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ORIGINAL ARTICLE

A 10-year Retrospective Analysis on the Incidence of Anesthesia Awareness with Recall in Adult Patients under Total Intravenous Anesthesia

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Background: Intraoperative awareness occurrence ranges between 0.005% and 1.12% of general anesthesia cases and could be a devastating experience for a patient. The incidence of intraoperative awareness in total intravenous anesthesia (TIVA) is higher than in volatile anesthesia without the depth of anesthesia (DOA) monitoring. This retrospective study aimed to evaluate the incidence of intraoperative awareness with recall during TIVA in the isolated health facility. **Methods:** We performed a retrospective analysis of the incidence of intraoperative awareness with recall during TIVA that involved a large number of patients over 10 years (from January 2008 to July 2018). Cases of death, coma, dementia, severe psychological disorder, incomplete data, or patients aged under 20 years were excluded from this study. All data from the operating rooms' database and the anesthesia records were analyzed. Intraoperative awareness was detected by the patients who spontaneously self-reported accidental awareness during postoperative anesthetic visits within 2 days following the surgery. Moreover, we also visited highly suspected intraoperative awareness patients on a postoperative day 1 for clarifying intraoperative awareness with recall. **Results:** Of 13,002 patients under TIVA, 11,433 were included in this study. Two confirmed cases of intraoperative awareness were detected, with an incidence of 0.017% (2 of 11,433). As of the type of surgery, a 67-year-old male received elective general surgery and another 45-year-old male received elective orthopedic surgery. Only one patient was under DOA monitoring, and in both instances, no long-term psychological sequelae were reported. **Conclusions:** This study suggests that the incidence of intraoperative awareness during TIVA is a very rare event if the well-trained anesthesia staff for TIVA is present and when the DOA monitoring is routinely used in high-risk patients. Furthermore, based on the study data, we conclude that the two intraoperative awareness cases could have been prevented.

Key words: Awareness, general anesthesia, total intravenous anesthesia, bispectral index

INTRODUCTION

Intraoperative awareness, also named general anesthesia awareness with recall (GAAWR), is the explicit recall of sensory perceptions that may occur during general anesthesia (GA).[1] The occurrence of GAAWR ranges from 0.005% to 1.12%.[2,3] Despite the low occurrence rate, intraoperative awareness is a severe problem that may cause serious psychological side effects. These may include sleep disturbances, depression, anxiety, and in rare cases, posttraumatic stress disorder.[4,5]

The incidence of intraoperative awareness is significantly higher in TIVA (1.1% to 1.94%) than in inhaled anesthesia (0.0095%).[3,6,7] Yu and Wu[3] reported that in the combined group of intravenous and inhaled anesthesia cases, three patients (0.44%) were confirmed with intraoperative awareness, while in the TIVA group, 11 patients (1.94%) had undergone intraoperative awareness.

The commonly used methods for preventing intraoperative awareness monitoring include depth of anesthesia (DOA) monitoring and brain function monitoring.[3] However, the effectiveness of bispectral index (BIS) monitoring in reducing

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or preventing the incidence of awareness remains to be controversial[7] due to diverse anesthetic conditions such as age, race, gender, acid–base imbalances, drugs administered to the patients which include neuromuscular blocking agents (NMBAs), and additional factors.[3]

Although a meta-analysis study conducted by Gao *et al*.[8] concluded that BIS index monitoring had a remarkable superiority in TIVA, the DOA monitoring is still recommended for TIVA with NMBAs.[9] In Taiwan, anesthesiologists do not routinely use DOA monitoring in TIVA due to the policy of national health insurance. In the present health facility, DOA monitoring is used exclusively in high-risk patients.

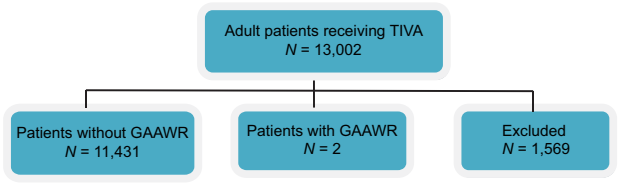
This 10-year retrospective study aimed to evaluate the incidence rates of GAAWR in TIVA and to assess the strategy of BIS monitoring usage for the prevention of intraoperative awareness.

METHODS

This study was approved by the Ethics Committee (TSGHIRB No: 2-108-05-027) of Tri-Service General Hospital (TSGH), Taipei, Taiwan (Chairman, Professor Yu Mu Hsien) on February 28, 2019. All methods were performed in accordance with the relevant guidelines and regulations by the domestic Institutional Review Board. The ethics committee of the Tri-Service General Hospital approved this retrospective study and waived the need for informed consent on February 28, 2019.

Relevant information was retrieved from the medical records and the electronic database of TSGH. A single-center retrospective study that involved adult patients under TIVA was conducted from January 2008 to July 2018 in Taipei, Taiwan. Eleven thousand four hundred and thirty-three patients with the American Society of Anesthesiologists (ASA) score of I–IV who had undergone elective or nonelective surgery under TIVA were included in the study. The exclusion criteria were death within 2 days, coma, dementia, severe psychological disorder, incomplete data, or age <20 years. Following these criteria, a total of 1569 patients were excluded from this study [Figure 1].

No premedication was given before anesthesia induction. Routine monitoring, including noninvasive blood pressure, electrocardiography (lead II), pulse oximetry, and end-tidal carbon dioxide, was established for each patient. Direct radial arterial blood pressure and a central venous catheter were used in patients undergoing major surgery. Before anesthesia induction, all IV infusion lines were examined. Anesthesia was induced with 2% lidocaine (1.5 mg/kg), fentanyl (2 μg/kg) or remifentanil (Minto model) at the effect-site concentration (Ce) of 2–4 ng/ml via a target-controlled infusion (TCI, Fresenius Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany), propofol (Schnider model) Ce 3–5 μg/mL, and rocuronium (0.6 mg/kg).



TIVA: total intravenous anaesthesia; GAAWR: general anesthesia awareness with recall.

Figure 1: Flow diagram detailing the selection of patients included in the retrospective analysis. 1569 patients were excluded due to death, coma, dementia, severe psychological disorder, incomplete data, or age <20 years

Anesthesia was maintained using TCI (Fresenius Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany) with propofol at an Ce of 2–4 μg/mL in FiO_2 of 100% oxygen at a flow rate of 0.3 L/min. Repetitive bolus injections of rocuronium (or cisatracurium) and fentanyl (or continuous infusion of remifentanil with TCI) were given as necessary throughout the operation. No neuromuscular block monitoring was applied during surgery. The BIS-guided protocol was conducted in high-risk surgical patients.[10] The BIS monitor (BIS™, Medtronic, Covidien, USA) was used in low blood pressure, low maintained concentration of propofol Ce, previous history of alcoholism, previous history of awareness, low body weight (body mass index [BMI] ≤18), obese patients (BMI ≥35 in female and ≥42 in male), poor functional activity (<4 metabolic equivalents (MET) s or ejection function <35%), and as per patients' request. Besides, 2.5–5.0 mg of midazolam was administered for prevention intraoperative awareness when higher propofol Ce (>6 μg/mL) was required for a patient to lose consciousness.

Maintenance of the Ce using TCI with propofol was adjusted upward and downward by increments of 0.2–0.5 μg/mL, when necessary, according to the hemodynamics or BIS monitoring. The end-tidal carbon dioxide level was maintained at 35–45 mmHg by adjusting the ventilation rate and maintained maximum airway pressure <30 cm H_2O. Patients were sent to the postanesthesia care unit (PACU) or intensive care unit and were assessed after surgery by the anesthesiologist in charge.[11-16]

The primary outcome assessment tested the incidence of intraoperative awareness, which was detected by the patients who spontaneously self-reported accidental awareness during the postoperative anesthetic visit within 2 days following surgery. Besides, we also visited highly suspected GAAWR patients on a postoperative day 1 for clarifying intraoperative awareness with recall.

Moreover, we evaluated the patients' characteristics (age, sex, height, weight, and ASA), and the type of surgery. The postoperative anesthetic records were completed by the anesthetic nurses, who were unaware of the anesthetic techniques. Medical information of the patients, along with the results of the postoperative evaluation, was analyzed.

Data were presented as the mean and standard deviation of a number of patients. The statistical analysis was performed using SigmaStat 3.5 for Windows.

RESULTS

Of 13,002 patients assessed for eligibility, 11,433 (87.9%) were enrolled in this study. Table 1 summarizes the characteristics of the patients and the type of surgery. Two definite cases of GAAWR were detected, corresponding to an incidence of 0.017% (2/11,433). The BIS monitoring was performed in 11% of the cases (1261/11,433). The average age was 54.74 ± 16.48 years, the height was 163.07 ± 6.95 cm, and the weight was 63.42 ± 10.97 kg. A total of 5291 men and 6142 women were enrolled in the study. Furthermore, the study included 1288 ASA I patients, 8888 ASA II patients, 1250 ASA III patients, and 7 ASA IV patients. The analysis of two patients with GAAWR is summarized in Table 2.

Table 1: Characteristics of the patients and surgery (*n*=11,344)

Total cohort eligible number	*n*=11,344
Age (year)	54.74±16.48
Height (cm)	163.07±6.95
Weight (kg)	63.42±10.97
Sex (male/female)	5291/6142
ASA	
I	1288
II	8888
III	1250
IV	7
BIS index monitoring use, *n* (%)	1261 (11.0)
Surgical modality, *n* (%)	
Elective	10,781 (94.3)
Emergence	652 (5.7)
Type of surgery, *n* (%)	
General surgery	3405 (29.8)
Colorectal surgery	671 (5.9)
ENT surgery	344 (3.0)
Orthopedic surgery	1038 (9.0)
Thoracic surgery	487 (4.3)
Cardiovascular surgery	348 (3.0)
Neurosurgery	1324 (11.6)
Urological surgery	353 (3.1)
Gynecologic surgery	850 (7.4)
Oral and maxillofacial surgery	99 (0.9)
Plastic surgery	728 (6.4)
Ophthalmologic surgery	1786 (15.6)

Data shown as mean±SD or *n* (%). SD=Standard deviation; ASA=American Society of Anesthesiology; BIS=Bispectral index; ENT=Ear, nose, and throat

Case 1

A 67-year-old male was scheduled for laparoscopic cholecystectomy. Preoperative anesthesia evaluation revealed that the patient was at high risk for postoperative complications due to poor heart function with echocardiography showing an ejection fraction of 30% and coronary artery disease with the three-vessel disease after stenting. During surgery, the patient's heart rate raised from 65 to 110 bpm, and blood pressure raised from 105/80 mmHg to 182/110 mmHg. At the same time, the BIS value increased from 45 to 78. All IV infusion lines were carefully examined, and it was found that propofol was refluxed to the standard saline solution bag. The propofol reflux was stopped immediately, resulting in stabilization of the hemodynamics and lowering of the BIS value to 35. On day 1 after the surgery, the patient spontaneously complained that he suffered from incision pain and the recall of the surgery. After a careful explanation, the psychological distress was resolved, and no additional psychological complications were reported [Table 2].

Case 2

A 45-year-old male was scheduled for open reduction internal fixation due to clavicle fracture. Preoperative anesthesia evaluation revealed that the patient was at high risk for awareness due to alcoholism and obesity with a BMI of 38.[17] The propofol Ce was initially set to 4.0 μg/mL; however, the propofol Ce of loss of consciousness was 7.0 μg/mL. BIS monitoring has not been used in this case due to the misjudgment of an inexperienced anesthetist. The maintenance of TIVA was performed with propofol Ce 3.0–3.5 μg/mL and with an intermittent bolus of 50 μg fentanyl, if necessary. The anesthesia and operation proceeded uneventfully, and the hemodynamics were stable. In the PACU, he recalled that the surgeon stretched his arm just before to fall asleep again. An examination of medical records showed that after the induction, the propofol Ce was adjusted to 2.5 μg/mL to prevent head-up position induced hypotension and then increased to 3.5 μg/mL before the skin incision. The GAAWR was noted in this period (during arm manipulation). After a careful explanation, the psychological distress was resolved, and no additional psychological complications were reported. In this case, the misjudgment of inexperienced anesthetist led to a poor decision not to use BIS monitoring during TIVA [Table 2].

DISCUSSION

In the present medical center, the incidence of GAAWR in TIVA was 0.017%, profoundly lower than previously

Table 2: Analysis for two patients with general anesthesia awareness with recall

	Past history	Surgical procedure	BIS inex during surgery	Cause analysis
Case 1 (67 Y/O male; ASA III)	CAD and CHF	Laparoscopic cholecystectomy	45-78	Failure to deliver the intended dose of propofol
Case 2 (45 Y/O male; ASA II)	Alcoholism	ORIF of clavicle	N/A	Against the principle of using BIS monitoring during TIVA

BIS=Bispectral index; Y/O=Years old; ASA=American Society of Anesthesiology; CAD=Coronary artery disease; CHF=Congestive heart failure; ORIF=Open reduction internal fixation; N/A=Not applicable; TIVA=Total intravenous anesthesia

reported rates under or not under TIVA.[2,3,6,7,18-21] Yu and Wu[3] reported that 11 patients (1.94%) in the TIVA group underwent intraoperative awareness. Errand *et al*.[6] also reported a higher incidence of awareness during TIVA (1.1%), compared to balanced volatile anesthesia (0.59%). A survey questionnaire conducted by Morimoto *et al*.[7] in Japan reported 24 intraoperative awareness incidents among 85,156 cases (0.028%). Moreover, 88% (21/24) of the confirmed awareness cases received TIVA. Nevertheless, the actual rate of TIVA in that study was unknown, whereas the study showed that volatile anesthetics were used more frequently than propofol.[5] Wang *et al*.[20] also reported that propofol maintenance was a risk factor for intraoperative awareness in GA. Moreover, a multicenter observational study conducted by Xu *et al*.[21] reported that TIVA might increase the risk of awareness. However, Morimoto *et al*.[7] report has been inconclusive about the TIVA as being a risk factor for awareness. Moreover, no substantial evidence was presented by other studies to support the fact that the incidence of intraoperative awareness was higher with TIVA.[22]

We had conducted TIVA education for anesthesia personnel, including anesthesiologists and anesthetic nurses, every quarter for 7 years. We followed at least seven guidelines for the safe practice of TIVA in the operating room.[9] First, all anesthetists were trained and competent in the delivery of TIVA with TCI. Second, the GA was maintained with propofol and remifentanil infusion by TCI. Third, the established target concentrations were based on the characteristics of the patient, coadministered drugs, and clinical situation. Fourth, only one concentration of propofol (1%) was available in stock, and remifentanil was always diluted to a single, standard concentration (50 μg/mL). Fifth, the infusion pumps were programmed after the syringe, containing the drugs for infusion, which has been placed in the pump. Sixth, the intravenous cannula or central venous catheter, through which the infusion delivered, was visible throughout the anesthesia. Seventh, all anesthetists in the hospital were familiar with the principles, interpretations, and limitations of DOA monitoring. Accordingly, the incidence of GAAWR is expected to be negligible if the TIVA is appropriately managed by skillful anesthesiologists.

According to Bergman's analysis, no apparent reason was determined in 16% of intraoperative awareness cases.[23] Therefore, it might not be preventable in some cases. By contrast, Pandit *et al*.[24] demonstrated that factors increasing the risk of accidental awareness may include female sex, age (younger adults, but not children), obesity, anesthetist seniority (junior trainees), previous history of intraoperative awareness, out-of-hours operating, emergencies, the type of surgery (obstetric, cardiac, and thoracic), and the use of NMBAs. In addition, female sex and the lack of neuromuscular monitoring were identified by Cascella *et al*.[25] as risk factors of intraoperative awareness. The female, rather than the male body, might be more susceptible to the resistance or tolerance to anesthetics.[25,26] Lack of using neuromuscular monitoring is often responsible for awareness during emergence from anesthesia, whereas the recall occurred in the phase of maintenance in their cases.[25]

In the current study, the two cases were males with explicit reasons for AWR. The causal analysis showed that case 1 has occurred due to failure to deliver the correct dose of propofol with hemodynamic changes, while case 2 arose from the misjudgment of an inexperienced anesthetist, which acted against the principle of using BIS monitoring during TIVA.[24,27]

The two most common reasons for accidental awareness during TIVA were the failure to deliver the required dose of drug and poor understanding of the underlying pharmacological principles.[9] In case 1, the patient encountered propofol reflux into the IV infusion line. Propofol might accumulate in the IV infusion line, rather than entering the bloodstream, due to a lack of anti-reflux valve in the fluid administration line, which is not required in Taiwan. Therefore, the drug and fluid lines should be joined as close to the patient as possible to minimize dead space to prevent this situation.[9] In case 2, the inexperienced anesthetist acted mistakenly against the principle of using DOA monitoring during TIVA. However, anesthetists do not routinely use DOA monitoring in TIVA due to the policy of national health insurance in Taiwan.

DOA monitoring is a complex electroencephalograph (EEG) derivative that assigns a numerical value to the probability of consciousness.[28] Previous reports suggest that BIS monitoring is effective in reducing the incidence of awareness.[29,30] Myles *et al*.[29] found that BIS-guided anesthesia resulted in an 82% reduction in the incidence of awareness in a double-blind study of the high-risk patients. Ekman *et al*.[30] investigated the incidence of awareness when the anesthetic administration

was monitored by BIS and found a 77% reduction in the incidence of awareness. Moreover, DOA monitoring is still suggested for TIVA with NMBAs by the Joint Guidelines from the Association of Anesthetists and the Society for Intravenous Anaesthesia.[9] However, Avidan *et al*.[31] reported that intraoperative awareness occurred even when BIS values and end-tidal anesthetic gas concentrations were within the target ranges. Processed EEG indices have been shown to correlate with serum propofol concentrations,[32] but there is no randomized controlled trial assessing whether BIS can decrease the incidence of awareness with TIVA. Besides, awareness despite low-spectral entropy values was reported during TIVA.[33] Accordingly, one of the strategies for preventing GAAWR in the current health facility is using DOA monitoring in high-risk patients during TIVA. However, the advantage of DOA monitoring for preventing awareness has not been fully evaluated.

This study has a few limitations. First, the study is a retrospective analysis in a single medical center. The additional, well-designed, multicentral studies are required to investigate this phenomenon further. Second, previous studies reported that female patients were more likely to experience awareness.[25,26] However, the association between the patient's sex and GAAWR was not determined in the present study, and additional studies will be necessary to establish the association. Third, the data were only collected from the patients who spontaneously self-reported accidental awareness during the postanesthesia visitation. Therefore, the incidence of GAAWR might be underestimated.[2] On the other hand, recently published observational study, in which the structured postoperative interviews were performed, reported the incidence of 1:800.[34] However, many patients might not choose to discuss their experience unless they were asked directly about it.[35] In addition, the patients might not remember their intraoperative experience until days, weeks, or several months following anesthesia. Therefore, in the current study, the anesthetists visited the patients within 2 days to improve the accuracy of detecting GAAWR. Fourth, we did not perform the psychological assessment of the patients. However, the two patients did not show any signs of mental discomfort, or severe and persistent psychiatric sequelae due to a short-duration GAAWR.

CONCLUSIONS

Our study suggests that the incidence of intraoperative awareness during TIVA is very low when DOA monitoring is routinely used in high-risk patients. The additional, longitudinal surveys and large prospective studies are required to validate the findings of this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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