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## REVIEW ARTICLES

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### INTRAOPERATIVE AWARENESS: MAJOR FACTOR OR NON-EXISTENT?

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#### Introduction

Intraoperative awareness has been brought to our attention and even sensationalized often by the media over the past few years, as a major problem during anesthesia. The true incidence and the actual incidence have been questioned. Others have even questioned if the complication has been reported in order to garner sympathy at the least and financial gain at the most.

Certainly the incidence of intraoperative awareness under general anesthesia is rare (0.1-0.2%)<sup>1-4</sup> but given that some 21 million anesthetics are administered annually in the United States alone, this figure translates to an occurrence of 20,000 to 40,000 cases. Worldwide the number of cases would easily reach into the millions, especially in countries that lack the resources to administer the newer inhalational anesthetics through state-of-the-art anesthetic machines.

To those who have experienced anesthesia awareness, it is considered a distressing complication which can cause significant psychological sequelae including post-traumatic stress disorder (PTSD)<sup>5</sup>. The syndrome and its sequelae have been discussed on television talk shows, and have been the topic of many articles and panels at national and international meetings.

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Towards the end of 2007, after great advance publicity, Hollywood released a movie, "Awake" which was touted to indicate the horrors of complete consciousness during heart transplant surgery. But, fortunately the movie contained almost no perioperative reality, and the rare clinical accuracies it did present were warped nearly beyond recognition to serve an outlandish plot. After midazolam, fentanyl and a vecuronium chaser, the anesthesiologist, who was not credentialed at that hospital and just happened by, intubated the patient and then left the room on a break to talk to his girlfriend and finish off the flask in his back pocket. Monitors, invasive lines, sterile equipment such as gloves, gowns and masks were not in evidence. Indeed the anesthetic machine was replaced by a cell saver. Concerns by the American Society of Anesthesiologists that the film might have major negative impact, were not realized and the movie closed very shortly after it opened. Nevertheless, anesthesia awareness has become a general public concern causing an increase in the professional liability burden, especially in the United States<sup>4-7</sup>.

The Joint Commission on Accreditation of Healthcare Organization (JCAHO), as part of its Sentinel Event Policy, issued an alert in 2004 on preventing and managing the impact of anesthesia awareness<sup>7,8</sup>. The Commission noted that patients experiencing awareness reported auditory recollections (48%), feelings of inability to breathe (48%), and pain (28%). Some 50% reported mental distress after surgery and many described the experience as the "worst possible" and determined never to have anesthesia again. Several recommendations were made including the use of premedication with amnestic drugs, using higher doses of induction drugs, avoiding muscle paralysis if possible, conducting periodic maintenance of all equipment and being aware of any maintenance medication that mask physiologic responses to inadequate anesthesia. The Commission acknowledged that anesthesia awareness cannot always be prevented in order to achieve other critically important anesthetic goals. Health care workers must be prepared to accept and manage the occurrence of the complication with compassion and diligence, reporting the situation to surgeons and nurses and offering the patient all psychiatric support.

Conclusions drawn were that anesthesia awareness is under-recognized and under treated by health care organizations. Several guidelines were offered to help prevent and manage anesthesia awareness. Among the measures to reduce the incidence are education about the complication, identification of patients at higher risk, effective application of monitoring techniques and appropriate postoperative follow up of patients who have undergone general anesthesia, including children.

Conducting anesthesia in the patient who has had previous intraoperative awareness is challenging and requires careful perioperative management, including a structured interview and considerable compassion and understanding towards the patient.

### *Definition of Awareness*

Intraoperative awareness is defined as a recalled event in which a patient becomes conscious during a procedure performed under general anesthesia. The term “awareness” is limited to ‘explicit memory’ during anesthesia and does not include the time before general anesthesia is fully induced or the time of emergence from general anesthesia<sup>9,10</sup>. Recall is the ability to retrieve stored memories. ‘Explicit memory’ is assessed by the patient’s ability to recall specific events that took place during general anesthesia. ‘Implicit memory’, which is not addressed in the American Society of Anesthesiologists Practice Advisory, is assessed by changes in performance or behavior without the ability to recall specific events that took place during general anesthesia that led to those changes. A report of recall may be spontaneous or elicited only after several interviews. Dreaming, although it is possibly associated with awareness<sup>4</sup>, is not considered intraoperative awareness<sup>10</sup>. Many patients may relate that they heard and were aware of everything during a previous anesthetic experience. On review of these cases, it is usual to discover that the procedure was performed under monitored anesthetic care or conscious sedation with or without an anesthesiologist in attendance. It is appropriate to inform all patients for whom this type of care is deemed appropriate that they may be aware of what is happening but will not feel pain or have any psychological

sequelae. Also, the patient should be made aware that any discomfort he may experience can be managed by additional medication immediately.

### *Detection of Awareness*

The most used employed diagnostic instrument for awareness detection is the structured interview. It should be performed as an ongoing process because the nature of awareness involves memory which may gradually emerge over time<sup>11</sup>. Previous studies revealed that patients who denied awareness when interviewed immediately after surgery in the post anesthetic care area, might confirm awareness at subsequent interviews<sup>12,13</sup>. Sebel et al uncovered 50% of the awareness cases at the second interview<sup>4</sup>. A delayed memory for awareness could be affected by residual anesthetic effects, divided attention to other symptoms such as pain, or nausea and vomiting during the early recovery phase. In addition, it has been suggested that the psychological trauma of awareness itself may lead to memory dissociation which impairs the recall process<sup>11</sup>. Therefore, the detection of awareness depends on the interview technique, timing and frequency, and structure of the interview. As long ago as 1970, Brice et al introduced an interview using a questionnaire as the standard tool to detect awareness<sup>14</sup>. the questionnaire was later modified and comprised five questions as follows<sup>3,4,15,16</sup>.

1. What is the last thing you remember before going to sleep?
2. What is the first thing you remember after waking up?
3. Do you remember anything in between?
4. Do you remember any dreams during your operation?
5. What was the worst thing about your operation?

It is recommended that patients are interviewed on three occasions; before the postanesthesia care unit (PACU) discharge, after 1-3 days and after 7-14 days using the structured interview modified from Brice et al<sup>13,14,17</sup>.

*Risk Factors for Awareness*

The low incidence of awareness provides limited data to identify risk factors. Also, many practitioners may be loathe to report awareness, either because of a believe that the patient is malingering or because such an acknowledgement might imply inadequate anesthetic care. However, the literature does indicate some significant risk factors for awareness (Table 1).

*Table 1*  
*Several risk factors have been identified as more likely to be associated with for awareness<sup>10,11</sup>*

<b>Patient-related</b>	<b>Anesthesia-related</b>	<b>Surgical-related</b>
<ul style="list-style-type: none"> <li>● Female</li> <li>● Young age</li> <li>● Obesity</li> <li>● Limited hemodynamic reserve</li> <li>● History of awareness</li> <li>● Genetic resistance to anesthetic effects</li> <li>● Conditions associated with increased anesthetic requirement</li> <li>● Chronic pain with high doses of opioids</li> <li>● Substance abuse</li> </ul>	<ul style="list-style-type: none"> <li>● Light anesthesia</li> <li>● History of difficult intubation or anticipated difficult intubation</li> <li>● Use of muscle relaxants</li> <li>● Use of nitrous oxide-opioid anesthesia</li> <li>● Defective anesthesia delivery system</li> <li>● Equipment misuse</li> <li>● Insufficient knowledge of awareness</li> <li>● Failure to use brain function monitors if appropriate</li> </ul>	<ul style="list-style-type: none"> <li>● Obstetrics</li> <li>● Cardiac procedures</li> <li>● Trauma surgery</li> <li>● Emergencies</li> <li>● Extensive surgery</li> <li>● Rigid bronchoscopy</li> <li>● Microlaryngeal endoscopic surgery using jet ventilation</li> </ul>

Both the ASA and the American Association of Nurse Anesthetists have stressed the importance of identifying patients at risk for intraoperative awareness by review of the medical record, a thorough physical examination, and a patient or patient-and-family interview<sup>10</sup>. Patient characteristics, such as female gender and younger age, have been suggested as risk factors for intraoperative awareness in the analysis of closed claims in 1999<sup>18</sup> and in other recent studies<sup>19-22</sup>. However, in a multicenter United States study, Sebel et al did not find an association between sex and age and awareness during anesthesia<sup>4</sup>. The discrepancy could be explained

by the loss to follow-up at the postoperative interviews especially at the institutions with high numbers of study patients. Obese patients may have a higher incidence of awareness perhaps due to an increased incidence of difficult airway situations requiring a longer time for endotracheal intubation or even an awake intubation and improper dosing of anesthetic agents resulting in light anesthesia<sup>11,23</sup>. Hemodynamic instability from poor cardiac reserve, such as in cases of severe blood loss or cardiomyopathy, often causes anesthesiologists to use lesser amounts of anesthetic agents which puts the patient at risk of intraoperative awareness. A patient with a history of intraoperative awareness must be carefully evaluated especially concerning the emotional impact of this complication, since the patient may be reluctant to reveal psychological changes to the medical personnel. Such a recalcitrant attitude is more likely to be encountered in South East Asian countries than in the United States where litigation is much more common. All patients should be provided with information about intraoperative awareness and reassurance that every effort to prevent awareness will be made<sup>24</sup>.

It is generally agreed that the most common cause of intraoperative awareness is light anesthesia or inadequate anesthetic dosing<sup>4,11,18,25</sup>. There are several situations when anesthesia personnel inadvertently deliver light anesthesia. Difficult endotracheal intubation, interruption of anesthetic drug supply, improper technique with low fresh gas flows, can all increase the risk of anesthesia awareness<sup>11,26</sup>. In addition, the rapid tapering of anesthesia during surgical closure, especially when short acting drugs are used such as desflurane, propofol or remifentanyl, in an attempt to facilitate operating room turnover, also increases the risk of intraoperative awareness<sup>8</sup>. The choice of anesthesia may also influence the incidence of anesthesia awareness. A closed claims analysis of awareness revealed an increased incidence when nitrous oxide, opioids, muscle relaxants and no or low concentrations of volatile agents constituted the main technique<sup>18</sup>. However, the question of whether the choice of anesthetic (intravenous versus volatile anesthetic agents) affects the incidence of awareness, has yet remained unanswered and seems controversial at present. Eger and Sonner

suggested that patients adequately anesthetized with a potent inhaled anesthetic at 0.5 MAC or more had a rarer incidence of awareness<sup>27</sup>. In contrast, Sebel, Bowdle et al cautioned against relying on a particular recipe of drug or dose due to the considerable biological variation in response to anesthetic agents and the various arousing effect of surgery among surgical patients<sup>4</sup>. Enlund also commented that no absolute answer had yet been made regarding the effect of choice of anesthesia on risk of awareness<sup>28</sup>.

Failure to use brain function monitors when appropriate has also been reported to be a risk. However, to date, no anesthesia brain monitor has been adequately validated in the presence of neuromuscular blocking drugs<sup>29</sup>. Therefore, the ASA Task Force on Intraoperative Awareness Practice Advisory Statement, recommends the use of a brain function monitor on a case-by-case basis for selected patients who are at risk of awareness<sup>50</sup>.

Intraoperative awareness has been linked to certain types of surgery. Descriptive studies and case reports have revealed an incidence of 0.2-0.4% in nonobstetric and noncardiac surgery<sup>15,25</sup>, 0.4% in cesarean section<sup>30</sup>, and 0.3-4% in cardiac surgery<sup>31-34</sup>. Major trauma surgeries have a high incidence of intraoperative awareness due to hypovolemia and hemodynamic instability necessitating light anesthesia<sup>35</sup>. Rigid bronchoscopy and microlaryngeal endoscopic surgery both of which are associated with excessive stimulation, have an increased risk of awareness reported at 1-7%<sup>36-38</sup>.

### *Management*

All patients who report previous intraoperative awareness and those with identified risk factors must be thoroughly evaluated to obtain details of the event and to discuss possible causes of awareness<sup>17</sup>. It is of prime importance to acknowledge the reality of the experience and to recognize the emotional impact to the patient<sup>39</sup>. In addition, once an episode of intraoperative awareness has been detected and verified by an adjudication committee following a structured interview, an occurrence report should be completed for the purpose of quality assurance and further follow up.

Patients should be offered counseling or psychological support on multiple occasions<sup>10,17</sup>. The study of Lennmarken et al reported a group of patients who denied any mental problems in the immediate postoperative period, but were found to suffer from moderate and severe symptoms 2 years later<sup>40</sup>. The experience of awareness can cause immediate suffering as well as long-lasting mental symptoms. Furthermore, awareness often leads to anesthesia dissatisfaction and fear of subsequent anesthesia<sup>1,41</sup>, not to mention poor public opinion of the anesthetic care provider. Psychological sequelae of awareness can differ among patients, especially over vastly different cultural backgrounds. Some patients report mild or no mental problems, but many develop symptoms of post-traumatic stress disorder (PTSD)<sup>5,18,40,42,43</sup> a serious psychiatric disease which has been most recently reemphasized as soldiers return from military campaigns. These men and women have exhibited high divorce rates, unemployment and irrational and sometimes severe criminal behavior. PTSD comprises 6 main diagnostic criteria as shown in Table 2<sup>17,44</sup>.

*Table 2*  
*Several criteria have been identified in the diagnosis of*  
*post-traumatic stress disorder<sup>7,44</sup> (PTSD)*

1	Intense fear, helplessness, horror
2	Recurrent and intrusive recollections of the traumatic event, including images, thoughts, perceptions, or dreams
3	Persistent avoidance of thoughts, feelings, conversation, or activities associated with the event
4	Persistent symptoms of increased arousal (not present before the trauma) by two or more of the following <ol style="list-style-type: none"> <li>1. Difficulty falling or staying asleep</li> <li>2. Irritability or outbursts of anger</li> <li>3. Difficulty concentrating</li> <li>4. Hyper vigilance</li> <li>5. Exaggerated startle response</li> </ol>
5	Duration of the disturbance (symptoms in criterion 2-4) is more than 1 month
6	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

The study of Lennmarken regarding long-term mental effect of awareness after 2 years, revealed the whole spectrum of diagnostic criteria<sup>40</sup>. Also, Samuelsson et al found that acute emotion as fear, panic and helplessness was significantly related to late psychological symptoms<sup>41</sup>. Therefore, it is recommended that professional psychiatric assessment, therapy and follow-up should be provided and constitutes standard practice for all patients who report an episode of anesthetic awareness<sup>17,40</sup>.

### *Prevention of Awareness*

The risk of intraoperative awareness can be minimized at three stages: preoperative assessment, preinduction phase of anesthesia, and intraoperative management.

During preoperative assessment, patients at risk of intraoperative awareness, as in Table 1, should be identified. The ASA Task Force on Intraoperative Awareness practice advisory statement suggested that patients at substantially increased risk of intraoperative awareness should be informed of the possibility of intraoperative awareness<sup>10</sup>. However, the patient should also be reassured that every effort will be used to prevent the complication. The previous anesthetic record should be analyzed and possible reasons for the event uncovered and discussed.

During the preinduction phase, anesthesia personnel must check the functioning of anesthesia delivery system, including vaporizers (ensuring that they are full and low levels alarms are functioning), infusion pumps, adequacy of fresh gas flow, and appropriate placement and functioning of intravenous cannulae<sup>10</sup>. The issue of the prophylactic administration of benzodiazepines has been studied widely. Many anesthesiologists believe that using benzodiazepines, such as midazolam, in the anesthetic regimen can reduce the risk of awareness<sup>25,31</sup>. One double-blind randomized clinical trial compared the efficacy of the prophylactic administration of midazolam and a placebo during ambulatory procedure, and reported a lower incidence of intraoperative awareness in the midazolam group<sup>45</sup>. Other two randomized clinical trials also reported reduced recall in

patients administered midazolam but subsequent intraoperative awareness was not examined<sup>46,47</sup>. Both studies indicated that midazolam could not be used to reliably produce retrograde amnesia. Thus, the ASA Task Force recommends the use of prophylactic benzodiazepine on a case-by-case basis for selected patients such as patients requiring smaller dosages of anesthetics, with the caution that delayed emergence might accompany the use of benzodiazepines<sup>10</sup>. It is important to note that midazolam is not available as an oral preparation in all countries. Thus, while prophylactic administration of this valuable amnestic agent is possible for many patients worldwide who are admitted on an ambulatory basis, the same does not hold true in the United States. There, patients can be advised to take a sleeping pill the night before (diazepam is available orally) but amnesia cannot be guaranteed.

Intraoperative management and monitoring includes consideration of clinical techniques, conventional monitoring and brain electrical activity monitoring<sup>10</sup>. Intraoperative awareness cannot be measured during the intraoperative phase of general anesthesia, because the recall component of awareness is determined by obtaining information from the patient directly postoperatively. Thus, at best, attempts to determine awareness during surgery are still far from perfect. Studies while not directly assessing the impact of an intervention on awareness, many times may report patterns that occurred at identifiable times during the perioperative period with the intention of predicting variations in anesthetic depth. Techniques used to assess intraoperative consciousness include observation of purposeful or reflex movement, response to commands, eye opening, presence of eyelash reflex and brisk pupillary responses. In the absence of muscle relaxants, patient movement and altered or irregular breathing patterns can be used to identify a patient who is inadequately anesthetized. These useful signs are absent if muscle relaxants are administered. Typical physiological responses of autonomic signs such as increased blood pressure and heart rate, sweating, tearing, and pupillary responses are also masked by patient medications such as beta-blockers and calcium channel blockers. The 'isolated forearm' technique has been used to evaluate depth of anesthesia in the presence

of neuromuscular blocking drugs<sup>29,48</sup>. However, the technique is quite cumbersome and has not been widely used<sup>24,49</sup>. Conventional monitoring systems include ASA standard monitoring such as electrocardiogram, blood pressure, heart rate, pulse oximetry, capnography, and end-tidal anesthetic gas analyses<sup>50</sup>. Correlation studies reported various prediction probability (Pk) values for the association between physiological responses and depth of anesthesia ranging from 0.5 (probability equal to chance) to 0.9 (near perfect association)<sup>51-55</sup>. These findings confirm that clinical techniques and conventional monitoring systems are valuable in the assessment of intraoperative consciousness as long as practitioners are aware of their limitations.

Brain function monitoring has been advocated to recognize ongoing intraoperative awareness. The monitoring systems can be subdivided into two groups; those that process spontaneous electroencephalographic (EEG) and electromyographic activity, and those that acquire evoked responses to auditory stimuli (AEPs)<sup>10</sup>. Both spontaneous EEG and AEP provide information about the hypnotic state of the patient. Because the raw waveforms are too complicated to interpret on a continuing basis, they are processed by advances in computerization into a dimensionless parameter<sup>10,24,49</sup> (Table 3). Most devices designed to monitor brain electrical activity and anesthetic effect, record electroencephalographic activity from electrodes placed on the forehead. Artifact recognition algorithms attempt to avoid contamination. Although electromyographic (EMG) activity from scalp muscles in the non paralyzed patient might be considered an artifact, it may prove to be an important source of clinically relevant information. The sudden appearance of frontal activity suggests somatic response to noxious stimulation from light anesthesia and may give warning of impending arousal. Thus, some monitors provide information on EMG activity Bispectral index (BIS<sup>®</sup>, Aspect Medical Systems, Natick, MA), Entropy (GE Healthcare Technologies, Waukesha, WI), Narcotrend<sup>®</sup>, (Monitor Technik, Bad Branstedt, Germany), Patient State Index (PSI, Physiometrix, North Billerica, MA), SNAP index (Everest Biomedical Instruments, Chesterfield, MO) and Cerebral State Index (Danmeter

A/S, Odense, Denmark) are scaled from 0 (deeply anesthetized) to 100 (awake)<sup>10</sup>. AEPs (AEP Monitor/2 Danmeter) are the electrical responses of the brainstem which is relatively insensitive to anesthetics. In contrast, early cortical responses, known as the middle-latency AEPs (MLAEPs), change predictably with increasing concentrations of both volatile and intravenous anesthetics by increasing latency and decreasing amplitude of the various waveform components. The typical AEP response to increasing anesthetic depth is increased latency and decreased amplitude of the waveform components. Recent signal filtering advances have resulted in an instrument (A-line<sup>®</sup>; Danmeter) that can record and rapidly update a single channel of AEPs from forehead electrodes. An AEP index is generated that provides a correlate of anesthetic concentration. The index is also scaled from 0-100 but low probability of consciousness corresponds to a value less than 25, rather than 70 as seen reported with the BIS<sup>®</sup> monitor<sup>10</sup>.

*Table 3*  
*Several monitors available for cerebral monitoring are compared*

BIS <sup>®</sup>	Converts a single channel of frontal EEG into an index of hypnotic level
Entropy	Describes irregularity, complexity or unpredictability characteristics of a signal. Algorithm in public domain
Narcotrend <sup>®</sup>	Derived from a system developed for the visual classification of the EEG patterns associated with stages of sleep
Patient State Analyzer	Derived from a 4 channel EEG
SNAP index	Calculates a SNAP index from a single channel EEG. Spectral analysis and burst suppression algorithms
Cerebral State Monitor	Handheld device to analyze a single channel EEG. Provides EEG suppression percentage and EMG activity

EEG = electroencephalogram. EMG = electromyographic activity.

BIS<sup>®</sup> values, with specific ranges of 40 to 60, are reported to reflect a low probability of consciousness under general anesthesia. However, two case reports revealed patients experiencing intraoperative awareness despite monitored values indicating adequate depth of anesthesia<sup>56,57</sup>. Also,

several case reports indicated that certain intraoperative events (e.g. cerebral hypoperfusion, gas embolism)<sup>58-61</sup> and patient conditions may affect BIS<sup>®</sup> values<sup>10,62-64</sup>. The B-Aware Trial which was a multicenter, double-blind, randomized trial reported two cases of intraoperative awareness in the BIS<sup>®</sup>-guided group although it showed a risk reduction of 82% ( $p = 0.022$ ) as compared to the routine care group<sup>65</sup>. Yet another randomized trial suggested that the use of either BIS<sup>®</sup> or PSI as a guide to administration of anesthetic drugs required caution to avoid awareness<sup>66</sup>. A recent small study also noted caution with the use of Narcotrend<sup>®</sup>-guided general anesthesia in the presence of neuromuscular blocking drugs<sup>67</sup>. Therefore, it has been recommended that all anesthesia brain monitors should be adequately validated before being used as guides to administration of anesthetic agents for individual patients<sup>68,69</sup>. At present, there is insufficient evidence to justify a standard guideline or absolute requirement that these brain function monitors be used, to reduce the occurrence of intraoperative awareness in high-risk patients undergoing general anesthesia. The ASA Task Force recommended that the decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients<sup>10</sup>.

Thus, intraoperative management and monitoring require multiple modalities, in addition to clinical techniques, conventional monitoring systems, brain function monitor when appropriate; vigilance, improved training, and supervision cannot be overemphasized. While both the ASA and the American Association of Nurse Anesthetists have developed guidelines and practice advisories for prevention of intraoperative awareness, JCAHO recommends that individual hospitals and departments of anesthesia develop and implement their own policies.

## Conclusion

Anesthetic awareness does exist but is a rare occurrence. Prevention may not be completely possible but the incidence can be reduced by identification of patients at risk, equipment checks, careful physiologic

monitoring, administration of adequate anesthesia and brain function monitoring. As appropriate, documentation of findings should be made on the anesthetic record in a timely manner. Should the complication occur, then it is appropriate to interview the patient, acknowledge the problem, attempt to determine the reason, provide psychological expertise and assure the patient that subsequent anesthetics may not necessarily have the same outcome.

## References

1. MYLES PS, WILLIAMS D, HENDRATA M, ET AL: Patient satisfaction after anesthesia and surgery: Results of a prospective survey of 10, 81 patients. *Br J Anaesth*; 2000, 84:6-10.
2. NORDSTROM O, ENGSTROM AM, PERSSON S, ET AL: Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. *Acta Anaesthesiol Scand*; 1997, 41:978-84.
3. SANDIN RH, ENLUND G, SAMUELSSON P, ET AL: Awareness during anaesthesia: A prospective case study. *Lancet*; 2000, 355:707-11.
4. SEBEL PS, BOWDLE TA, GHONEIM MM, ET AL: The incidence of awareness during anesthesia: A multicenter United States study. *Anesth Analg*; 2004, 99:833-9.
5. OSTERMAN JE, HOPPER J, HERAN WJ, ET AL: Awareness under anesthesia and the development of post-traumatic stress disorder. *Gen Hosp Psychiatry*; 2001, 23:198-204.
6. SACKEL DJ: Anesthesia awareness: an analysis of its incidence, the risk factors involved, and prevention. *J Clin Anesth*; 2006, 18:483-5.
7. KENT CD, DOMINO KB: Awareness: practice, standards, and the law. *Best Pract Res Clin Anaesthesiol*; 2007, 21:3:369-83.
8. Joint Commission on Accreditation of Healthcare Organization (JCAHO), Preventing and managing the impac of anesthesia awareness, *Sentinel Event Alert* 32(2004), pp. 1-3.
9. GHONEIM MM: Awareness during anesthesia. *Anesthesiology*; 2000, 92:2:597-602.
10. American Society of Anesthesiologists Task Force on Intraoperative Awareness. Practice advisory for intraoperative awareness and brain function monitoring: a report by the American Society of Anesthesiologists Task Force on Intraoperative Awareness. *Anesthesiology*; 2006, 104:847-64.
11. GHONEIM MM: Incidence of and risk factors for awareness during anesthesia. *Best Pract Res Clin Anaesthesiol*; 2007, 21:3:327-43.
12. MACLEOD A, MAYCOCK E: Awareness during anaesthesia and post-traumatic stress disorder. *Anaesth Intensive Care*; 1992, 20:378-82.
13. RUSSELL I, WANG M: Absence of memory for intraoperative information during surgery under general anaesthesia. *Br J Anaesth*; 1997, 78:3-9.
14. BRICE DD, HETHERINGTON RR, UTTING JE: A simple study of awareness and dreaming during anaesthesia. *Br J Anaesth*; 1970, 42:535-41.
15. LIU WHD, THROP TA, GRAHAM SG, ET AL: Incidence of awareness with recall during general anaesthesia. *Anaesth*; 1991, 46:435-7.
16. ENLUND M, HASSEN HG: Intraoperative awareness: detected by the structured Brice interview? *Acta Anaesthesiol Scand*; 2002, 46:345-9.
17. LENNMARKEN C: Psychological consequences of awareness and their treatment. *Best Pract Res Clin Anaesthesiol*; 2007, 21:3:357-67.
18. DOMINO KB, POSNER KL, CAPLAN RA, ET AL: Awareness during anesthesia: a closed claims analysis. *Anesthesiology*; 1999, 90:1053-61.
19. GAN TJ, GLASS PS, SIGL J, ET AL: Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *Anesthesiology*; 1999, 90:1283-7.
20. LOPEZ U, ISELIN-CHAVES I, HABRE W, ET AL: Incidence of awareness during general anaesthesia in children. *Br J Anaesth*; 2004, 93:490P-1P.
21. DAVIDSON AJ, HUANG GH, CZARNECKI C, ET AL: Awareness during anesthesia in children: a prospective cohort study. *Anesth Analg*; 2005, 100:653-61.
22. BUCHANAN FF, MYLES PS, LESLIE K, ET AL: Gender and recovery after general anesthesia combined

- with neuromuscular blocking drugs. *Anesth Analg*; 2006, 102:291-7.
23. GUERRA F: Awareness and recall. *Int Anesthesiol Clin*; 1986, 24:75-99.
  24. MYLES PS: Prevention of awareness during anaesthesia. *Best Pract Res Clin Anaesthesiol*; 2007, 21:3:345-55.
  25. RANTA SO, LAURILA R, SAARIO J, ET AL: Awareness with recall during general anesthesia: incidence and risk factors. *Anesth Analg*; 1998, 86:1084-9.
  26. DOMINO K, AITKENHEAD A: Medico-legal consequences of awareness during anesthesia. In Ghoneim MM (ed). *Awareness during anesthesia*. Oxford: Butterworth-Heinemann 2001, pp. 155-72.
  27. EGER EI, SONNER JM: How likely is awareness during anesthesia? *Anesth Analg*; 2005, 100:1544-45.
  28. ENLUND M: TIVA, awareness, and the Brice interview. *Anesth Analg*; 2006, 102:967.
  29. RUSSELL IF: The Narcotrend 'depth of anaesthesia' monitor cannot reliably detect consciousness during general anaesthesia: an investigation using the isolated forearm technique. *Br J Anaesth*; 2006, 96:346-52.
  30. LYONS G, MACDONALD R: Awareness during caesarean section. *Anaesthesia*; 1991, 46:62-4.
  31. PHILLIPS AA, McLEAN RF, DEVITT JH, ET AL: Recall of intraoperative events after general anaesthesia and cardiopulmonary bypass. *Can J Anaesth*; 1993, 40:922-6.
  32. RANTA S, JUSSILA J, HYNYNEN M: Recall of awareness during cardiac anaesthesia: influence of feedback information to the anaesthesiologist. *Acta Anaesthesiol Scand*; 1996, 40:554-60.
  33. RANTA SO, HERRANEN P, HYNYNEN M: Patients' conscious recollections from cardiac anaesthesia. *J Cardiothorac Vasc Anesth*; 2002, 16:426-30.
  34. DOWD NP, CHENG DCH, KARSKI JM, ET AL: Intraoperative awareness in fast-track cardiac anaesthesia. *Anesthesiology*; 1998, 89:1068-73.
  35. BOGETZ MS, KATZ JA: Recall of surgery for major trauma. *Anesthesiology*; 1984, 61:6-9.
  36. BARR AM, WONG RM: Awareness during general anaesthesia for bronchoscopy and laryngoscopy using the apnoeic oxygenation technique. *Br J Anaesth*; 1973, 45:784-900.
  37. DUNCAN AW, BARR AM: Diazepam premedication and awareness during general anaesthesia for bronchoscopy and laryngoscopy. *Br J Anaesth*; 1973, 45:1150-2.
  38. HEWIT JM, BARR AM: Premedication with lorazepam for bronchoscopy under general anaesthesia. *Br J Anaesth*; 1978, 50:1149-54.
  39. OSTERMAN JE, VAN DER KOLK BA: Awareness during anaesthesia and posttraumatic stress disorder. *Gen Hosp Psychiatry*; 1998, 20:274-81.
  40. LENNMARKEN C, BILDFORS K, ENLUND G, ET AL: Victims of awareness. *Acta Anaesthesiol Scand*; 2002, 46:229-31.
  41. SAMUELSSON P, BRUDIN L, SANDIN RH: Late psychological symptoms after awareness among consecutively included surgical patients. *Anesthesiology*; 2007, 106:26-32.
  42. MOERMAN N, BONKE B, OOSTING J: Awareness and recall during general anesthesia: facts and feeling. *Anesthesiology*; 1993, 79:454-64.
  43. SCHWENDER D, KUNZE-KRONAWITTER H, DIETRICH P, ET AL: Conscious awareness during general anaesthesia: patients' perception, emotions, cognition and reactions. *Br J Anaesth*; 1998, 80:133-9.
  44. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4<sup>th</sup> ed. Washington, DC. American Psychiatric Association 1994.
  45. MILLER DR, BLEW PG, MARTINEAU RJ, ET AL: Midazolam and awareness with recall during total intravenous anaesthesia. *Can J Anaesth*; 1996, 43:946-53.
  46. BULACH R, MYLES PS, RUSSNAK M: Double-blind randomized controlled trial to determine extent

- of amnesia with midazolam given immediately before general anesthesia. *Br J Anaesth*; 2005, 94:300-5.
47. TWERSKY RS, HARTUNG J, BERGER BJ, ET AL: Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. *Anesthesiology*; 1993, 78:51-5.
  48. RUSSEL IF: Midazolam-alfentanil: an anesthetic? An investigation using the isolated forearm technique. *Br J Anaesth*; 1993, 70:42-6.
  49. BRUHN J, MYLES PS, SNEYD R, ET AL: Depth of anaesthesia monitoring: what's available, what's validated and what's next? *Br J Anaesth*; 2006, 97:85-94.
  50. American Society of Anesthesiologists. Standards for basic anesthetic monitoring. *American Society of Anesthesiologists Standards, Guidelines, and Statements*, October 25, 2005.
  51. LESLIE K, SESSLER DI, SMITH WD, ET AL: Prediction of movement during propofol/nitrous oxide anesthesia: performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. *Anesthesiology*; 1996, 84:52-63.
  52. DUTTON RC, SMITH WD, SMITH NT: Wakeful response to command indicates memory potential during emergence from general anesthesia. *J Clin Monit*; 1995, 11:35-40.
  53. SCHMIDT G, BISCHOFF P, STANDL T, ET AL: Comparative evaluation on the Datex-Ohmeda S/5 entropy module and the bispectral index monitor during propofol-remifentanil anesthesia. *Anesthesiology*; 2004, 101:1283-90.
  54. SCHMIDT GN, BISCHOFF P, STANDL T, ET AL: Narcotrend and bispectral index monitor are superior to classic electroencephalographic parameters for the assessment of anesthetic states during propofol-remifentanil anesthesia. *Anesthesiology*; 2003, 99:1072-7.
  55. SCHMIDT GN, BISCHOFF P, STANDL T, ET AL: Comparative evaluation of Narcotrend, bispectral index, and classical electroencephalographic variables during induction, maintenance, and emergence of a propofol-remifentanil anesthesia. *Anesth Analg*; 2004, 98:1346-53.
  56. MYCHASKIW G II, HOROWITZ M, SACHDEV V, ET AL: Explicit intraoperative recall at a bispectral index of 47. *Anesth Analg*; 2001, 92:808-9.
  57. RAMPERSAD SE, MULROY MF: A case of awareness despite an "adequate depth of anesthesia" as indicated by a bispectral index monitor. *Anesth Analg*; 2005, 100:1363-4.
  58. CHAZOT T, LIU N, TREMELOT L, ET AL: Detection of gas embolism by bispectral index and entropy monitoring in two cases. *Anesthesiology*; 2004, 101:1053-4.
  59. HAYASHIDA M, CHINZEI M, KOMATSU K, ET AL: Detection of cerebral hypoperfusion with bispectral index during paediatric cardiac surgery. *Br J Anaesth*; 2003, 90:694-8.
  60. KIN N, KONSTADT S, SATO K, ET AL: Reduction of bispectral index value associated with clinically significant cerebral air embolism. *J Cardiothorac Vasc Anesth*; 2004, 18:82-4.
  61. MOURISSE J, BOOII L: Bispectral index detects period of cerebral hypoperfusion during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*; 2003, 17:76-8.
  62. CHINZEI M, SAWAMURA S, HAYASHIDA M, ET AL: Change in bispectral index during epileptiform electrical activity under sevoflurane anesthesia in a patient with epilepsy. *Anesth Analg*; 2004, 98:1734-6.
  63. HAGIHIRA S, OKITSU K, KAWAGUCHI M: Unusually low bispectral index values during emergence from anesthesia. *Anesth Analg*; 2004, 98:1036-8.
  64. SCHNIDER TW, LUGINBUHL M, PETERSEN-FELIX S, ET AL: Unreasonably low bispectral index values in a volunteer with genetically determined low-voltage electroencephalographic signal. *Anesthesiology*; 1998, 89:1607-8.
  65. MYLES PS, LESLIE K, MCNEIL J, ET AL: Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomized controlled trial. *Lancet*; 2004, 363:1757-63.

66. SCHNEIDER G, GELB AW, SCHMELLER B, ET AL: Detection of awareness in surgical patients with EEG-based indices-bispectral index and patient state index. *Br J Anaesth*; 2003, 91:329-35.
67. RUSSELL IF: The Narcotrend® 'depth of anaesthesia' monitor cannot reliably detect consciousness during general anaesthesia: an investigation using the isolated forearm technique. *Br J Anaesth*; 2006, 96:346-52.
68. SCHNEIDER G, KOCHS EF, HORN B, ET AL: Narcotrend® does not adequately detect the transition between awareness and unconsciousness in surgical patients. *Anesthesiology*; 2004, 101:1105-11.
69. WATCHA MF: Investigations of the bispectral index monitor in pediatric anesthesia: first things first. *Anesth Analg*; 2001, 92:805-7.