

Awareness during emergence from anesthesia: Features and future research directions

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Abstract

The anesthesia awareness with recall (AAWR) phenomenon represents a complication of general anesthesia consisting of memorization of intraoperative events reported by the patient immediately after the end of surgery or at a variable distance from it. Approximately 20% of AAWR cases occur during emergence from anesthesia. Clinically, these unexpected experiences are often associated with distress especially due to a sense of paralysis. Indeed, although AAWR at the emergence has multiple causes, in the majority of cases the complication develops when the anesthesia plan is too early lightened at the end of anesthesia and there is a lack of use, or misuse, of neuromuscular monitoring with improper management of the neuromuscular block. Because the distress caused by the sense of paralysis represents an important predictor for the development of severe psychological complications, the knowledge of the phenomenon, and the possible strategies for its prophylaxis are aspects of considerable importance. Nevertheless, a limited percentage of episodes of AAWR cannot be prevented. This paradox holds also during the emergence phase of anesthesia which represents a very complex neurophysiological process with many aspects yet to be clarified.

Key words: Intraoperative awareness; Anesthesia awareness with recall; Explicit memory; Emergence from anesthesia; Neuromuscular monitoring; Butyrylcholinesterase deficiency

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Core tip: Approximately 20% of all awareness with recall cases regard the end stage of anesthesia. Of note, emergency-related complications are associated with distress, especially due to paralysis. On these premises, it is of fundamental importance to recognize the mechanisms that lead to the complication and to implement appropriate preventive strategies.

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INTRODUCTION

The state of unconsciousness and amnesia of events that occur during surgery represent the main objectives of general anesthesia (GA). Although these goals are almost always reached, memorization of intraoperative events can rarely occur and are reported by the patient-in terms of self-reporting or as an elicited report through structured interviews-immediately after the end of surgery or at a variable distance from it^[1]. This is a fearsome and underestimated complication of GA generally defined as awareness or more properly anesthesia awareness with recall (AAWR) where the presence of recalling of the event presupposes the activation of the long term declarative memory (explicit memory) which includes episodic and semantic memory types^[2]. Another awareness subgroup is realized by bypassing explicit memory and presupposes the activation of "hidden" memory, a type of memory which, according to Robert Veselis, "exists but we do not know we possess"^[1] and which is more properly called non-declarative implicit memory. For this reason, this awareness subtype is referred to as awareness without explicit recall. In other words, an unintentional episode of consciousness during anesthesia can follow different memory processing pathways being consolidated in different long term memory modes. The path of consolidation *via* declarative memory configures the AAWR and manifests itself as a spontaneous or induced report, at the end of anesthesia or later. This episode must be clearly distinguished from possible suggestions or phenomena of dreaming under anesthesia^[3]. Alternatively, not all episodes of intraoperative consciousness follow the path of explicit memory and can be consolidated in terms of unconscious, or implicit memory. These episodes, numerically more significant than the explicit episodes, are not reported spontaneously or in induced form, at the end of surgery and can clinically manifest as changes in behavior or performances^[4].

Despite the rarity of the complication, the clinical features are indicative of a failure of anesthesia whereas the potential psychological complications can be devastating, passing through acute stress disorder and leading to syndromal pictures until post-traumatic stress syndromes^[5]. Furthermore, a medico-legal analysis calculated that about 2% of the claims against anesthesiologists concern awareness complications^[6].

In terms of the size of the phenomenon, it is difficult to refer to certain data, as the real AAWR incidence depends on the method of investigation used. The results obtained by the 5th National Audit Project indicate an overall incidence of approximately 1:19000 (0.005%)^[7] although the study methodology (*e.g.*, the absence of a structured interviews) has been widely criticized^[8]. Subsequent investigations such as the SNAP-1 Study, conducted through specific tools for the diagnosis of awareness (the modified Brice questionnaire), confirmed an incidence of 1:800 GAs (0.12%)^[9]. The retrospective evaluation aimed at the numerical understanding of the phenomenon seems to be very complex and is reliable only in specific settings where complete information flow is available^[10].

The meticulous reconstruction of the events reported by the patients allows reporting the episode to specific intraoperative moments. The complication, therefore, can occur in one of the three phases of anesthesia, induction, maintenance, emergence. This distinction appears most appropriate, as incidence, causes, mechanisms, as well as clinical aspects and potential sequelae, differ depending on the timing of occurrence of awareness^[11]. This paper will focus on the awareness phenomenon that occurs in the awakening phase of anesthesia, generally defined as emergence anesthesia or simply "emergence".

CHARACTERISTICS OF AWARENESS DURING THE EMERGENCE PHASE

Considering the temporal context of the phases of anesthesia, around 20% of cases of AAWR events occur in the awakening period^[7]. In practical terms, since almost all of these events can be effectively predicted, a shrewd anesthesia strategy focused on a

safe emergence can help prevent around 1/5 of all awareness episodes. This data is very significant as unexpected awareness complications during the awakening stage are very often associated with distress especially due to a sense of paralysis. Moreover, this distress represents an important predictor for the development of severe psychological complications^[12] (Table 1).

CAUSES AND MECHANISMS

The lack of neuromuscular monitoring, or improper use, represents the main risk factor for the occurrence of emergence awareness^[7]. In a study conducted on the topic, the authors found that approximately 80% of these complications occurred in patients not managed by neuromuscular monitoring^[13]. Of note, the cohort encompassed patients with butyrylcholinesterase (BChE) deficiency. The effect of a missed or erroneous use of neuromuscular monitoring, indeed, is especially evident in some clinical events where the metabolism of neuromuscular blocker agents (NMBAs) undergoes significant alterations. BChE deficiency is a typical case in which there is considerable lengthening in the half-life of the NMBAs succinylcholine and mivacurium, as BChE-a sister enzyme of acetylcholinesterase-works to hydrolyze these medications. In terms of awareness, around half of patients suffering from a congenital or acquired variable degree of enzyme deficiency reported experiences of intraoperative awareness. The acquired enzyme deficiency recognizes a multifactorial genesis and, for example, different substances and drugs such as caffeine, theophylline, quinidine, barbiturates, morphine, codeine, atropine, epinephrine, phenothiazines, folic acid, and vitamin K may decrease the activity and levels of BChE. Moreover, increasing age, pregnancy, severe liver disease, and burn injuries can impair BChE functioning. Of note, individuals deficient in BChE appear asymptomatic. The hereditary form of BChE deficiency is transmitted as an autosomal recessive trait and is due to mutations in the BChE gene (OMIM 177400) which is located into the E1 locus of chromosome 3 (3q26.1-q26.2). The prevalence of the defect is higher in the Caucasian population in which about 4% of the individuals present a partial defect. By contrast, the complete deficit has a prevalence of 1/100000. More than 70 mutations have been reported in human BChE with a variable effect on the enzymatic function in terms of catalytic functioning or protein expression. The effect is a different impact on the enzymatic function that involves a variable lengthening of the action of NMBAs, succinylcholine, and mivacurium. The variant RS1799807 involves prolonged apnea following the use of the curare subject to the metabolism of the BChE. Research from the Danish Cholinesterase Research Unit showed several mutations in the BChE gene, identifying seven new types (I373T, G467S, W518R, L184S, V421A, M462I, and R577H)^[14]. Although the awareness problem seems to be of primary importance in case of alterations of the metabolism of the succinylcholine and mivacurium, the lack of neuromuscular monitoring, represents an important risk factor for emergence awareness regardless of the type of curare used.

A human error linked to an improper anesthesia technique (*e.g.*, failure to accurately calculate the anesthetic dose) is a further cause of awareness during the emergence. An early anesthesia lightening associated or not with an incorrect calculation of surgical times (*e.g.*, delay in surgical suture) can expose the patient to awareness risk. In this case, the use of neuromuscular monitoring can also provide important indications about the degree of the neuromuscular blockade. The potential malfunctioning of equipment and devices are primarily responsible for awareness during induction and maintenance of anesthesia. Nevertheless, the technical problem may still be responsible for awareness in the final stage of anesthesia, when the effect of amnesic drugs (anesthetics and benzodiazepines, BDZs) is being finished and instrumental monitoring can offer an excessive sense of security masking the occurrence of complication.

In a limited percentage of cases, the cause of AAWR is not identifiable. It has been calculated that around 15% of awareness episodes (in all phases of anesthesia) have an undeterminable genesis^[15]. The explanation of these events appears extremely complex. Apart from certain conditions such as tobacco smoke, excessive consumption of alcohol and centrally acting drugs responsible for a "physiological resistance" to anesthetics through drug-induction action, there could be a possible genetic resistance to the anesthetics. This pharmacodynamic aspect represents a fascinating and little known phenomenon. For example, preclinical experimental data, collected from the analysis of *Drosophila* mutant strains, have shown that numerous genes (*e.g.*, implicated in coding for structural proteins, ion channels subunits, second messengers, and various synaptic proteins) and the relative isoforms, are involved in the ordinary response to anesthetics^[16]. Nevertheless, the neurofunctional question is

Table 1 Features of awareness during emergence

Features	
Incidence	About 20% of all awareness with recall episodes ^[7]
Clinical features	Distress especially due to sense of paralysis
Causes and mechanisms	Inappropriate anesthesiological management: 1 Anesthesia plan is lightened too early 2 Lack of use, or misuse, of neuromuscular monitoring 3 Awake extubation Butyrylcholinesterase deficiency (in case of succinylcholine and mivacurium use) Human error (<i>e.g.</i> , dose calculation) or devices malfunctioning
Predisposing factors	Resistance to anesthetics genetically determined Drug induction by alcohol, tobacco or centrally acting drugs
Assessment	When awareness is suspected at the emergence, patients should be assessed before the postanesthesia care unit discharge, after 1-3 d, and after 7-14 d using a structured interview
Psychological sequelae	Frequent and of variable entity depending on the distress, duration, and type of event
Management	Multidisciplinary approach and specialized interventions by properly trained personnel (psychiatrist / psychologist). It is mandatory to accept the patient's report as truthful, to characterize it and to carry out a root case analysis with all the medical personnel, and not, involved in the operating theatre

more complicated. Emergence from anesthesia, in fact, is not simply the opposite process of induction but is subject to the control of distinct neural circuits^[17]. In other words, induction and awakening follow non-specular paths and are subject to regulatory mechanisms that only partially collimate^[18]. This phenomenon which characterizes anesthetic state transitions is called "hysteresis of anesthesia" or neural inertia^[19] and can differ between anesthetic agents. An alteration in these processes, with a sudden awakening phase, could explain those cases of awareness upon awakening that find no other plausible explanation.

PREVENTION OF EMERGENCE AWARENESS

The prevention of emergence awareness episodes is of fundamental importance, both for the clinical significance of the complication in this phase of anesthesia and for the statistical data that indicates that careful prophylaxis can allow the prevention of over 90% of these events^[7]. Only in very rare cases, awareness in the ending stage of anesthesia has a cause that cannot be identified and, thus, cannot be - at least theoretically - prevented. Several practical suggestions can be provided for the prevention of emergency awareness. These measures can be applied to the pre-surgical phase and intraoperative management (Table 2).

Identification and information of patients at risk

The risk factors related to the patient are divided into non-modifiable risk factors and modifiable risk factors. These latter include a high American Society of Anesthesiologists (ASA) status (ASA > III) and limited hemodynamic reserve. While it seems that female gender and younger age are not associated with a higher risk, the question still needs to be better defined. Patients at risk of awareness are mainly individuals with chronic pain treated with high doses of opioids, those with a history of drug abuse such as due to opioids, BDZs, amphetamines, and cocaine, or in treatment with centrally acting drugs (*e.g.*, tricyclic antidepressants or I-MAO). Obesity is more associated with awareness during induction due to the possible difficulty in airway management. Diabetes mellitus and the use of beta-blockers may represent risk factors as they are capable of masking stimuli. Finally, an episode of awareness of a previous one represents another significant risk factor^[20]. The red-hair phenotype-often linked to mutations involving the melanocortin-1 receptor gene and postulated as a condition with increased general anesthetic requirements-is not associated with a higher AAWR risk^[21]. Of note, the ASA task force on intraoperative awareness recommended informing the patient at high risk about the eventuality of AAWR. Indeed, this strategy does not seem to increase the state of anxiety and the

Table 2 Prophylactic strategies for prevention of awareness in the awakening phase

Preoperative phase
Identification of patients at risk and correction of modifiable risk factors
Careful information of patients at risk such as those who have experienced awareness
Check of anesthesia devices and instruments
Intraoperative management
Use of neuromuscular monitoring (quantitative > qualitative)
Maintenance of an adequate anesthesia state until complete recovery of the neuromuscular block
Careful dose adjustment of neuromuscular blocking drugs
Careful management of the reversal (train of four at least 4)
Avoid, if possible, extubation with a fully conscious patient
Use of brain monitoring devices (especially in high-risk patients)
Set threshold alarms of devices following the manufacturer's specifications
Maintain professionalism in the theatre

risk for the complication^[22].

Neuromuscular monitoring

The use of neuromuscular monitoring is the most effective strategy for the prevention of the complication. Although the introduction of special devices to the anesthesiology practice dates back to the 70s, the clinical value of this type of monitoring seems to be still underestimated. Similarly, the effects of incorrect management of NBAs are now clearly documented by large-size multicentre studies^[23]. Intraoperative neuromuscular monitoring can be achieved through conventional peripheral nerve stimulators (PNSs) (subjective/qualitative approach) or by objective/quantitative methods. The systems indicate different clusters of nerve stimulation such as the train-of-four (TOF), double-burst, tetanic, and post-tetanic count. Conventional PNSs have several limitations as they do not provide an objective evaluation of the amplitudes of the twitch heights but work on subjective visual or tactile estimation of the relative strength of the twitches. Thus, the lack of a fade measured with a PNS may not be exhaustive for excluding a residual neuromuscular block which is defined as a TOF ratio (TOFR)-the ratio of the amplitudes of the fourth twitch to the first twitch-less than 0.9 at the ulnar nerve (adductor pollicis). TOFRs of 0.4-0.6 can be detected even when fade is no longer recognized. This occurs because when a TOFR is 0.5 (*i.e.*, the amplitude of the fourth twitch is half of the amplitude of the first one) the system calculates four equal twitches and fails to detect the fade. In turn, the TOFR ranging from 0.40 to 0.90 is also defined as the "zone of blind paralysis". Clinical investigations confirmed these findings as the RECITE study found a high rate of residual paralysis (63%) at the time of extubation despite the use of conventional PNS^[24]. The clinical significance is very important above all in consideration of the awareness phenomenon during emergence and tracheal extubation. On the contrary, objective technologies such as acceleromyography, which is the most widely used method, or mechanomyography, electromyography, kinemyography, compressomyography, and phonomyography allow a quantitative approach. Some of these methods (acceleromyography, electromyography, kinemyography, compressomyography) are marketed as devices, while others are used only for research purposes. These systems act by stimulating the peripheral nerve while also quantifying numerically the induced responses. Thus, they seem to be more accurate for evaluating the gradation of muscle weakness as they can reliably assess TOFR throughout its complete range^[25]. Quantitative methods seem to be a better strategy to prevent a conscious patient from being unable to communicate due to residual neuromuscular block^[26]. While the use of quantitative methods and their superiority over conventional subjective monitoring is well defined by a recent consensus statement^[27] and guidelines^[28], objective approaches are used only in less than 20% of patients^[13]. When only a conventional PNS is applicable, its use should be mandatory in any patient receiving NMBAs.

Careful management of the curare reversal

Neuromuscular monitoring should guide the reversal process. Since in the presence of the first twitch the success rate (TOFR of 0.9 in 10 min) is almost zero, it has been recommended to reverse the action of NMBAs through anticholinesterase (*e.g.*, neostigmine) when TOF count is 4^[29]. As a practical suggestion, if the TOF count is 3, or less, it should be advised against the lightening of the anesthesia plan. The scenario

changes in the case of other reversal approaches. Sugammadex is an encapsulating agent for the aminosteroidal NMBAs rocuronium and, in a minor way, vecuronium. In the rocuronium-induced moderate block (TOFR T1/T0=0.2) recovery (TOFR 0.9) occurs within 2 minutes (sugammadex 2 mg/kg) whereas it can reverse profound block-TOF undetectable and a post-tetanic count is 1-2-in approximately 1.5 minutes when administrated at the dose of 8 mg/kg^[30].

Avoid extubation when the patient is fully conscious

This suggestion is not applicable to all surgical and/or anesthetic settings. In bariatric surgery, for example, and in the anesthesiological management of the severely obese patient, extubation is recommended when there is a complete recovery of consciousness and recovery of spontaneous breathing^[31,32].

Use of brain monitoring devices

As amply demonstrated by clinical studies and analysis of evidence-based medicine, these processed electroencephalographic (pEEG) based devices, also called Depth of Anesthesia (DoA) monitors, certainly do not reduce the risk of complication^[33]. Their main limitation is that they are not sensitive and specific enough to discriminate between the potential consciousness states during GA. Again, the pEEG monitors reliability during emergence is affected by an important functional brain disturbance probably due to the activation of specific sub-cortical sleep-wake cycle regulating systems^[34]. However, several scientific societies such as the ASA^[22], the Australian and New Zealand College of Anesthetists^[35] and the Association of Anaesthetists of Great Britain and Ireland^[36] have specified that the use of brain anesthesia monitoring should be performed in high-risk patients, including those undergoing totally intravenous anesthesia and managed through in deep sedation^[37]. As evidence of the effectiveness of the recommendation, a recent Cochrane analysis showed that in high-risk patients the use of the Bispectral Index can reduce the awareness incidence of up to 75%^[38].

Communicate with the patient during awakening

During the emergence phase, continuous communication with the patient and verbal consoling can relieve any recall episodes^[39].

Postoperative analgesia

The planning of postoperative analgesia through the use of parenteral analgesics, local (wound infiltration) and/or loco regional techniques (single or continuous blocks), plays an important role in the prevention of awareness, as the intraoperative perception of pain is an expression of awareness.

Other prophylactic strategies, such as the use of BDZs in premedication^[40], are less effective in preventing emergence awareness than with respect to awareness during the induction and maintenance phases.

FUTURE RESEARCH DIRECTIONS

Although the research focused on better elucidating the mechanism of action of anesthetics has achieved remarkable results, there are still many gaps that need to be filled. Moreover, since anesthesia acts by impacting consciousness and memory, research on anesthesia has significant implications in different fields of neuroscience. In other words, GA offers an incredible experimental model for studying the phenomena of higher cognitive functions and pathological conditions such as certain states of coma. The phenomenon of anesthesia emergence is fully part of this trend, above all because the awakening mechanisms involve the activation of specific pathways. Therefore, a better knowledge of awakening systems under anesthesia can be of help both to avoid the awareness complication and to offer important information to be translated in all areas where consciousness and memory are studied.

Pharmacogenomic variability and anesthesia

An important research aspect concerns AAWR episodes where a precise cause is not identifiable. Preclinical studies suggest that there is an important variability in the response to anesthetics due, for example, to mutations (and different composition between subunits) of the type-A γ -aminobutyric (GABA_A) receptor. This class of ligand-gated chloride receptors has complicated pharmacology and despite the wide knowledge of the structural characteristics, the working mechanisms and the modulation features-especially concerning the structural variants-still have dark sides. For instance, although the GABA_A modulators BDZs are widely used, their

mechanism of action is still unclear. A better knowledge of the physiology of this and other anesthesia-targeted receptors may stimulate research aimed at developing safer and more specific anesthetics^[41]. Clinical research in this direction is already at work as an on-going observational study is aimed at evaluating the identification of genetic polymorphisms related to propofol requirement and recovery (NCT03087383).

Anesthesia emergence mechanisms

Since the induction of anesthesia (and loss of consciousness, LOC) and emergence (and recovery of consciousness, ROC) are not specular phenomena, a better characterization of these events is necessary. This topic is also closely related to the pharmacogenomic issue as electrophysiological studies have shown that there are specific emergence-related EEG patterns^[42] combined with a poorly understood individual variability. In other words, neurophysiology suggests that LOC and ROC are non-overlapping processes, and in the context of emergence, various EEG correlates indicate the possibility of processes that vary according to the type of anesthetic and, among different patients, on the different conformation of receptors impacted by anesthetics^[43]. The clinical research can help to overcome the limitations of EEG analysis and for dissecting the electrophysiological correlates during the different phases of anesthesia. For this purpose, some surgical settings can represent a valid and non-invasive opportunity. For instance, in a cohort of neurosurgical patients with medically refractory epilepsy who will have implanted with intracranial electrocorticography (ECOG) electrodes, the investigators are performing characterization and comparison of EEG and ECOG activities during consciousness transitions (NCT03629743).

Clinical investigations in high-risk patients

Controlled research is necessary to better evaluate the modality of the impact of anesthesia (and neural correlates) on consciousness, memory and emergence modalities in cohorts of high-risk patients. In these patients, the AAWR risk approaches 1%. Probably, in these individuals, a more effective consolidation of memory traces is achieved. However, being able to isolate the components of consciousness and memory to establish functional interconnections is extremely difficult. In this case, it is easier to refer to animal models and preclinical investigations. In the meantime, clinical investigations are needed for evaluating in patients with higher risk profile the relationship between Bispectral Index, anesthesia dose and concentration, end-tidal anesthetic gas concentration, and EEG parameters. In this direction, the road has been traced by the BAG-RECALL trial which showed that a protocol of anesthesia management based on the Bispectral Index device was not superior to that based on End-Tidal Anesthetic-agent Concentration guidance^[44].

Emergence and recovery of muscular tone

Since the use of NAMBs and the lack of use of the neuromuscular monitoring are the main factors involved in the genesis of AAWR upon awakening, an important aspect of the research must be focused on a better understanding of the correlation between ROC processes and reactivation of muscle tone at the end of the intervention. In this regard, recent EEG studies demonstrated that electromyography activation at the emergence is characterized by cortical and sub-cortical dissociation. Moreover, electromyography activation correlates to volatile gas anesthetic concentrations in the brain through distinct processes^[45].

Depth of anesthesia monitoring

Despite the initial enthusiasm, the introduction of DoA monitors has not represented a definitive solution to the problem of awareness^[46,47]. About the reliability of these instruments, many aspects, such as the impact of NMBA on evoked potential, potential noxious stimulation as well as the EEG variability related to the patient's age and type of agent used, and their reliability during emergence, still need to be clarified. The research is directed to the improvement of algorithms of devices currently on the market and to the development of new methodologies. An observational investigation in children is on-going to develop pEEG-based indexes from analysis of 40 channels beta, alpha and theta waves to ameliorate the dosage of anesthetics and for prevention of intraoperative awakening in this population (NCT03705338). Other researchers are trying to find the anesthesia-induced EEG difference in aging by using the empirical mode decomposition to calculate EEG power (NCT03303443). About the development of new monitoring and effective systems, an interesting perspective is the implementation of the closed-loop control approach. These systems work through a DoA device that automatically regulates the dose of intravenous anesthetics (target-controlled infusion) to be administered to the patient. Different pEEG-based indices have been used for this purpose^[48] and a study

focused on the closed-loop coadministration of propofol and remifentanyl under the guidance of the qCon and qNox indices is on-going (NCT03540875). Finally, different methodologies of brain functioning could be adopted for investigating on the anesthetic brain effects. Some of them such as those that combine EEG, transcranial magnetic stimulation and functional brain imaging techniques (*e.g.*, positron emission tomography, PET, and functional magnetic resonance imaging, fMRI) are at an advanced stage of experimentation and widely used for research purposes^[49].

CONCLUSION

The best strategy for preventing awareness in the awakening phase of anesthesia seems to be a dynamic combination of elements. Compared to the induction and maintenance stages, the emergence offers fewer prophylactic approaches (*e.g.*, use of short-acting BDZs in premedication to prevent AAWR at the induction). However, few practical suggestions can be particularly effective for the prevention of this complication even during emergence. The optimal approach should include identifying patients at risk combined with appropriate strategies for anesthesia management. These prophylactic strategies are the careful administration of drugs and the use of instrumental monitoring. Since most cases of awareness of emergence can be traced to a lack of neuromuscular recovery with a patient in full recovery of consciousness, neuromuscular monitoring through quantitative methods is of fundamental importance. It should be noted, however, that despite all the precautions that can be implemented, a limited percentage of episodes of AAWR cannot be prevented. This paradox holds especially in the emergence phase which represents a very complex neurophysiological process with many aspects yet to be elucidated.

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