in post anesthesia care unit and of the cases of post-surgery nausea and vomiting, its cost (5,55$ per patient) does not make the routine use of BIS cost effective[37].

This fact underlines the need of preventing and diagnosing awareness in time in order to make sure that the patient will get the best possible treatment.

Prevention – Postsurgical Management

Specific measures can contribute to prevention and reduction of awareness cases[3,20]. Firstly, the right preoperative evaluation of the patient is very important. The presence of the risk factors, which are mentioned above, must be checked. Although there is doubt whether the patients must be informed about the possibility of being "awake" during the operation or whether this information can cause anxiety[6], the American Society of Anesthesiology recommends that patients in high risk of awareness must be informed. The preoperative evaluation must definitely include estimation of the patient's anxiety and previous history of awareness.

The checking of the anesthesia device and of the other devices which will be used during administration of anesthesia must always be done. The protocol of device checking must be complete and signed.

In any case there must be an anesthetic plan designed for every patient individually. Extra care must be given for the dosage of the inhaled and intravenous drugs and it is better to avoid the use of neuromuscular blocking agents when it is possible. The preventive use of benzodiazepines, which affect memory, does not have any results in preventing awareness[9], while the use of a b-blocker decreases the possibility of post-traumatic stress disorder in case awareness occurs[38]. The use of BIS must be limited only to the high risk patients. Although it has been proved that intraoperative values less than 55 inhibit memory function[39] and that its use can decrease the cases of awareness, its cost does not allow routine use to every patient.

Because postoperative amnesia is not a good indicator of absence of intraoperative awareness[5], all the patients must take the Brice interview[9,13,20] (Table 6). The interview includes five questions which can diagnose a possible awareness incident. These questions should be asked not only shortly after operation but also within 14 days posr-operatively[4,9].

Table 6: The Brice interview.

1)	Which is the last thing you remember before surgery?
2)	Which is the first thing you remember after surgery?
3)	Do you remember anything happening during surgery?
4)	Did you have any dreams during surgery?
5)	Which is the worst thing about your surgery?

If a case of awareness is diagnosed, specific measures must be taken[5,20] (Table 7) . The doctor must ensure the patient that his problem will be definitely taken under serious consideration and take as much information as possible about his/her intraoperative experiences. Explanations must be given to the patient who must be exactly informed about what happened and why. The anesthesiologist must be ready to answer every question to the pa-

Table 7: Measures after a case of awareness.

1)	Patient insurance
2)	Gathering of as much information as possible about the patient's experience
3)	Explanations
4)	Frequent postsurgical visits
5)	Detailed recording of all the actions
6)	Administration to a psychiatrist
7)	Inform all the persons involved

tient and to apologize. The post-anesthetic visits must be thoroughly recorded and repeated daily until the patient is discharged. Every day visit and discussion with awareness patients for three weeks contributed, according to Sandin et al, to the fact that all these patients left the hospital satisfied and without any psychological disorders[9]. In case disorder of mental health is observed the patient must definitely admitted to a psychiatrist in order to receive special treatment[4,40].

The anesthesiologist must have a copy of all the actions taken after the incident. Finally the surgeon, the nurses of the operating room, the manager and the legal service of the hospital and the personal doctor of the patient must be informed.

Conclusions

Intraoperative awareness is an important problem for the patient and the doctor. The patients have a very unpleasant experience which can affect their mental health and the rest of their life. The doctor from his side, faces a problem which is very difficult to be detected and prevented and can have legal, moral and financial consequences.

The complete and proper preoperative evaluation, the checking of the anesthesia device and the postoperative visits are very important. Also the possibility of subconscious memory and learning during general anesthesia has not been excluded and raises questions about what the patient should "hear" during the operation. Until definite conclusions are made on these subjects, the stuff of the operating room ought to be very careful about what they are talking about during surgery[5,9].

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