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Review Article

REVIEW ARTICLE

Intraoperative awareness: controversies and non-controversies

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Abstract

Intraoperative awareness, with or without recall, continues to be a topic of clinical significance and neurobiological interest. In this article, we review evidence pertaining to the incidence, sequelae, and prevention of intraoperative awareness. We also assess which aspects of the complication are well understood (i.e. non-controversial) and which require further research for clarification (i.e. controversial).

Key words: anaesthesia, awareness, consciousness, post-traumatic stress disorder

Editor's key points

- Recent large prospective studies have addressed the incidence, detection, and prevention of awareness under general anaesthesia.
- While important controversies remain, a number of concepts regarding intraoperative awareness can be considered non-controversial.
- Controversies remain in both the aetiological and the neurobiological bases of awareness.

The unintended experience and memory of surgical or procedural events can be devastating for patients and remains a dynamic area of investigation. Intraoperative awareness, with or without explicit episodic recall, is relevant to patient safety, standards for intraoperative monitoring, and the search for the neural correlates of consciousness. The objective of this narrative review is to assess the state of the field by addressing key topics related to intraoperative awareness and to consider whether the evidence associated with these topics should be deemed controversial or non-controversial (see Figure 1 for summary).

Non-controversial: the modified Brice interview detects more instances of intraoperative awareness with explicit recall than alternative methods

Multiple prospective studies using the modified Brice interview[1] as the method of assessing intraoperative awareness with explicit recall have consistently found an incidence of approximately 1–2 per 1000[2–4] or higher.[5–10] In contrast, studies using instruments without specific questions pertaining to awareness (such as Pollard and colleagues),[11] quality assurance data (such as Mashour and colleagues)[12] or spontaneous reports [such as the recent National Audit Project (NAP) 5][13 14] have consistently found the incidence to be lower by an order of magnitude (Table 1).[11–14] It was unclear from these conflicting reports whether the differences in incidence resulted from disparities in patient population, anaesthetic technique, clinical severity, or method of detection. In an attempt to resolve the controversy across studies and study populations, Mashour and colleagues[15] compared the incidence of intraoperative awareness with explicit recall in a single population of surgical patients who received both a standard postoperative evaluation (without a structured interview intended to detect awareness) and a single modified

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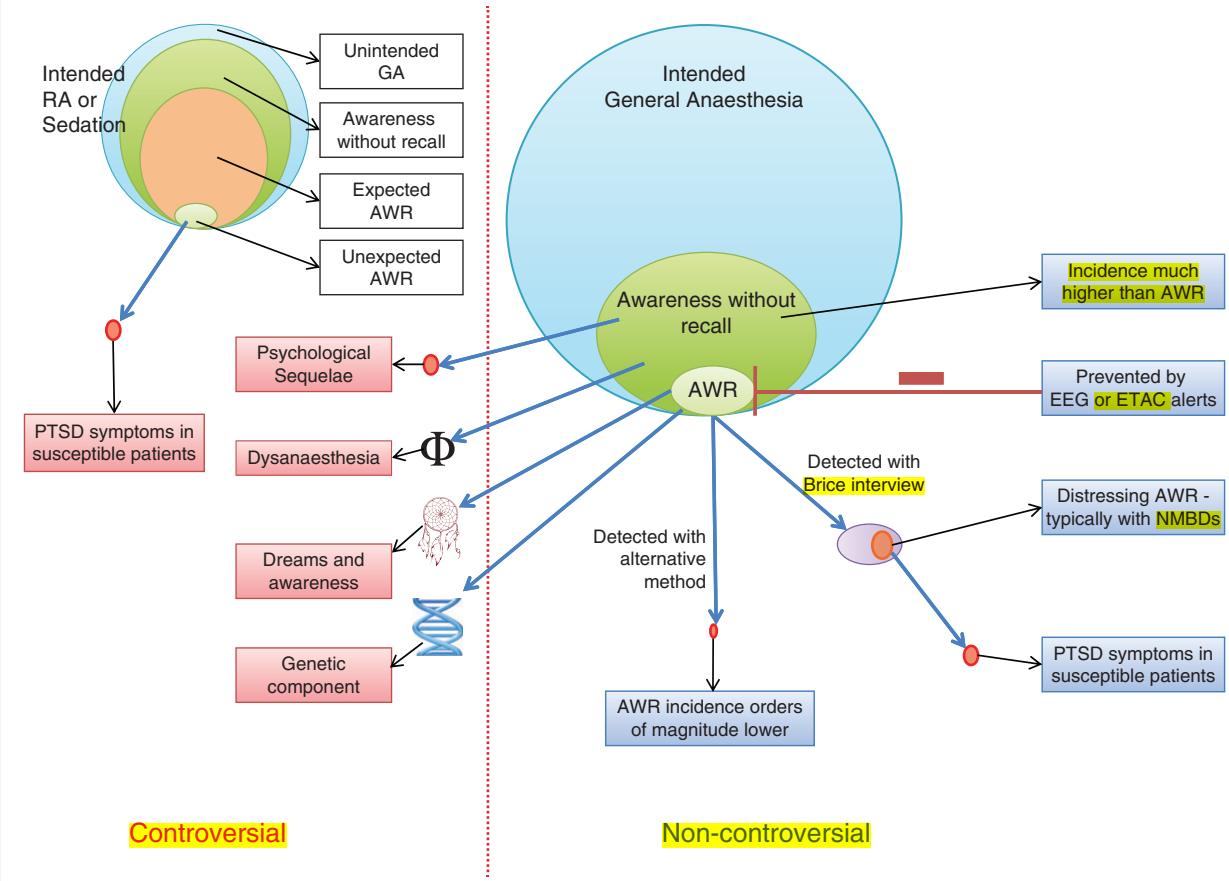

Fig 1 Controversial and non-controversial aspects of intraoperative awareness research and clinical practice. AWR, awareness with recall; EEG, electroencephalogram; ETAC, end-tidal anaesthetic concentration; GA, general anaesthesia; NMBD, neuromuscular blocking drugs; PTSD, post-traumatic stress disorder; RA, regional anaesthesia.

Brice interview at 30 days. The modified Brice interview detected 19 instances of definite intraoperative awareness with explicit recall in approximately 19 000 surgical patients.[15] Of these 19 instances, only three were detected independently based on spontaneous report.[15] Importantly, no instances were spontaneously reported that were not detected by the modified Brice interview. Although the modified Brice interview cannot be regarded as a 'gold-standard' psychometric test for awareness and memory, it has been associated consistently with a higher incidence compared with alternative methods. Thus, recent quality assurance initiatives that determined awareness incidences based on spontaneous reports[13 14] are likely to have underestimated the awareness incidence in the populations of interest, based on documented methodological limitations with this approach.[15 16]

Non-controversial: the incidence of awareness without explicit recall is higher than with recall

Consciousness and memory are dissociable cognitive processes, and the anaesthetic doses required for unconsciousness are higher than the doses required for amnesia. It is therefore not unexpected that a proportion of surgical patients receiving general anaesthesia could at times be both conscious and amnesic. Indeed, use of the isolated forearm technique (IFT) during intended general anaesthesia has revealed a high rate of response to command, the current standard for determining consciousness. For example, in a study of 113 patients by Tunstall and Sheikh,[17] 42% of patients responded to a command 2–5 min after what was presumed to be the induction of general anaesthesia. Importantly, none of the patients who responded had any explicit memory of the event. Remarkably, a study using the IFT found that 97% of patients had a positive response after skin incision; again, none of these patients had explicit recall of the episode.[18] Sanders and colleagues[19] summarize a number of studies using the IFT and demonstrate unequivocally that the incidence of awareness without explicit recall is significantly and consistently higher than the incidence of awareness with recall.

Non-controversial: intraoperative awareness with explicit recall can lead to post-traumatic stress disorder

The first case series of intraoperative awareness with explicit recall described a symptom constellation consistent with post-traumatic stress disorder (PTSD).[20] Since then, longitudinal evaluations of patients originally recruited for prospective observational or interventional awareness studies have revealed a notable incidence of PTSD.[21 22] However, closed claims studies[23] and the assessment of psychological consequences of past awareness events in patients returning to surgery[24] suggest that postawareness PTSD is not a

Table 1 Studies that have investigated the incidence of intraoperative awareness in various contexts. Excluded from this table are cohorts where there was an intervention (e.g. bispectral index-guided protocol or end-tidal anaesthetic-guided protocol) to prevent awareness. ASAPS, American Society of Anesthesiologists Physical Status; ETAC, end-tidal anaesthetic concentration; PACU, postanaesthesia care unit; TIVA, total i.v. anaesthesia

Study and country	Method of awareness detection	Number of patients studied	Number (incidence) of definite awareness	Number (incidence) of definite or possible awareness	Comments
Sandin and colleagues[2] Sweden	Prospective Brice; PACU, 1–3 and 7–14 days postoperative	11 785	18 (0.18%)		0.1% when excluding neuromuscular blocking agents. Anxiety and psychological symptoms only with pharmacological paralysis
Sebel and colleagues[3] USA	Prospective Brice; PACU and >7 days postoperative	19 575	25 (0.13%)	71 (0.36%)	Risk factors: higher ASAPS. 6.04% dreaming
Pollard and colleagues[11] USA	Prospective modified Brice; PACU and 1–2 days postoperative	87 361		6 (0.0068%)	All patients who reported awareness received neuromuscular blocking agents. Used balanced anaesthesia protocols, including halogenated anaesthetic compounds combined with i.v. narcotics. No specific question about intraoperative awareness
Errando and colleagues[5] Spain	Prospective; PACU, 7 and 30 days postoperative	3921	39 (1.0%)		Risk factors: TIVA, emergency, Caesarean section, no benzodiazepine premedication, night surgery. Avoidable factors in most instances. >50% dreaming
Ye and colleagues[8] China	Prospective; 24 and 96 h postoperative	1800	13 (0.72%)		Risk factors: higher ASAPS. 8.1% dreaming
Xu and colleagues[7] China	Prospective; 1st and 4th day postoperative	11 101	46 (0.41%)	93 (0.82%)	Risk factors: TIVA, higher ASAPS, previous anaesthetic. 3.19% dreaming
Mashour and colleagues[12] USA	Retrospective quality control review of spontaneous self-reports	44 006	10 (0.023%)		The incidence of undesired intraoperative awareness was 0.03% among those who did not have general anaesthesia
Wang and colleagues[10] China	Prospective; two postoperative structured interviews	2300	21 (0.91%)	226 (9.82%)	Risk factors: TIVA, higher ASAPS
Mashour and colleagues[4] USA	Prospective Brice; 30 days postoperative	3384	5 (0.15%)		
Shi and Wang[9] China	Prospective postoperative interview	6305	16 (0.25%)		Risk factors: TIVA, no ETAC monitoring, no benzodiazepine premedication. All patients received neuromuscular blocking agents
Pandit and colleagues[13] UK	Survey of anaesthetists	Estimated as 2 358 342		153 (0.0065%)	
Pandit and colleagues[14] UK	Spontaneous patient reports	Estimated as 2 800 000		141 (0.00084%)	The incidence was approximately 0.012% with neuromuscular block and 0.000088% without. Risk factors: female sex, age (younger adults, but not children), obesity, junior trainees, previous awareness, out-of-hours operating, emergencies, type of surgery (obstetric, cardiac, thoracic), and use of neuromuscular blocking agents

significant problem. In one study, even a long-term follow-up of surgical patients who had been formally determined to have intraoperative awareness with explicit recall demonstrated no long-term consequences.[25] However, this might be attributable to the fact that the initial experiences themselves were not particularly traumatic. A recent multicentre study demonstrates that PTSD symptoms are indeed more common after definite or possible awareness with recall,[26] and the NAP5 audit highlights the importance of neuromuscular paralysis in psychologically traumatic experiences.[27] Thus, although certain screening methods or patient populations might be associated with apparently low incidences of PTSD after awareness reports, it is no longer a matter of controversy as to whether or not intraoperative awareness with explicit recall can lead to PTSD or PTSD symptoms.

Non-controversial: processed electroencephalographic monitoring is useful in preventing intraoperative awareness with explicit recall compared with clinical signs but not compared with anaesthetic concentration alarms

The role of processed electroencephalographic devices, such as the bispectral index (BIS) monitor, in the prevention of intraoperative awareness with explicit recall is sometimes regarded as controversial, but should not be. Clear and consistent findings have emerged from the five major randomized controlled trials focused on the BIS.[4 28–31] The B-Aware trial[28] demonstrated that the BIS monitor was effective in reducing definite awareness events compared with routine clinical care in patients at high risk for the complication; this has also been demonstrated for patients receiving total i.v. anaesthesia.[31] In contrast, the BAG-RECALL and B-Unaware trials demonstrated that alarms based on the BIS are not superior to alarms based on end-tidal anaesthetic concentration in preventing awareness with explicit recall in patients at high risk for the complication.[29 30] The Michigan Awareness Control Study has confirmed these findings (i.e. BIS superior to clinical signs but not to anaesthetic concentration alerts) in patients at all risk levels for awareness with explicit recall.[4] An article synthesizing the evidence and an updated Cochrane systematic review reflect the complementary findings of all five studies, allowing a non-controversial recommendation that, when patients receive neuromuscular blocking agents, the BIS is superior to clinical signs alone, especially in patients receiving total i.v. anaesthesia.[32 33] An electroencephalographic device may be particularly useful during total i.v. anaesthesia because of higher interindividual variability of sedative–hypnotic response and the inability routinely to monitor or set alarms for i.v. anaesthetic levels. In contrast, BIS monitoring is not superior at preventing awareness when a potent volatile anaesthetic agent is administered and an alarm is set for a low anaesthetic concentration.[32 33] It is highly likely that the same findings would hold true for other devices in the current generation of processed electroencephalographic monitors.[32]

Non-controversial: the incidence of intraoperative awareness and distressing awareness is higher when neuromuscular blocking agents are administered

It is self-evident that the avoidance of neuromuscular blocking agents does not in itself prevent intraoperative awareness if insufficient concentrations of hypnotic agents are administered. In 1846, Abbott received ether for a tumour removal and was aware, although not in pain, during the procedure.[34] Gray[35] popularized the use of neuromuscular blocking agents as essential components of general anaesthesia in Liverpool in the late 1940s. The underlying principle of the new technique was 'minimal narcotization with adequate curarization.'[35] The motivations were to minimize the cardiovascular depressant effects of high concentrations of ether, cyclopropane, kemithal, or thiopental and to facilitate more rapid emergence of patients from the vulnerable state of general anaesthesia after surgery.[35] Despite the advent of modern general anaesthetic agents over the last four decades, with less cardiovascular depression and rapid elimination, the practice of pharmacological paralysis with limited hypnotic administration continued to be popular and still has proponents in modern practice. In the seminal observational study by Sandin and colleagues,[2] the incidence of unintended awareness among patients who received general anaesthesia without neuromuscular blocking agents was 0.1%, compared with 0.18% when patients were pharmacologically paralysed. A mundane explanation for the reduction in awareness in non-pharmacologically paralysed patients is that patient movement can potentially alert anaesthetists to the possibility of inadequate general anaesthesia. However, it is also possible that the need for or use of neuromuscular blocking agents covaries with other important risk factors for intraoperative awareness. Interestingly, only patients who had been pharmacologically paralysed reported anxiety and psychological symptoms in relationship to their awareness experience.[2] In a comprehensive literature review, Ghoneim and colleagues[36] endorsed the finding that pharmacological paralysis was an important risk factor for distressing awareness experiences. This important insight has again been corroborated in the recently published NAP5 study,[27] where the overwhelming majority of awareness reports were from patients who had received neuromuscular blocking drugs and also where the anaesthetic concentration was reduced towards the end of surgery before antagonizing neuromuscular blockade. The avoidance or minimization of pharmacological paralysis might be the most effective currently available method to prevent traumatic intraoperative awareness.

Controversial: intraoperative awareness with explicit recall has a genetic component

It has been argued that awareness with recall is caused by insufficient anaesthetic dosing.[36 37] Although this assertion is true in what might be considered a tautological sense—that is, insufficient anaesthesia is caused by insufficient anaesthesia—the argument is meant to suggest that awareness with explicit recall is preventable by attention to anaesthetic dosing rather than the search for occult factors that enable consciousness and memory despite what reasonable clinicians might consider adequate anaesthesia. It is well known based on experimental data that genetic background can influence sensitivity to the sedative–hypnotic and, independently, the amnesic effects of general anaesthetics.[38–41] Furthermore, patients with a history of intraoperative awareness with explicit recall had an incidence of awareness of almost 1 in 50 with subsequent surgery and an estimated five-fold adjusted increase in risk for awareness compared with matched patients who also had at least one risk factor for awareness.[42] It is also striking that several studies in Chinese populations have found surprisingly high incidences of awareness.[6 10 31] It is therefore unclear whether, in some instances, genetically mediated resistance to anaesthetic-induced

unconsciousness or amnesia contributes to awareness with recall. Furthermore, even assuming a genetic contribution to anaesthetic resistance, it is unclear whether reduced potency or reduced efficacy is the primary cause, which has implications for how best to alter anaesthetic care in patients at risk. A pharmacogenomics approach might help to resolve this controversy, although the rarity of the disorder and the probable lack of parsimonious genetic culprits (e.g. single nucleotide polymorphisms) could render genetic explorations unhelpful.

Controversial: undesired awareness with explicit recall of procedures performed under sedation is a clinical problem

Self-reports of undesired intraoperative awareness with explicit recall occur with the same frequency in patients receiving general anaesthesia as in those receiving sedation, regional, or neuraxial anaesthesia.[12] This is likely to be the result of mismatched expectations regarding levels of consciousness in patients who are not receiving general anaesthesia during surgery or other invasive procedures.[43] Recent studies have suggested that undesired awareness and explicit recall in patients receiving sedation, regional anaesthesia, or neuraxial anaesthesia can be associated with long-term psychological consequences.[27 44] A study based on the American Society of Anesthesiologists Anesthesia Awareness Registry found comparable rates of long-term psychological sequelae in those reporting awareness during general anaesthesia and those reporting awareness during alternative anaesthetic techniques.[44] Recent data from the NAP5 study[27] support the possibility that undesired awareness and explicit recall during non-general anaesthetic procedures can be associated with long-term psychological consequences. Although these data would suggest that undesired awareness in this population is a true clinical problem, the use of sedation for minor procedures, such as endoscopy, is extremely common. If psychological sequelae occurred in a significant proportion of these instances, the absolute number of patient reports would probably be a salient signal that would already have captured the attention of medical professionals. Instead, this phenomenon has only recently been observed coincidentally through systematic study of intraoperative awareness with explicit recall after an intended general anaesthetic. Although the data remain incomplete and controversial, it is important for anaesthesia providers to set appropriate expectations and ensure that patients understand the planned level of consciousness and the potential for remembering events during the surgery or procedure. In some instances, this might mitigate the dissatisfaction with or consequences of undesired awareness and recall.

Controversial: intraoperative awareness without recall has psychological consequences

It is well known that the incidence of awareness without recall is significantly higher than with recall. This situation generates an important question: is it ethically acceptable if a patient is transiently conscious but has no explicit memory of the event? Furthermore, would the complete elimination of consciousness during surgery require anaesthetic regimens that result in other and potentially more dangerous adverse effects?[45] It is a philosophical question as to whether consciousness without memory is ethically tenable during surgery, but the clinically relevant question relates to the potential for postoperative psychological consequences. Although we have focused on explicit recall in relationship to conscious experience, there is also the possibility of implicit (or unconscious) recall. It has been argued that implicit recall of a surgical event—especially involving pain—might result in PTSD even in the absence of explicit recall.[46] We support the opinion that—independently of recall—appropriate analgesia during surgery is of paramount importance given the known potential for intraoperative awareness. However, it is less clear whether there is compelling epidemiological evidence for a negative effect of implicit memory on postoperative psychological function. Given the high incidence of awareness without recall (as demonstrated by IFT studies)[19]—especially at the time of strong nociceptive stimuli, such as laryngoscopy or surgical incision—even a small proportion of patients experiencing psychological sequelae as a result of implicit memory would translate to a high absolute number of distressed patients. However, the number of postoperative patients suffering PTSD without recall of surgical events appears to be low. When PTSD is precipitated by perioperative events, the most likely contributing factors include pain, prolonged intubation, unpleasant experiences in the intensive care unit, physical debility, traumatic explicit memories, and distressing diagnoses. There is currently little evidence to suggest that implicit memories are important contributors. However, the dichotomous determination of PTSD or not might be less relevant in awareness without recall; subsyndromal PTSD must also be explored in addition to psychological morbidity (such as mood or anxiety disorders) that cannot necessarily be linked to an index event or experience. As a result of the ethical implications of this controversy, further data are required.

Controversial: positive responses to an isolated forearm test reflect a distinct state of consciousness

A positive and unequivocal response to the command 'squeeze my hand' at the end of a surgical procedure is traditionally taken to constitute sufficient evidence that consciousness has returned. Likewise, one could argue that a positive and unequivocal response to the command 'squeeze my hand' during a surgical procedure—for example, a positive IFT response—constitutes sufficient evidence that consciousness has returned. Until there is compelling evidence to the contrary, this should be the default assumption. Sanders and colleagues[19] have clarified the possibilities of perioperative behaviour and experience with a model of responsiveness, connected consciousness, and disconnected consciousness (e.g. a dream state). A recent theoretical perspective suggests an alternative possibility for IFT responses, although no data have yet been provided. Pandit[47 48] argues that the positive IFT response does not signify the full return or persistence of consciousness but rather a 'third state' (referred to as dysanaesthesia) in which patients can follow a simple command in the absence of a conscious self (see also Wang and colleagues, this issue). It is unclear, of course, whether such a state is possible and, if so, what the candidate neural correlates would be. This assertion is provocative but should be tested empirically and/or potentially situated in broader frameworks of consciousness.[49]

Controversial: true reports of intraoperative awareness can be distinguished reliably from false reports of intraoperative awareness and from dreaming

Detection of intraoperative awareness is unreliable because it depends on patient reports rather than objective measures.

Prospective methods using structured questionnaires detect substantially more awareness events than approaches based on spontaneous patient reports. However, a concern regarding the questions in the Brice questionnaire is that they have not been psychometrically validated and might have the potential to elicit false reports or memories.[1 15] This latter possibility is consistent with the finding that a significant proportion of patients only report awareness at later time points after multiple structured interviews.[2 3] Regardless of the detection method, distinguishing true from false awareness reports is difficult. Occasionally, a patient report is so detailed and specific in describing intraoperative experiences, events, or discussions that independent arbiters can concur that awareness definitely occurred.[4 28–30] Commonly, however, patient reports are vague and experts express divergent opinions regarding whether or not a patient was truly aware.[4 28–30] If many of the possible awareness reports do represent true awareness, this would mean that the incidence of intraoperative awareness has been even higher than studies have suggested. In contrast to possible awareness experiences, it is important to clarify that most reports of intraoperative dreaming, which were previously viewed as possible or near awareness experiences, are likely to be unrelated to intraoperative awareness and do not necessarily indicate that patients were insufficiently anaesthetized during surgery.[50–52] Based on clinical and electroencephalographic evidence, it is possible that dreaming occurs during emergence from general anaesthesia, when patients are sedated or in a physiological sleep state.[50 51] However, Samuelsson and colleagues[53] found that, while the content of dreams was unrelated to awareness, the incidence of intraoperative awareness was 19 times more common among patients who reported a dream after surgery. Therefore, the precise relationship between awareness and dreaming remains unresolved.

Conclusion

Substantial progress has been made in understanding the incidence, consequences, and prevention of intraoperative awareness with explicit recall. We are not arguing that further research is unnecessary in these aspects of the field, but rather that new studies with disparate results do not necessarily create 'controversy' unless the methodology is clearly superior and results are particularly novel compared with the existing literature. The truly controversial aspects in this field relate less to the epidemiology and prevention of awareness and more to the underlying aetiology (e.g. genetic contribution) and whether there exist unique states of the brain in association with certain levels of anaesthesia. These questions may or may not have clear clinical relevance, but certainly represent some of the most interesting neuroscientific and philosophical dimensions of intraoperative awareness.

Authors' contributions

G.A.M. conceived the project. G.A.M. and M.S.A. wrote the manuscript.

Declaration of interest

M.S.A. is a member of the Associate Editorial Board of the *BJA*.

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