Title: Retrospective analysis of reported cases of intraoperative awareness in a large multi-hospital health system

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Abstract

Background: Awareness with recall under general anesthesia remains a rare but important issue that warrants further study. Methods: We present a series of seven cases of awareness that were identified from provider-reported adverse event data from the electronic anesthesia records of 647,000 general anesthetics. Results: The low number of identified cases suggests an under-reporting bias. Nonetheless, some important themes emerge from this small series that can serve as important reminders to anesthesia providers to ensure delivery of an adequate anesthetic for each patient. Commonalities between a majority of our identified anesthetic awareness cases include: obesity, use of total intravenous anesthesia, use of neuromuscular blockade, and either a lack of processed electroencephalogram (EEG) monitoring or documented high depth of consciousness index values. An interesting phenomenon was observed in one case, where adequately-dosed anesthesia was delivered without technical issue, processed EEG monitoring was employed, and the index value suggested an adequate depth of consciousness throughout the case. Conclusions: Provider-reported adverse event data in the immediate post-operative period is likely insensitive for detecting cases of intraoperative awareness. Themes identified in this series of cases of awareness under general anesthesia provide important reminders for anesthesia providers for maintain vigilance in monitoring depth and dose of anesthesia, particularly with total intravenous anesthesia.

Background

Accidental intraoperative awareness with recall (AWR) is the unanticipated explicit recollection of intraoperative events during anesthesia. Though important to understand and prevent, it is fortunately a rare event. In fact, the incidence estimates vary widely, likely due to methodology differences in identification of awareness events. Several randomized controlled trials with AWR as the primary endpoint have used structured interviews to detect awareness events and expert panel review to adjudicate possible cases of AWR [1-6]. Averaging across the data from these trials gives an incidence of 0.25% for definite AWR and an additional 0.32% of patients having possible AWR. This is corroborated by an incidence of 0.44% in a recent meta-analysis that included randomized trials focused on either anesthetic regimens or anesthetic depth monitors (but not necessarily specifically focused on AWR detection) [7].

Retrospectively identifying cases of AWR, when no structured patient interview has been conducted, is expected to have a lower sensitivity. This is illustrated by much lower calculated incidences of AWR within retrospective studies of varying methodology: 0.023% in a single-institution retrospective chart review [8] and 0.0051% in the United Kingdom's 5th National Audit Project [9]. Thus, retrospective anlayses have limited sensitivity, and may detect AWR events at rates 10-100 times lower than propsective trials. Surveying practicioners seems equally insensitive, with rates of 0.0043% [10] and 0.0065% [11] reported.

Despite this low prevalence, AWR is a clinically important phenomenon to understand and prevent. The Psych-SOS study completed post-traumatic stress disorder (PTSD) assessments of patients from three major awareness prevention trials and found a 43% incidence of PTSD in those who experienced AWR, compared to 16% in a matched cohort without AWR [12]. Though the longevity of PTSD has not been studied in a large cohort of AWR patients, symptoms can last for many years after the event [13, 14]. Even without a PTSD diagnosis, many AWR patients experience some negative symptoms such as sleep disturbance, anxiety, fear, panic, depression, and inability to work [15-17].

The purpose of this investigation was to identify cases of AWR at our institution by a retrospective review of routinely collected adverse event data. We expected to find many AWR cases, based on the very large number of anesthetic records available for review. However, the small number of cases identified precluded a formal analysis. Our results are presented as an AWR case series, focused on general anesthetics. Commonalities between these cases are discussed to highlight some important considerations to maintain vigilance in AWR prevention.

Methods

Cases of AWR were collected from the Electronic Anesthesia Record (EAR) system of the University of Pittsburgh Medical Center. This is a large multi-hospital health system, with a mix of tertiary/academic centers and suburban hospitals that share a centralized EAR. The system-wide EAR was queried for all available electronic anesthesia records over the period 9/13/2010 to 1/12/2019. Patients with AWR were identified using quality improvement records attached to our EAR. In this system, providers voluntarily denote an adverse event flag (labelled “Intraoperative Recall”) any time before the EAR chart is finalized, which is typically after patient discharge from Post-Anesthesia Care Unit (PACU). Following identification of those anesthetics that had the adverse event flag for “Intraoperative Recall”, the patient charts were reviewed by the authors for data thought to be relevant to the awareness event. We limited the subsequent analysis to cases done under general anesthesia. Data abstracted included the surgery performed, anesthetics administered, patient characteristics, and the patient’s past medical and surgical histories. Written documentation was searched for descriptions of the character of the experiences reported by the patients during the awareness event. Case durations were calculated using the induction and emergence times documented on the EAR. In the UPMC system, the BIS monitor (Medtronic/Covidien, Mansfield, MA, USA) is the processed electroencephalographic (EEG) monitoring device typically available in most anesthetizing locations.

Results

During the study period, 1,273,060 total anesthetic records were available for query. Only 10 cases were identified in which the “Intraoperative Recall” event flag was marked. Thus, the calculated incidence of AWR from this dataset, using this method of identification was only 0.00079%. Three of these cases were documented as sedation with monitored anesthesia care, and were excluded from further analysis. The number of general anesthesia cases queried was 647,009, giving a calculated incidence of 0.0011% of AWR under general anesthesia in our EAR. We briefly describe the 7 identified cases of AWR during general anesthesia in a condensed case series below. A summary of key characteristics is provided in Table 1.

Case 1 occurred in a 35-year-old male with American Society of Anesthesiologists (ASA) physical status (PS) II. This patient had a mass of 70 kg and body-mass index (BMI) of 21.6 kg/m^2. The surgical case was an elective posterior spinal fusion and internal fixation of levels L5 and S1. The patient was premedicated with 50 mg of fentanyl and 2 mg of midazolam. General anesthesia was induced with 130 mg of propofol, and muscle paralysis initiated with 50 mg of rocuronium. Intermittent boluses of rocuronium were used to maintain paralysis. Maintenance of anesthesia was with sevoflurane, and the lowest concentration during the majority of the 3.5 hour-long case was 1.77%. However, the concentration decreased to 0.9 to 1.1% in the approximately 10 minutes prior to turning the patient supine. This volatile anesthetic was augmented with a remifentanil infusion at 0.1 to 0.2 mcg/kg/min, and this infusion was discontinued approximately 10 minutes prior to turning supine. A total of 200 mcg of fentanyl was given in divided doses after extubation, approximately 20 minutes after discontinuation of the remifentanil infusion. Mean arterial pressures (MAP) was maintained in the range 80 mmHg to 120 mmHg, but this required a phenylephrine infusion at rates up to 0.5 mcg/kg/min plus intermittent boluses of ephedrine. His heart was in sinus rhythm, rates ranging 45 to 80 beats per minute (bpm). Processed EEG monitoring was not used.While in the PACU, the patient recalled waking up while in the prone position. There was no further documentation describing specific recollections of the patient or any interventions during the postoperative period. There is no documentation of psychiatric follow up.

Case 2 occurred in a 72-year-old male, ASA-PS III, with mass of 126 kg BMI of 43.6 kg/m^2, for elective endoscopic sinus surgery. He was premedicated with 50 mcg of fentanyl and 2 mg of midazolam. General anesthesia was induced with 200 mg of propofol and 100 mcg of fentanyl. Muscle paralysis was maintained with boluses of rocuronium. Maintenance of anesthesia was achieved with intermittent boluses of fentanyl and sevoflurane; the lowest end-tidal sevoflurane concentration was 1.45%. Vitals were remarkable for atrial fibrillation, with heart rates between 60 to 95 bpm and no hypotension. Processed EEG monitoring was not used. Case duration was 2.5 hours. While in the PACU, the patient report recalling intraoperative conversations. He was unable to quote what was being said but “definitely heard talking”. He did not endorse recalling pain or distress; though paralyzed, he did not try to speak or move. The patient declined any psychiatric follow up.

Case 3 occurred in a 61-year-old woman, with ASA-PS III, mass of 107 kg, and BMI of 36.7 kg/m^2. She presented after a ground level fall that caused a distal tibia-fibula fracture. She was taken to the operating room for placement of a tibial intramedullary nail. She was premedicated with 2 mg of midazolam. General anesthesia was induced with 180 mg of propofol, and 100 mg of lidocaine was given. Muscle paralysis initiated with 190 mg of succinylcholine and 30 mg of rocuronium. Maintenance of anesthesia was achieved with sevoflurane, and end-tidal concentrations ranged from 0.3 to 1.3% during the case. The BIS monitor was applied, and the highest BIS index value recorded was 54.8. Case duration was two hours. Vital signs during the case were heart rates between 55 to 75 bpm and MAP ranging from 95 mmHg to 115 mmHg, with minimal support by intermittent phenylephrine and ephedrine. After extubation and while still in the operating room, the patient stated that she was awake during the entire procedure but, could not say anything because of the endotracheal tube. She described trying to wiggle her foot to get the surgeon's attention but was unable to move. She recalled feeling instrumentation including “the drill in my leg” and “a hammer on my knee” during the case. She was distressed having felt pain through the entire duration of the case. There is no documentation of psychiatric follow up.

Case 4 occurred in a 33-year-old female, with ASA-PS III, with mass of 124 kg, with BMI of 48.1 kg/m^2. She presented for elective laparoscopic splenectomy, and received no premedication. Anesthesia was induced with 200 mg of propofol, 16 mcg of dexmedetomidine, and 20 mg of ketamine. Muscle paralysis initiated with 160 mg of succinylcholine and 90 mg of rocuronium with intermittent boluses of rocuronium throughout the case to maintain paralysis. The patient had a history of difficult airway management, but was uneventfully intubated with a Glidescope. Total intravenous anesthesia (TIVA) was maintained with three infusions: propofol ranging from 100 to 150 mcg/kg/min, with additional intermittent boluses; dexmedetomidine at 0.4 mcg/kg/hr; and ketamine at 0.2 mg/kg/hr. Processed EEG monitoring was utilized during the case, but not applied until 5 minutes after incision, which was about 30 minutes after induction. The BIS index ranged 65-75 in the first 30 minutes after application. At this time, a relief in hands-on providers occurred, and midazolam 2 mg was given. The highest recorded BIS index was 79.2, and this occurred during the middle portion of the case approximately 45 minutes after induction. The BIS index was > 65 for the majority of the surgical case. Vital signs were unremarkable with no support. Case duration was just over two hours. While in the PACU, the patient stated that she remembered the endotracheal tube in her throat, though that she was extubated shortly afterwards. The patient described no further awareness during the case and that she was not under stress from this memory. There is no documentation of psychiatric follow up.

Case 5 occurred in a 54-year-old female, with ASA-PS III, mass 67 kg, and BMI of 26.1 kg/m^2. She presented for inguinal lymph node dissection. She was premedicated with midazolam 2 mg. Anesthesia was induced with 150 mg of propofol followed by rocuronium 30 mg to facilitate tracheal intubation. TIVA was maintained using a propofol infusion with a basal rate of 100 mcg/kg/min, with intermittent boluses, dexmedetomidine infusion at 0.2 mcg/kg/hour and ketamine infusion at 0.2 mg/kg/hour. The highest documented BIS index was 46.6. Vitals signs were remarkable only for mild bradycardia, with heart rates in the 50's pre-induction. She was normotensive throughout the two hour case, with no support. In the PACU, she reported intraoperative pain and recalled "feeling the stitches" being placed. There is no documentation of psychiatric follow up.

Case 6 occurred in a 61-year-old-female, with ASA-PS II, mass 59 kg, and BMI of 27.5 kg/m^2, who underwent an elective bilateral breast augmentation. Prior anesthesia complications included postoperative nausea and vomiting. She was premedicated with midazolam 2 mg. General anesthesia was induced with 50 mg of propofol and 50 mcg of fentanyl. Paralysis was maintained with intermittent boluses of rocuronium. Maintenance of anesthesia employed remifentanil at 0.2 to 0.6 mcg/kg/min and dexmedetomidine between 0.2 to 0.7 mcg/kg/hr. Approximately 20 minutes after surgical incision (and 40 minutes after induction) a propofol infusion at 50 mcg/kg/min was started, and the dose was subsequently increased to 75 mcg/kg/min for the last hour of the case. Vitals were unremarkable, with minimal intermittent doses of phenylephrine and ephedrine. The highest BIS index of 75.2 occurred near the start of surgery, about 15 minutes after induction. The patient was administered more fentanyl and propofol and that time, and the BIS index subsequently remained between 47 and 61 for the remainder of the two hour case. Other than selection of the "Intraoperative Awareness" flag, there is no further documentation of awareness or psychiatric follow up.

Case 7 occurred in a 29-year-old-female, with ASA-PS III, mass 98 kg, and BMI of 30.8 kg/m^2. She presented for elective abdominal panniculectomy, bilateral brachioplasty, and bilateral mastopexy for redundant soft tissues after excess weight loss. Patient was premedicated with 2 mg of midazolam. General anesthesia was induced with 200 mg of propofol and 100 mg of lidocaine was given. Muscle paralysis was initiated with 10 mg of vecuronium and maintained with intermittent boluses. Maintenance of anesthesia was attempted with a TIVA approach utilizing infusions of propofol at 75 mcg/kg/min, dexmedetomidine at 0.6 mcg/kg/hour and intermittent boluses of midazolam (6 mg additional given). Vitals were notable for MAP ranges between 70 mmHg to 110 mmHg, sinus rhythm with heart rates 75 bpm to 100 bpm. Processed EEG monitoring was utilized during the case and notable BIS index ranging from 68 to 75 in the 25 minutes following incision. Despite additional intravenous (IV) medications including another 2 mg of midazolam, 150 mg of propofol bolus, and increased infusion dose of propofol to 125 mcg/kg/hour, the BIS index remained elevated above 70. An additional 10 mg dose of vecuronium was given and did not result in loss of TOF. It was then recognized that her IV access

had been lost. The patient was started immediately on sevoflurane at 3.5%. A right internal jugular line was placed for definitive access. Additional midazolam was given and prior maintenance TIVA was continued. Notably, the BIS index ranged 30 to 40 for the remainder of the two-hour case. The awareness flag was selected by the anesthesiologist with concern for possible awareness. There is no further documentation of AWR or psychiatric follow up. The patient had another augmentation surgery the following year, and there was no mention of prior awareness documented in her pre-operative evaluation.

Discussion

To our knowledge, this is the largest pool of cases systematically evaluated for adverse event data related to anesthetic AWR. Even using conservative estimates of the incidences of AWR (0.01%), one might anticipate ~100 cases from a dataset of over 1 million anesthetic records. However, our actual results were an order of magnitude lower, consistent with lower estimates using some other non-prospective identification methodologies [9-11]. We strongly suspect that our health system's EAR adverse event data significantly underestimates the true incidence of AWR in our patient population. Thus, our case cohort is a potentially biased sample of early-presenting AWR cases, and we recognize that our identified cases have significant limitations in their predicitive ability for AWR. Nonetheless, we are presenting the series of seven general anesthetic cases identified and have recognized some themes that are worthy of discussion.

Most well-known risk factors for AWR are based on descriptive data or case reports [18, 19]. The occurrence of AWR during cardiac, obstetric, and trauma surgical cases, seems intuitive, as these are situations in which it is likely to deliver lower anesthetic doses. Some patient-related risk factors are also not surprising, as they would predispose to anesthetic-resistance, including obesity and chronic alcohol or sedative use. Notably, most of these case- or patient- related risk factors did not emerge in our cohort, except that 4/7 were obese. In fact, all but one (case 3) were elective patients admitted from home.

Several risk factors for AWR related to medication choices have been variably reported in the literature. Relevant to our case series, the use of neuromuscular blocking drugs can mask patient movement that would likely provide an early clinical sign of light anesthesia. Correlation between pharmacologic paralysis and AWR has been suggested [20, 21], as well as increased distress of AWR patients who were unable to move during the awareness event [19]. It is notable that paralysis was used in all seven of our identified cases, substantiating this correlation. The pre-induction administration of benzodiazepines intuitively should be protective against AWR, by providing amnesia. In some studies, their administration has been anti-correlated to AWR risk [22, 23]. However, similar to larger studies [24], our series demonstrate that AWR can certainly still occur despite benzodiazepine premedication, as these were part of the anesthetic in all but case 4.

The use of TIVA has been correlated to AWR [24]. It is hard to argue that the use of TIVA does not add some risk, for two reasons related to specific favorable properties of volatile anesthetics. First, end-tidal gas monitoring allows breath to breath measurement of the dose of anesthetic delivered. If used in combination with processed EEG monitoring, expired anesthetic concentration provides potentially synergistic information that can be used to ensure an adequate dose and depth of anesthesia. Second, IV failure can cause an occult disruption of anesthetic delivery, and this is much more likely to go unrecognized than a breathing circuit disconnect. Only one case of IV infiltration was identified within the cohort of general anesthetics. However, it is worthy of note that one of the three sedation cases with AWR that were identified by our initial query also had IV infiltration noted as the suspected etiology. This highlights the importance of particular vigilance in assuring IV patency during TIVA cases to avoid AWR.

Improper or no use of depth of consciousness monitoring could play a role in AWR. The utility of processed EEG monitoring in preventing awareness has been shown not superior to end-tidal anesthetic gas concentration alarms, but is better than clinical signs alone [24]. This could seem to suggest that processed EEG monitoring should be applied in TIVA cases, whenever possible. However, notably the ASA's practice advisory only recommends that their use be considered on a case-by-case basis [18]. It does, however, stands to reason that, if a processed EEG monitor is employed, the anesthetic should be modified if index values are consistent with light anesthesia. In our series, cases 1 and 2 did not employ BIS monitoring, likely due to field avoidance concerns, but these cases did employ volatile anesthesia. Cases 4 and 6 (both TIVA) employed BIS monitoring, but index values were elevated during most of the case. Though retrospective and anecdotal, this does raise the question as to whether additional or multimodal anesthetics would have both reduced the BIS index and/or prevented AWR. Case 3 illustrates the situation of reassuring BIS index, but a low anesthetic gas concentration. This suggests that clinicians should consider ensuring both adequate empiric anesthetic dose and reassuring depth of consciousness index values.

The timeline within the case in which AWR seemed to occur in our case series is also worthy of note. Cases 1, 4, and 5 document specific recall of events near the end of their surgical experiences. Case 1 recalled waking up prone. Case 4 recalled waking up with the endotracheal tube in place. Case 5 reported feeling stiches, which presumably was during wound closure (though documentation is not totally clear). These examples serve as a reminder that AWR most often occurs with light anesthesia, and all patients experience a light plane of consciousness during emergence. Providers must balance the desire for a timely wake-up against the risk of a patient becoming aware while still experiencing noxious stimulation. Though not suggested by events in our case series, this can also be an issue in cases with a prolonged time between IV induction and initiation of the maintenance anesthetic, as with difficult airway

management. The administration of additional anesthetic should be considered during this initial period, as appropriate.

Finally, patients with a history of AWR are at 5-fold increased propensity for experiencing AWR again - even when they are enrolled in an AWR-prevention trial [25]. This seems to suggest that a subset of the population might show anesthetic resistance, even in the setting of reassuring depth of consciousness monitoring and clinical signs. This is illustrated by case 5, where the BIS index and vital signs did not give any non-reassuring signs of an inadequate anesthetic. An interesting population-based measure of this phenomenon is illustrated by the spread of data in the first figure of Aranake's previous study on AWR [25]. The top of the figure shows many data points with BIS indices above 60, despite being in a range of age-adjusted MAC that should be clinically-adequate to ensure unconsciousness and amnesia. This unusual discordance in EEG response to anesthetics may be an area for future neuroscience investigation, to provide better, more personalized, anesthetic care for patients.

For future directions, we plan to implement local provider education surrounding anesthetic awareness prevention to reduce the occurrence of these potentially devastating events, including highlighting some of the important themes suggested by these cases. We are also reviewing our event reporting system, in general, with an aim to improve the capture rate of AWR and other rare, but important adverse events. Finally, the lack of specificity in documentation surrounding this series of AWR events suggests the need for a structured form to be used when both collecting data and offering follow-up to patients after an AWR event.

Conclusions

In a systematic, retrospective analysis of electronic anesthesia records, we have demonstrated that provider-reported adverse event data recorded in the immediate post-operative period is insensitive for detecting cases of intraoperative awareness. In the series of cases of awareness under general anesthesia that were identified, there are several important points for anesthesia providers to consider, including maintaining vigilance in monitoring depth and dose of anesthesia, particularly with total intravenous anesthesia.

Abbreviations

ASA – American Society of Anesthesiologists

AWR – awareness with recall

BMI – body-mass index

bpm – beats per minute

EAR – electronic anesthesia record

EEG – electroencephalogram

IV – intravenous

MAP – mean arterial pressure

PACU – post-anesthesia care unit

PS – physical status

PTSD – post-traumatic stress disorder

TIVA - total intravenous anesthesia

Declarations

Ethics approval and consent to participate: This study was approved by the University of Pittsburgh institutional review board (STUDY 18100077) on 11/26/2018. The need for individual patient consent was waived for this minimal-risk retrospective review.

Consent for publication: No consent for publication was needed for this study.

Availability of data and materials: Data sharing is not applicable to this article, as no datasets were generated or analyzed.

Competing Interests: The authors declare that they have no competing interests.

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Author's contributions: ASD acquired, analyzed, and interpreted data and drafted the manuscript. MPS assisted with data acquisition, interpreted the data, and substantially revised the manuscript. JWI interpreted the data and substantially revised the manuscript. KMV conceived of the project, assisted with data acquisition, interpreted the data, and drafted and substantially revised the manuscript. All authors have read and approved the final manuscript.

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Tables

Due to technical limitations, table 1 is only available as a download in the supplemental files section.

Supplementary Files

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- supplement1.pdf