CME Awareness During Anesthesia: Risk Factors, Causes and Sequelae: A Review of Reported Cases in the Literature

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BACKGROUND: Awareness during anesthesia is uncommon. The number of cases that are found in one single study are insufficient to identify and estimate the risks, causal factors and sequelae. One method of studying a large number of cases is to analyze reports of cases of awareness that have been published in scientific journals.

METHODS: We conducted an electronic search of the literature in the National Library of Medicine's PubMed database for case reports on "Awareness" and "Anesthesia" for the time period between 1950 through August, 2005. We also manually searched references cited in these reports and in other articles on awareness. We used two surgical control groups for comparative purposes. The first group in a study by Sebel et al. consisted of patients who did not experience awareness. The second group, from the 1996 data from the National Survey of Ambulatory Surgery included patients who received general anesthesia. We also used data from the National Center for Health Statistics to compare weight and Body Mass Index.

RESULTS: We compared the data of 271 cases of awareness with 19,504 patients who did not suffer it. Aware patients were more likely to be females ($P < 0.05$), younger ($P < 0.001$) and to have cardiac and obstetrics operations ($P < 0.0001$). Only 35% reported the awareness episode during the stay in the recovery room. They received fewer anesthetic drugs ($P < 0.0001$), and were more likely to exhibit episodes of tachycardia and hypertension during surgery ($P < 0.0001$). A much larger percentage of these patients (52%, $P < 0.0001$) voiced postoperative complaints related to awareness. Inability to move and feelings such as helplessness, sensation of weakness, and hearing noises and voices were related to the persistence of complaints such as sleep disturbances and fear about future anesthetics ($P < 0.041–0.0003$). Twenty-two percent of the patients suffered late psychological symptoms.

CONCLUSIONS: Our review suggested light anesthesia and a history of awareness as risk factors. Obesity and avoidance of nitrous oxide use did not seem to increase the risk. Light anesthesia was the most common cause. Our findings suggest preventive procedures that may lead to a decrease in the incidence of awareness.

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The term "awareness" during anesthesia, as used in the anesthesia literature, implies that during a period of intended general anesthesia, the brain is aroused by stimuli that are stored in memory for future explicit recall. Patients who experience awareness will recall such experiences during a state of inadequate anesthesia.[1] Awareness is an uncommon phenomenon, occurring in about 0.1% to 0.2% of cases.[2] A recent study, using the data from hospitals' quality improvement systems, reported an incidence of 0.007%.[3] Prospective studies have been used to study the incidence of the event. However, the number of cases that are reported is insufficient to identify and estimate the risks, causal factors and sequelae, which need to be known in order to develop effective preventive measures. In an effort to recruit more cases, advertising, referral from other physicians and closed claims analysis have been used. Myles et al.[4] recruited patients undergoing specific types of surgery, e.g., cardiac and obstetric, which have an increased incidence of awareness. These methods still do not provide enough cases and lead to selection bias, e.g., excessive recruitment of "complainers" and those with financial motives or incentives and restriction to specific types of surgery and patients. For the alleged victims of awareness who are identified by these methods, with the exception of those of the prospective study of Myles et al.,[4] remembering the past is not merely a matter of activating or awakening a dormant trace or picture in mind, but

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instead involves a far more complex interaction between the current environment at the time of investigation, what one expects to remember and what is retained from the past. Biases and suggestive techniques tilt the balance among these contributors, so that present influences may play a larger role in determining what is remembered than what actually happened.[5]

One method of studying a large number of awareness cases, much larger than has been done so far, is to study reports of awareness that have been published in scientific journals. Case reports have sometimes had a greater impact on science and clinical practice than most prospective randomized investigations.[6] The report by Scoville and Milner in 1957[7] of a patient identified as HM, began the modern study of memory storage by localizing memory to a specific site in the brain and provided the first evidence of implicit memory storage. It became the most cited article in the field of brain and behavior research. The report by Winterbottom in 1950[8] emphasized the danger of awareness during the use of muscle relaxants as anesthetic adjuvants, and opened the gate for studies of awareness. The description by Albright[9] of cardiac deaths after bupivacaine administration alerted the anesthesia community to the dangerous cardiovascular toxicity of the drug. There are many other examples. The American Society of Anesthesiologists (ASA) recognized very recently the value of case reports and, in March, 2007, opened an electronic awareness registry to recruit cases,* with the declared goal of "gathering detailed and relevant information with the aim of increasing our knowledge about intraoperative awareness and its risk factors." Our review of published cases shares the same goals.

METHODS

We conducted an electronic search of the literature in the National Library of Medicine's PubMed database for case reports on "Awareness" and "Anesthesia" for the time period between 1950 (when the first case report was published) through August, 2005. We also manually searched references cited in these reports and in various articles on awareness. All the retrieved articles were limited to the English language and peer-reviewed publications. We excluded publications devoted to pediatric cases, cases in which a large part of the data that we wanted to collect were missing, cases caused by administration of muscle relaxants in error to an awake patient, cases reporting only out-of-body experiences (a patient sees his or her body from a location outside the physical body), dreams and cases which could only be categorized as possible as opposed to definite or probable. We collected 271 cases.

The data extracted for each case were the article authors' names, title, name of the journal, publication dates, age, gender, race, weight, height, Body Mass Index (BMI), ASA classification, history of awareness, history of drug use, premedication, drugs for induction of anesthesia, difficulty and duration of laryngoscopy and intubation, drugs for maintenance of anesthesia, monitors used, autonomic changes during anesthesia, patient movement, time of awareness, time of report of awareness, type of operation, patients' complaints and postoperative sequelae, management of the report of awareness by the anesthesiologists, and possible cause of awareness. The materials for each case were searched by two of the authors (MG and either MH or MM) to ensure accuracy of the data summary.

We used two surgical control groups for comparative purposes. The first group consisted of 19,504 patients who did not experience awareness in the study by Sebel et al.,[2] which investigated the incidence of awareness. The data compared for this group included the patient's age, gender, ASA classification, premedication, drugs used for induction and maintenance of anesthesia, intraoperative hypertension and/or tachycardia, type of surgery, and postoperative sequelae. Because these data were recent and the awareness case reports spanned many years, we also used, for comparative purposes, age and gender of patients who received general anesthesia in the 1996 data from the National Survey of Ambulatory Surgery (similar data are not readily available for hospitalized patients),† and weight and BMI in the 1988–1994 data from the National Health and Nutrition Examination Survey‡ of the United States household population.

Frequency distributions of qualitative characteristics and means of quantitative characteristics were derived from the 271 awareness case reports that were identified. The frequency distribution for each characteristic was based on all cases that provided information concerning that characteristic, regardless of whether they lacked data concerning other characteristics. The frequency of missing data for each characteristic was tabulated separately. χ^2 tests were used to examine associations of complaints during episodes of awareness during anesthesia with postoperative sequelae. Negative binomial regression was used to examine whether the average numbers of case reports per year changed over different time periods. From the fitted model, estimates of the number of cases per year for each time period were obtained and pairwise comparisons that compared 1990–99 and 2000–05 with each of the earlier time periods were performed. The level of significance used was $\alpha < 0.05$. The analyses were done with SAS 9.1 for Windows software.

*www.awaredb.org Accessed December 13, 2007.

†National Center for Health Statistics. National Hospital Discharge and Ambulatory Surgery Data. http://www.cdc.gov/nchs/nsas.htm. Accessed December 13, 2007.

‡National Center for Health Statistics. National Health and Nutrition Examination Survey. http://www.cdc.gov/nchs/nhanes.htm. Accessed December 13, 2007.

Table 1. Journals in Which Most Reports of Awareness Were Published

	Percentage of reports[a]
Acta Anesthesiologica Scandinavica	6
Anesthesia	4
Anesthesia & Analgesia	17
Anesthesiology	12
British Journal of Anesthesia	25
Canadian Anesthetists' Society Journal	4
Journal of the American Medical Association	3
The Lancet	12

[a] Seventeen percent of the reports were published in a variety of other journals.

In comparing the data from the awareness case reports with the three other data sets derived from Sebel et al.,[2] the National Survey of Ambulatory Surgery, and the National Health and Nutrition Examination Survey, the statistical tests used were the Wilcoxon's ranked sum test for ASA classification, χ^2 tests for other qualitative characteristics, and *t*-tests for quantitative characteristics. For these comparisons, individuals younger than 20-yr-old were excluded; there were only two such individuals (<1%) among the awareness case reports. Data from the National Survey of Ambulatory Surgery and the National Health and Nutrition Examination Survey were treated as population values, and, when compared with the awareness case reports, were matched for gender when comparing age and for age when comparing gender, weight, and BMI. Raw data were used for the National Survey of Ambulatory Surgery. Published means were used for the National Health and Nutrition Examination Survey; separately for men and women, we obtained population means for weight and BMI from this published information by taking weighted averages of the means over the different age categories, with the weights corresponding to the percent distribution by age of the reported cases of awareness. Because of the time frames of these sources and the possibility of changes over the years in some of the characteristics that were compared, e.g., weight, these comparisons were done both excluding and including the older awareness case reports, i.e., those published prior to 1984. The results were not meaningfully affected by including the older awareness case reports, so only the comparisons excluding them are reported.

RESULTS

Journals and Time Periods of Publication

The tabulation of percentages of case reports of awareness during anesthesia that were published in different journals (Table 1) indicates that four journals (*Anesthesia & Analgesia, Anesthesiology, British Journal of Anesthesia, and The Lancet*) accounted for about two-thirds of the cases. The percentages of case reports published in different time periods from 1950 through 2005 are shown in Table 2. There was a marked increase in case reports since 1990, with more than 75% of case reports published since then. The average numbers of case reports per year were larger for 1990–99 and 2000–05 than for each of the earlier decades, with significance ranging from $P < 0.04$ to $P < 0.0001$.

Table 2. Percentages of Reports of Awareness Published in Different Time Periods

Years of publication	Percentage of case reports
1950–1959	1
1960–1969	6
1970–1979	10
1980–1989	5
1990–1999	45
2000–2005[a]	33

[a] Until August only.

Exclusions

We excluded the characteristics for which more than 60% of the data were missing. These were the ASA classification of patients (identified only in 31% of the reports) and postoperative management (identified only in 30% of the reports).

Quantitative Characteristics

Quantitative characteristics of patients who experienced awareness during anesthesia that were examined were age, weight, and BMI (Table 3). The patients described in the awareness case reports were younger than the patients who did not experience awareness in the study of the incidence of awareness during anesthesia by Sebel et al.[2] ($P = 0.001$), but did not differ in age from the patients in the National Survey of Ambulatory Surgery ($P = 0.69$). The patients described in the awareness case reports did not differ in weight or BMI from subjects in the National Health and Nutrition Examination Survey ($P = 0.39$ or larger). Based on categories of BMI,§ the percentages of patients described in the awareness case reports who were underweight, normal weight, preobese or obese were 5%, 41%, 35%, and 19%, respectively.

Qualitative Characteristics

There were also some qualitative characteristics of patients and procedures described in the awareness case reports that could be compared to those of patients who did not experience awareness in the study by Sebel et al.[2] Table 4 provides information about five such characteristics for which data were available for almost all patients in Sebel et al.'s study. For one of these characteristics, gender, the awareness case reports could also be compared with patients in the National Survey of Ambulatory Surgery. The

§World Health Organization. BMI Classification. http//www/who.int/bmi/index.jsp?introPage=intro_3.html. Accessed December 13, 2007.

Table 3. Comparisons of Quantitative Characteristics of Awareness Reports With Other Data Sets

	Awareness reports	Sebel et al.[2] nonawareness cases	NSAS	NHANES
	mean ± SD	mean ± SD	mean	mean
Age (yr)*	46 ± 15	49 ± 15	46	—
Weight (kg)				
Men	84 ± 19	—	—	83
Women	70 ± 14	—	—	70
Body mass index (kg/m^2)				
Men	27 ± 6	—	—	27
Women	26 ± 5	—	—	27

Values of the awareness reports were compared by *t*-tests with the three other data sets.

SD's are not specified for NSAS and NHANES because their means were considered to be population values. Age, weight, and Body Mass Index were reported (or, in the case of Body Mass Index, could be calculated from weight and height) for 98%, 55%, and 43% of the awareness cases, respectively.

NSAS = National Survey of Ambulatory Surgery; NHANES = National Health and Nutrition Examination Survey.

* $P = 0.001$ for difference of awareness reports from patients of Sebel et al.[2] who did not experience awareness.

Table 4. Comparisons of Qualitative Characteristics of Awareness Reports With Other Data Sets

	Percentage of reports	Percentage of nonawareness cases of Sebel et al.[2]	Percentage, NSAS
Characteristics of patients			
Male*	38	43	38
Surgery and associated hemodynamic responses			
Operation†			
Abdominal	26	24	—
Cardiac	18	2	—
Ear-nose-throat	5	11	—
Gynecological	12	9	—
Neurosurgical	1	2	—
Obstetric	11	0.1	—
Ophthalmic	1	1	—
Orthopedic	11	20	—
Thoracic	3	5	—
Vascular	2	3	—
Other	10	23	—
Tachycardia†	20	1	—
Hypertension†	18	3	—

Tachycardia and hypertension were defined as changes of 30% or more. Differences were tested by a Wilcoxon rank-sum test for ASA classification and chi-square tests for the other characteristics.

Significance is indicated as follows: * $P < 0.05$, † $P < 0.0001$ for difference of awareness case reports from Sebel et al.'s[2] patients who did not experience awareness.

The percentages of the awareness reports for which each characteristic was reported were 98%, 99%, 56%, and 56% for gender, operation, tachycardia and hypertension, respectively.

NSAS = National Survey of Ambulatory Surgery.

patients described in the awareness case reports included a smaller percentage of men than Sebel et al.'s patients who did not experience awareness ($P < 0.05$), but did not differ in gender from the patients in the National Survey of Ambulatory Surgery ($P = 0.80$). Relative to Sebel et al.'s patients who did not experience awareness, the case reports of awareness involved a different frequency distribution of types of surgery ($P < 0.0001$), particularly an over-representation of cardiac and obstetric procedures, and exhibited more episodes of tachycardia ($P < 0.0001$) and hypertension ($P < 0.0001$).

Anesthetic Regimens, Characteristics of Episodes of Awareness and its Management

Table 5 provides information about the anesthetic regimens used. No volatile anesthetic or propofol was administered during maintenance of anesthesia to 23% of patients. A volatile anesthetic or propofol was administered along with nitrous oxide during maintenance of anesthesia to 43%, and without nitrous oxide to 34% of patients with awareness. Most categories of drugs that were used showed less frequent use in the awareness case reports than in Sebel et al.'s control patients; this was the case for benzodiazepines for premedication; thiopental or propofol for induction; isoflurane, sevoflurane, or desflurane for maintenance; propofol for maintenance; and opioids as co-adjuvants ($P < 0.0001$ by χ^2 test for each). The only drugs that did not show such a difference were nitrous oxide and neuromuscular blockers. Patient movement was noted in about one in seven awareness case reports and development of tachycardia and hypertension occurred in about one in five. Episodes of awareness occurred most frequently during maintenance of anesthesia, less during induction and least during emergence. The time after surgery when

Table 5. Anesthetic Regimen Used, Characteristics of Episodes of Awareness and its Management

	Percentage of case reports
Anesthetic regimen	
Premedication	
Benzodiazepine	31
Scopolamine	9
Induction of anesthesia	
Hypnotic	89
Opioid	56
Muscle relaxant	85
Other drugs	8
Maintenance of anesthesia	
Nitrous oxide	62
Volatile anesthetic	62
Propofol	18
Opioid	51
Muscle relaxant	61
Other drugs	15
Characteristics of episodes of awareness	
Time of awareness[a]	
Induction	28
Maintenance	74
Emergence	4
Difficult and Prolonged intubation	4.5
Patient movement during anesthesia	14
Development of tachycardia	20
Development of hypertension	18
Time of report	
Recovery room	35
Day of surgery after discharge from recovery room	14
1–4 d after surgery	28
5–8 d after surgery	5
Other time of report	37

The percentages of the case reports for which each characteristic was reported or could be clearly inferred were 59%, 70%, 70%, 62%, 89%, 56%, 56%, 56%, and 70% for premedication, induction of anesthesia, maintenance of anesthesia, time of awareness, difficult and prolonged intubation, patient movement during anesthesia, development of tachycardia, development of hypertension and time of report, respectively.

[a] Some cases occurred during both induction and maintenance of anesthesia.

awareness was first reported varied. A good number of cases, 37%, were reported after more than a week postoperatively.

Complaints Caused by Awareness and its Sequelae

Table 6 provides frequencies of complaints and postoperative sequelae. Sebel et al.'s[2] control patients voiced these complaints infrequently (10%), while a larger percentage of the awareness case reports patients did (52%; $P < 0.0001$ by χ^2 test). Table 7 shows significant associations of patients' complaints during episodes of awareness with sequelae. Inability to move and feelings of helplessness, anxiety, panic, impending death or catastrophe were each associated with four of the five sequelae that were tabulated. Sensation of weakness or paralysis, noises that were identified, hearing voices and other complaints were each associated with one of the five sequelae. Pain was not associated with any of the sequelae.

Table 6. Complaints Caused by Awareness and Postoperative Sequelae

	Percentage of case reports
Pain during episodes of awareness	
None	62
Light	3
Moderate	3
Severe	17
Present, but intensity not specified	15
Complaints other than pain during episodes of awareness	
Sensation of weakness or paralysis	17
Inability to move	34
Hearing noises	17
Noises that were identified, e.g., noise of instruments	11
Hearing voices	66
Voices that were identified, e.g., male or female, voice of surgeon	20
Specific words or sentences recalled	38
Feelings of helplessness, anxiety, panic, impending death or catastrophe	34
Postoperative sequelae	
Sleep disturbances	19
Nightmares	21
Daytime anxiety	17
Fear about future anesthetics	20
Late psychological symptoms	22

Pain and other complaints during episodes of awareness were reported in all case reports, and postoperative sequelae in 48%.

Risk Factors and Causes of Awareness

A history of awareness was present in 1.6% of cases and a difficult and prolonged laryngoscopy and intubation in 4.5%. The most frequent cause of awareness was overly light anesthesia (Table 8). Increased anesthetic requirement was assigned as the cause when the anesthetic was considered as adequate for the patient and the surgery and when malfunction or misuse of the anesthetic machine could be excluded.

DISCUSSION

The adoption of randomized controlled designs to answer important questions about awareness is prevented by its low incidence, ethical concerns about exposing patients to potential risk factors, e.g., very light anesthesia and inability to randomize clinical situations and practices, e.g., difficult and prolonged laryngoscopy and intubation (which is often unanticipated and has a low rate of occurrence)[10] and complete muscle paralysis during maintenance of anesthesia (which is undesirable, but may be required by surgical conditions). Therefore, a major part of the literature concerning the causative and risk factors, autonomic and motor changes during the episodes, the nature of patients' complaints in the postoperative period and the sequelae, is derived from anecdotal experiences and personal beliefs. We chose to analyze reported

Table 7. Associations of Complaints Caused by Episodes of Awareness with Postoperative Sequelae

	Sleep disturbances	Nightmares	Daytime anxiety	Fear about future anesthetics	Late psychological symptoms
Any pain	—	—	—	—	—
Severe pain	—	—	—	—	—
Sensation of weakness or paralysis	—	0.042	—	—	—
Inability to move	0.0003	0.014	—	0.002	0.008
Hearing noises	—	—	—	—	—
Noises that were identified	—	—	—	0.010	—
Hearing voices	—	—	—	0.011	—
Voices that were identified	—	—	—	—	—
Specific words or sentences recalled	—	—	—	—	—
Feelings of helplessness, anxiety, panic, impending death or catastrophe	0.0003	0.020	—	<0.0001	0.012

All significant associations were in the direction of greater frequency of complaints during episodes of awareness being associated with greater frequency of sequelae.

The values are *P* values based on χ^2 tests.

— = not significant.

Table 8. Potential Risk Factors and Causes of Awareness

	Percentage of case reports
Potential risk factors	
History of awareness	1.6
Absence of volatile anesthetic or propofol during maintenance of anesthesia	23
Cause of awareness	
Overly light anesthesia	87
Increased anesthetic requirement	7
Machine malfunction	5
Misuse of machine	4

The percentages of the case reports for which each characteristic was reported or could be clearly inferred were 89%, 70%, and 42% for history of awareness, absences of volatile anesthetic or propofol during maintenance of anesthesia and causes of awareness, respectively.

cases of awareness in the modern era from the first one in 1950 through August, 2005.

The sources of the awareness reports are of interest. While the major source came as expected from anesthesia journals, *The Lancet*, the prestigious *British Medical Journal*, published as many reports as *Anesthesiology*. Historically, the first report of awareness during anesthesia in the modern era came from the United Kingdom (and was published in a general medical journal[8]), and most of the studies of its incidence came from the United Kingdom and Scandinavia.

The incidence of awareness in general has decreased from 1.2% and 0.8% in the 1960s and 1970s to the current figure of 0.1% to 0.2%[11] (with the exception of the reported incidence of 0.007% by Pollard et al.[3]). However, a different trend in the number of reports is apparent in the present study (Table 2). Winterbottom's report in 1950[8] was followed by a hiatus of 9 yr, during which awareness was ignored as far as publications were concerned. Then, there followed a progressive increase that reached its peak from the 1990s onward. This increase may be partly explained by the trend toward publication of multiple reports in a single article, but equally important is the increased prominence of the subject. There is a heightened interest in the subject by anesthesia providers, as evidenced by studies of the effect of anesthetics and sedative-hypnotics on explicit and implicit memories, introduction of monitors that assess the depth of anesthesia, studies of the psychological and medicolegal consequences of awareness, review articles, book chapters, and a book. The public news media and entertainment industry also became interested in the subject and, through them, the patients.

Females were over-represented relative to males in the reported cases of awareness when compared to the control sample in Sebel et al.'s study. This is consistent with the results of other studies.[11–14] Women recover more rapidly from anesthesia than men, which may suggest that they may be less sensitive to the effects of anesthetics on the brain.[12,15,16] It has been suggested[11,17] that there may be a higher incidence of awareness in obese patients for several reasons, including the often prolonged time for endotracheal intubation, the use of higher concentrations of oxygen in nitrous oxide-oxygen mixtures and the difficulty of giving appropriate doses of drugs without causing postoperative respiratory depression. Our survey does not corroborate this supposed risk. The preponderance of cardiac and obstetric procedures in the awareness reports compared to the nonawareness sample is to be expected, because of the tendency to use light anesthesia in these cases.[11] Our findings regarding the time of reporting of awareness corroborate the current practice of interviewing patients more than once, including the recovery room.[11]

The anesthetic regimens that were reported in awareness cases used less premedicants, induction and maintenance anesthetics and less opioids as compared with the control sample. Patient movement

during the operation was also noted in a relatively high number of awareness cases as was the development of hypertension and tachycardia. These signs, as well as the use of smaller amounts of anesthetic drugs and their adjuvants, are correlates of overly light anesthesia, which was the most common cause of awareness. An alternative explanation for the higher incidence of hypertension and tachycardia in the awareness sample is the attention, over approximately the last decade, to strict control of arterial blood pressure and heart rate during anesthesia, which could be displayed more in the control sample. There were no differences between the frequency of use of nitrous oxide and neuromuscular blockers in the awareness and nonawareness samples. There are no studies that rigorously assessed the risk of avoidance of nitrous oxide on the incidence of awareness. In a meta-analysis of the effect of omitting nitrous oxide in general anesthesia on postoperative emesis,[18] an incidental finding was that omitting nitrous oxide increased the incidence of awareness. However, the representativeness of this finding is debatable, as only 29% of the trials that were analyzed included awareness as an outcome measure, the search strategy did not indicate that awareness was intended as an outcome, and the increased incidence of awareness when nitrous oxide was omitted was derived in large part from a single study[19] in which the results were not significant. It was also clear that the total anesthetic dose, as defined by minimum alveolar anesthetic concentration multiples, was larger in the group given nitrous oxide.

Our finding of the absence of differences in the use of neuromuscular blockers between the experimental and control samples is not surprising. It does not contradict the reasoning that awareness is, to a large degree, an iatrogenic mishap caused by the use of muscle relaxants. The use of neuromuscular blockers has been ubiquitous since their introduction in 1942. Indeed, the first case report of awareness involved the use of curare.[8] As opposed to the paralyzed but inadequately anesthetized patient who may regain consciousness while remaining motionless, a nonparalyzed patient will usually (but not invariably) communicate his or her wakefulness by movement, which alerts the anesthesia provider to deepen the anesthetic and thus lessens the incidence of recall. It is sound preventive advice to avoid muscle paralysis unless it is needed and even then to avoid total paralysis.

Many patients who become aware during surgery report a variety of complaints that are associated with considerable dissatisfaction with their anesthesia care.[20] The most common complaint in this study was auditory perception (voices in 66% and noises in 17% of cases), followed by loss of motor function (inability to move in 34%, and sensation of weakness or paralysis in 17% of cases), pain (38%), and feelings of helplessness, anxiety, panic, impending death or catastrophe (34%). In a recent study by Samuelsson et al.,[21] auditory and tactile perceptions were the most common (70% and 72% respectively), followed by feelings of helplessness, acute fear, and panic (56%, 58%, and 43% respectively). Pain was experienced by 46% of the patients.

Awareness may lead to postoperative sequelae that may persist for varying durations. Sleep problems were common (sleep disturbances in 19% and nightmares in 21% of patients). Fear of future anesthetics was reported in 20% of patients and daytime anxiety in 17%. Late psychological symptoms, which may lead to a severe and debilitating illness (posttraumatic stress disorder), were first described by Meyer and Blacher in 1961.[22]. We noted these symptoms in 22% of our patients. In the Samuelsson et al. study,[21] there was a 33% incidence. In our review, inability to move and feelings such as helplessness, anxiety and panic were significantly related to the persistence of late psychological symptoms. Wang,[23] based on his studies of victims of awareness in his practice, has suggested that frequently the inability to move during surgery raises the patient's misconception that the state is irreversible, causing acute psychological trauma that may persist if it is not explained. Some authors have expressed their belief (without evidence) that pain would be a precipitating cause of prolonged psychological effects.[1,24] Yet, pain and hearing voices or noises were not related to the late psychological symptoms in our review. These results are also corroborated by those of Samuelsson et al.[21] and Guerra.[25] It is interesting that Blacher[26] has claimed earlier that patients who are wide awake, although they may suffer greatly during the procedure, may have fewer traumatic symptoms afterward than those who are in an obtunded state, perhaps because while awake what happens is not in doubt. Perhaps patients who complain initially of inability to move and experience feelings of helplessness, anxiety, panic, impending death or catastrophe should be paid particular attention and be referred early for psychiatric help. Guerra[25] has suggested that the response to awareness may also depend on the patient's personality and psychiatric history. Other factors, e.g., failure of the surgery to cure the patient, or the emergence of serious postoperative complications, may also play a part.[27]

This review suggested two risk factors for awareness during anesthesia. The first is the use of light anesthesia. The second is the presence of a history of awareness. The late Professor Utting[28] warned anesthesiologists in 1975 that "a history of awareness should always be treated seriously and the anesthetic should be given with scrupulous care by a consultant anesthetist if medico-legal trouble is to be avoided." It seems that this advice has not always been followed.

Difficult and prolonged laryngoscopy and intubation were associated with awareness in only 4.5% of the cases. Considering that the overall incidence of difficult intubation varies from 4.5% to 7.5%,[10] it was

not found to play a major role as a risk factor. Administration of supplemental doses of induction hypnotics should prevent the patients from regaining consciousness when this problem arises.

The major cause of awareness was overly light anesthesia at the time of the episode. Anesthetic machine malfunction or misuse and increased anesthetic requirement were much less frequent. The end-tidal anesthetic gas concentrations that prevent awareness are unknown. In a recent study by Avidan et al.,[29] there were sustained periods during surgery when these concentrations were under 0.7 minimum alveolar concentration in 75% of 1937 patients who nevertheless did not experience awareness. In cases where light anesthesia is deemed necessary, the use of even small doses of amnesic drugs, e.g., scopolamine, midazolam, subanesthetic doses of ketamine, or inhaled anesthetics and/or regional anesthesia, should be considered.[1] The use of a cerebral function monitor may reduce the incidence of awareness.[3]

Proper maintenance of anesthesia equipment, checkout protocols before administration of an anesthetic, gas analyzers sampling the inspired and end-tidal concentrations of the inhaled anesthetics, setting of alarms when vaporizers become empty and using total IV anesthesia only when the anesthesia providers have continuous access to the entire anesthetic delivery system can reduce the incidence of machine malfunction or misuse. Variability in response to anesthetics is common in everyday practice. It is possible that chronic use of alcohol, opioids and sedative hypnotics may increase the anesthetic dose needed to produce and maintain unconsciousness.[1] Unfortunately, there was not enough information in our data about the use or abuse of these substances. Increased anesthetic requirement of some patients may be detected by the use of brain function monitoring.

The main strength of the present study is the large number of cases that were reviewed, increasing the confidence in our results and conclusions. However, issues relating to bias pose several challenges. Publication of case reports depends on voluntary efforts by the authors and acceptance by the editors of scientific journals. Another source of bias is the inability to precisely match the reported cases of awareness with control groups coming from the same time period. Although the majority of the cases were published in the period from 1990 to 2005, 22% of the cases came from an earlier period. Therefore, comparisons between data sets may have been influenced by changes over the years in certain characteristics, e.g., obesity of the general population or use of β-blockers in the perioperative period, which could affect the incidences of tachycardia and hypertension. Other differences in characteristics between the reported cases of awareness and the patients of Sebel at al.[2] may have influenced the comparisons, and it was not feasible to control these, e.g., by analysis of covariance. A third source of bias relates to the lack of data in some reports concerning factors such as race, use of recreational drugs and others that may be relevant to the phenomenon of awareness. The high rates of missing data for some of the characteristics that we examined also limit confidence in the conclusions that can be reached concerning these characteristics. We do not know whether the individuals for whom information concerning a characteristic was not reported had the same distribution on that characteristic as the individuals for whom information was reported. Although we omitted any characteristic with more than 60% missing data from consideration, our conclusions may be regarded as tentative, pending independent confirmation.

In conclusion, we reviewed 271 cases of awareness and compared their data with those for patients who did not suffer from awareness. Despite the steady decline in the incidence of awareness since the 1960s and 1970s, an opposite trend in the number of reports was found. A preponderance of females was equivocal, and obesity did not seem to increase the incidence. About one-quarter of the aware patients received no volatile anesthetic or propofol during maintenance of anesthesia and there was less frequent use of premedicants and induction and maintenance drugs, except neuromuscular blockers, in this group. The use of nitrous oxide did not make a difference in the incidence of awareness. There was an over-representation of cardiac and obstetric procedures. Patients' movements, tachycardia and hypertension were relatively common during surgery. Only 35% of patients reported the awareness episode during their stay in the recovery room. The most common complaints of patients were auditory perception and loss of motor power. Awareness may lead to both immediate and late psychological problems. Inability to move and feelings such as helplessness, anxiety and panic were significantly related to the persistence of late psychological symptoms. We suggest light anesthesia and a history of awareness, as risk factors; light anesthesia was the most common cause. We discussed our findings in light of the existing literature and suggest measures to decrease the incidence.

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