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Awareness and Dreaming during Anaesthesia

Incidence and Importance

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Cover picture: Oil painting made by an unidentified artist. The painting is a gift from my retired colleague Jan Albert, who told me that it likely illustrates memories from some kind of painful experience.

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"Utan tvivel är man inte klok"
- Tage Danielsson

"Vad är dröm och vad är verklighet,
Finns det nån som egentligen vet"
- Dag Vag

CONTENTS

ABSTRACT **1**

LIST OF PAPERS **2**

ABBREVIATIONS **3**

INTRODUCTION **4**

General Anaesthesia **4**
Memory function **5**
Awareness **7**
Definition 7
Incidence 7
Prevention 11
Consequences 13
Dreaming during anaesthesia **17**
Definition 17
Incidence 17
Content and form 21
Consequences 21

AIMS **22**

MATERIAL AND METHODS **23**

Patients **23**
Paper I 23
Paper II 23
Paper III 24
Paper IV 24
Interviews and classification **25**
Paper I 25

Paper II 25
Paper III 26
Paper IV 26
Statistics 28
Paper I 28
Paper II 28
Paper III 28
Paper IV 28

RESULTS 30
Paper I 30
Paper II 33
Paper III 34
Paper IV 35

DISCUSSION 37
Incidence, details, and prevention of awareness 37
Consequences of awareness 40
Dreaming during anaesthesia 43

CONCLUSIONS 45

SUMMARY IN SWEDISH (SVENSK SAMMANFATTNING) 46

ACKNOWLEDGEMENTS 47

REFERENCES 48

ABSTRACT

The definition of awareness used consistently in this thesis is: Explicit recall of intraoperative events during general anaesthesia. Since there is no objective method to detect awareness, the patients must be interviewed after anaesthesia. The form and timing of the interview is crucial. To rely on spontaneous disclosure of awareness episodes is not sufficient. The total number of awareness-victims is considerable although the incidence may seem modest. A number of these patients look upon the awareness experience as the worst experience in their life. Suffering can include pain, mental distress and delayed psychological symptoms. However, the experience of awareness is not uniform and not all patients suffer.

A comprehensible definition for dreaming during anaesthesia is: Any recalled experience, excluding awareness, which occurred between induction of anaesthesia and the first moment of consciousness upon emergence. Some findings point in the direction that dreaming during anaesthesia may be related to light or insufficient anaesthesia, but other findings do not. Some patients find dreaming during anaesthesia distressing, but generally the overall impression is that consequences of dreaming during anaesthesia seem to be small and of minor importance to the majority of patients.

In this thesis I have found the following:

The incidence of awareness is approximately 0.2% when neuromuscular blocking drugs are used and awareness also exists without these drugs, albeit to a lesser extent. These findings represent standard practice in an adult population at normal risk. 50% of awareness cases may have delayed recall of awareness.

Using a consecutive inclusion design we found initial awareness suffering comparable to previous studies, but a lower incidence and less pronounced severity of late psychological symptoms. The incidences found among the awareness-victims in our study were; experience of pain 46%, immediate mental distress 65%, any late psychological symptom 33%, and PTSD below 10%.

A memory of an intraoperative dream after general anaesthesia is not an early interpretation of delayed awareness, indicating that no routine follow up of dreaming-only patients is indicated.

Dreams reported after anesthesia are generally not related to insufficient anesthesia defined as high BIS, and should not be regarded as near awareness.

LIST OF PAPERS

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals.

I. Sandin RH, Enlund G, Samuelsson P & Lennmarken C. Awareness during anaesthesia: a prospective case study. Lancet 2000; 355: 707–711.
II. Samuelsson P, Brudin L & Sandin RH. Late psychological symptoms after awareness among consecutively included surgical patients. Anesthesiology 2007; 106: 26-32.
III. Samuelsson P, Brudin L & Sandin RH. Intraoperative dreams reported after general anaesthesia are not early interpretations of delayed awareness. Acta Anaesthesiologica Scandinavica 2008; 52: 805–809.
IV. Samuelsson P, Brudin L & Sandin RH. BIS does not predict dreams reported after anaesthesia. Acta Anaesthesiologica Scandinavica 2008; 52: 810–814.

ABBREVIATIONS

BIS	Bispectral index scale
BMI	Body mass index
EEG	Electroencephalogram
ETAGC	End-tidal anaesthetic gas concentration
MAC	Minimum alveolar concentration
NMB	Neuromuscular blocking drugs
NMDA	N-methyl D-aspartate
NP-dreams	Neutral/pleasant dreams
N_2O	Nitrous oxide
OR	Odds ratio
PACU	Post anaesthesia care unit
PTSD	Posttraumatic stress disorder
REM	Rapid eye movement
SD	Standard deviation
U-dreams	Unpleasant dreams

INTRODUCTION

General Anaesthesia

It is difficult to exactly define both the notion general anaesthesia and the prerequisite for this state – unconsciousness. Nevertheless, from a clinical point of view, anaesthetists are in reasonable agreement what these concepts stand for. The common goal is to put the patient into a reversible state unresponsive to the trauma of surgery or other distress. This is done with drugs that make the patients unconscious in a way that they neither perceive nor recall noxious or other stimulation during the procedure. The following four components are often included in the term general anaesthesia; hypnosis, analgesia, autonomic reflex stability and muscle relaxation. Depending on the needs for the particular procedure, more or less of the four components must be considered, but hypnosis is central. To minimise drug side effects, it is common to target the different components with combinations of different drugs that have diverse major actions:

- Hypnotics: Inhalational agents (e.g. isoflurane, desflurane, sevoflurane, nitrous oxide) and Intravenous agents (e.g. thiopental, propofol, ketamine, benzodiazepines).
- Analgesics: e.g. opioids, anti-inflammatory drugs, local anaesthetics, ketamine, nitrous oxide.
- Muscle relaxants: e.g. rocuronium, atracurium, suxamethonium.

The combinations of these and other drugs form a complex pharmacologic action that counteracts the stimulation of the procedure. It is the balance between these two forces that decides a third ill defined, but commonly used concept, namely “the anaesthetic depth”.

Memory function

Before going into details of awareness, some background concerning memory function will be provided. The very complicated concept of memory can be simplified as follows. Memories can be short-term (working memory) or long-term. Long-term memories can be unconscious (implicit) or conscious (explicit).

Short term memories are transient and only last for a few seconds if they are not anchored to the mind using constant rehearsal (1). New information keeps coming in, and since the short term memory capacity is limited, this results in loss of other information. To be able to remember more than a few seconds, without rehearsal, the information must be transferred into long term memory.

Long term memory can last for a lifetime and the capacity is very large. It is distributed in a network in the brain, without exact location (2). However, certain regions are known to be important for memory. The hippocampus is a central region for long term explicit memory formation (3), and fearful memories involve processes mediated by the amygdala (4). Long term personal explicit memories can be recalled, and are also called episodic memories. Not all memories are remembered for life, and we constantly forget, change and retrieve memories (5, 6).

Many anaesthetic drugs impair memory, that is, they have amnesic properties. Amnesia due to sedation seems to be caused by impaired information encoding and this applies to several agents. However, some intravenous anaesthetics produce a remarkable amnesic effect also at only minimal sedation level. This phenomenon is often called drug-induced amnesia, and is predominantly caused by increasing the forgetting (7). This means that information transferred and encoded into long term memory under the influence of anaesthetics like propofol and benzodiazepines, may soon be forgotten. On the other hand, when these drugs are administered after the stimulus, an amnesic effect has never been demonstrated. That is, drug induced retrograde amnesia can not be expected.

Unconscious, or implicit, memory is more obscure. These are memories that we are unaware of. They are encoded by the brain without our conscious attention. Implicit memories may change our behaviour or performance without any conscious recollection of the previous exposure, meaning that

they can influence and facilitate certain responses when re-exposure takes place (8). This is called priming, and is used to describe implicit memory in the same way that learning is used for explicit memory. Priming can take place during anaesthesia, probably also at clinically adequate drug concentrations, but is more likely with lighter anaesthesia and during surgical stimulation (4, 9, 10). Implicit memory may be impossible to completely avoid during anaesthesia, has not been shown to cause any significant harm to patients, and will not be further discussed in this thesis.

Awareness

The first two papers in this thesis deal with awareness (I, II). The first paper was published eight years before this thesis and has become frequently cited in other studies since then. The second paper has also been commented and used in review articles. Therefore, these two papers, referred to by the Roman numbers I and II, appear already in this introduction, but more details will be found in the appropriate paragraphs of this thesis.

Definition

It would be convenient to be able to use the word awareness with one single definition. This has unfortunately not always been the case, and many different definitions and terms have been used the last decades. One explanation to this confusion is the observation that patients may clearly respond to verbal and visual stimuli under the influence of anaesthetic drugs, without recall afterwards (11-13).

The definition of awareness used consistently in this thesis has now also gained a broad acceptance in the literature; Explicit recall of intraoperative events during general anaesthesia.

Incidence

The incidence of awareness was not known before 1960. That means that the first 100 years of anaesthesia were performed without this knowledge. There is reason to believe that this complication was well known and fairly common. Other problems with severe morbidity and mortality during general anaesthesia overshadowed complications such as awareness, and it was not until after these problems were at least partly solved that the interest for awareness became an issue. The first study from 1960 showed an awareness incidence of 1.2% (14). Since then there has been a tremendous development in

the field of anaesthesia. New technical achievements as well as new drugs have been introduced. This has probably affected the incidence of awareness, including drug-induced impaired memory function. The way to design studies on awareness has also changed including the number of patients, questioning and timing. In ten studies from 1975 to 2004, from different countries with mixed patient materials, the incidence has decreased with time and is currently around 0.2% (15-23, I). This incidence represents standard practice in an adult population at normal risk.

Detection

Since there is no objective method to detect awareness, identification relies on patient recollection. Thus, the patients must be interviewed after anaesthesia. This can be done in different ways and at different times. The questions asked must not suggest answers. A set of such questions was introduced in 1970 (24) and modified in 1991 (15). This "modified Brice interview", using five questions are:

1. What was the last thing you remember before you went to sleep?
2. What was the first thing you remember after your operation?
3. Can you remember anything in between?
4. Did you dream during your operation?
5. What was the worst thing about your operation?

These questions have been used in many studies, and have become standard practice in detecting awareness. In a paper presenting a very large patient material and an extremely low awareness-incidence, a doubtful modification of the standard interview was used (25). This may significantly have affected the possibility to identify cases of awareness.

To rely on spontaneous disclosure of awareness episodes is not sufficient. Patients may have several causes not to tell their health care providers about awareness spontaneously (26):

- Fear of appearing ungrateful.
- Fear of retaliation.
- Fear of being described as insane.
- Wishing to forget the experience.
- Forgetfulness.
- Insignificance.

This means that even patients with severe trauma due to awareness can be missed if you do not ask (27). Questioning may also trigger recall (28).

The timing of the interview is crucial. Early interviews in the recovery room may underestimate the incidence of awareness because the patients are still under the influence of anaesthetic drugs which makes it difficult to concentrate or remember. Patients may also be occupied with more obvious and common problems, like pain and nausea. A third explanation could be that the trauma of awareness can lead to dissociation of memories with difficulties to develop a narrative of the events, a phenomenon which may decline over time (28). Several studies have shown that patients may have delayed recall of awareness. In two very large investigations up to 50% of the patients showed this phenomenon (16, I).

Reliability of reports

Patients' reports of awareness, either obtained by interview or spontaneous, must be scrutinised. In some cases the awareness is obvious, but more often it is not that clear. The situation is often very complex for the patient, and it is easy to mistake other experiences as awareness. These can be fantasies, dreams, inputs during the recovery phase or during operations performed under regional anaesthesia and sedation. It is recommended to avoid leading questions and to use a research team, trained in the field of awareness (26). Having followed this advice, it was found that the number of reports judged not to represent awareness was twice the number of confirmed cases in one recent study (29), and a similar finding was found by us (II). Because of inevitable need for subjective judgement, awareness incidences are often classified as "definite" or "probable"/"possible".

Some decades ago it was probably common that awareness-cases were ignored, but that is hopefully not the case any more.

Risk Factors

In addition to variations in awareness incidence due to the method of collecting cases, incidence also varies in different situations. This can be due to factors linked to the patient, surgery, drugs, and equipment:

- Cardiac surgery

Due to the nature of cardiac surgery associated with the anaesthetic technique traditionally used, heightened risk of awareness was previously generally found, with incidence figures ranging from 1.1-23% (30-32). With increasing

vigilance of the problem and change in technique, more recent studies show incidences closer to normal risk, 0.3-0.5% (29, 33-35).

- Obstetric surgery

The same discussion as above also applies to Caesarean section. With knowledge and changes in anaesthesia technique, earlier high incidences have been reduced and a decrease to 0.4% was shown in 1991 (36). Two recently published studies conclude that a somewhat elevated risk for awareness compared to standard population remains (23, 37). In favour of reducing the problem even more is the fact that the vast majority of Caesarean sections nowadays are performed using regional anaesthesia. On the other hand there will always be an increased risk for difficult intubation in these patients, a well known risk factor for awareness (I).

- Trauma surgery

Awareness and trauma surgery have been linked, and high incidences have been reported (31), with up to 43% when deliveries of anaesthetic agents were deficient. The reason for awareness is low doses of anaesthetics, based on the need for controlling hypotension during hypovolaemia, and the risk of awareness probably applies to any extensive surgery with significant uncontrolled blood loss (8). Improvement has been made also in this segment of anaesthesia and no case of awareness was found among 96 trauma cases in a study published 1999 (38).

- Female gender

Females have been overrepresented as awareness victims in many studies during the past decades (14, 17-20). The reason for this finding is not clear. Proposed explanations include that women recover faster from anaesthesia (39-41), and that they may be more inclined to report awareness (40, 42). In three incidence-studies from the current decade, this gender-difference seems to level out (16, 22, I).

- Children

Awareness in children is not as intensely investigated as in adults, only a few studies have been published, and the adult definition of awareness also excludes children under the age of three (43). It seems that children may have a higher incidence of awareness. In a study including children aged 5-12 years, 0.8% awareness was reported despite that a majority in this study did not receive neuromuscular blocking agents (44). One explanation could be that

MAC and MAC-awake are higher in children (45, 46), with possible under-dosage of inhalational anaesthetics.

- Deficient equipment and knowledge

Equipment defects or misuse can lead to unwanted light anaesthesia and accompanying awareness, described in many cases and studies. This applies to both inhaled and intravenous maintenance of anaesthesia. Regular service and daily checks of the equipment, as well as education on both the "hardware" of machines and the "software" of awareness-knowledge are justified to overcome these problems and prevent awareness.

- Neuromuscular blocking drugs (NMB)

In addition to autonomic responses (tachycardia, hypertension, sweating, lacrimation) during anaesthesia, the oldest "monitor" of possible awareness is the ability for the patient to move during anaesthesia. Autonomic responses can not predict awareness (8), and movement without awareness and awareness without movement is a reality in patients anaesthetised without NMB (11-13, I, II). Nevertheless, it is recommended to use NMB only when necessary, since the sign of movement is considered to be both simple and useful (47). There is no randomised controlled study designed to compare awareness-incidence with and without NMB, but one large cohort study found 0.2% with and 0.1% without NMB, albeit the latter incidence is based on only 4 cases (I). As mentioned before, children may have a higher incidence than adults even in the absence of NMB (44).

Prevention

Generally, awareness is prevented if enough anaesthetics are delivered in every specific situation to every specific patient. This statement implies that attention has to include all these three variables.

Knowledge and vigilance

This presupposes both knowledge of anaesthesia care giving as well as the equipment used. Many studies report that a large proportion of awareness-

cases can be prevented, and 19 of 22 cases fell into this group in a recently published study (23).

Procedures and patients

Some factors associated with procedures and patients can be identified in advance, facilitating prevention:

- Patients with a history of awareness (22, 23, I, II), patients using a lot of alcohol, sedatives or analgesics (47), and children (44).
- Difficult intubation (48, I).
- Specific surgery (cardiac surgery, caesarean section, trauma surgery). Other high risk procedures have been proposed in the literature, albeit lacking evidence.

Drugs used and parameters monitored are in some cases of special interest concerning awareness prevention:

Drug induced amnesia

Benzodiazepines are anaesthetic drugs with well known amnesic properties (49). Recently a reduction in awareness-incidence was for the first time found using benzodiazepines as premedication compared to opioids (23). However, to rely on benzodiazepines for awareness prevention may be inappropriate for two reasons. First, the method is unpredictable and awareness is not trustworthy prevented using these drugs (29, I). Second, there might be ethical considerations if amnesia is used deliberately as a substitute for appropriate anaesthesia, although this has been recommended in cases where light anaesthesia is demanded (8).

End-tidal anaesthetic gas concentration

End-tidal anaesthetic gas concentration (ETAGC) monitoring has become common practice when volatile anaesthetic agents are used. Several benefits from this monitoring can be adduced, but it has not been shown that ETAGC monitoring reduces awareness-incidence in a randomised controlled study. In one study similar incidences (0.2%) were found regardless if ETAGC was used or not (I). In another recent study awareness occurred in a cohort of patients where an ETAGC-protocol was used, at the same incidence-level (50). This

later study claimed that patients with high risk of awareness were included, and a higher incidence may thus have been anticipated. But since only high risk patient inclusion may not have been the case, the study was underpowered and the incidence of 0.2% is thus not remarkably deviant due to wide confidence intervals. Anyway it should be remembered that ETAGC monitoring predicts gas concentration, not the pharmacodynamic effect.

Depth of anaesthesia monitors

Monitors measuring depth of anaesthesia using processed electroencephalogram (EEG) have been utilised during the last decade. The most commonly used is called Bispectral Index Scale™ (BIS, Aspect Medical Inc., Norwood, MA, USA), and it uses a scale of hypnotic depth from 1-100. The BIS monitor has been studied regarding two separate points of interest. First, if it is possible to reduce anaesthetic drug administration to get a faster recovery with less side-effects, and second, if the incidence of awareness can be reduced using the monitor. A five-fold decrease in awareness-incidence has been demonstrated in two studies with differing designs (29, 48). In both these studies two cases of awareness occurred in spite of BIS monitoring, but all these four cases occurred at relatively high BIS values. Thus, theoretically an even more profound effect on preventing awareness could be possible using this monitor, but this also indicates that monitoring itself does not abolish awareness without action from the anaesthesia care giver. In a third study, comparing a BIS-protocol with an ETAGC-protocol, no difference was found (50). However, in addition to being underpowered, a remarkable finding in this later study is that the two awareness-cases in the BIS guided group were found in patients were the levels of BIS and ETAGC are both sparsely documented and outside the intended ranges. To sum up BIS monitoring and awareness-incidence, the results points in favour of monitoring, especially in patients at high risk of awareness (47). If this justifies the accompanied increased economic cost is partly a question of ethics and partly an economical question, and depends on how the consequences of awareness are interpreted.

Consequences

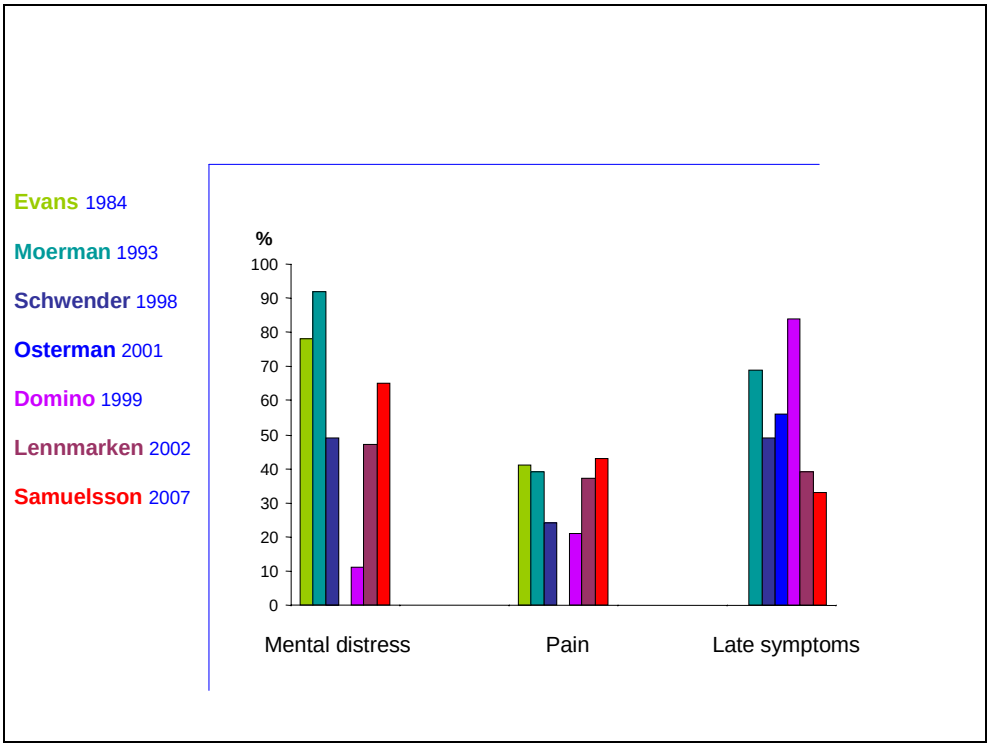
Since a tremendous amount of patients require surgery every year, the total number of awareness cases is considerable although the incidence may seem

modest (51). A number of these patients look upon the awareness experience as the worst experience in their life (52), and awareness is by far the factor with highest odds ratio for causing dissatisfaction among post-operative patients (21). Expectations may explain parts of these findings. However, the experience of awareness is not uniform and not all patients suffer, a fact found already in the first awareness-study 48 years ago (14).

All awareness-victims experience some kind of explicit recalled sensory perception during the awareness episode. The most common perceptions are auditory and tactile, and to a lesser extent pain, a feeling of being paralysed and visual perception (II). These perceptions can cause acute emotional responses like fear, panic, and helplessness. These responses, in turn, are very different depending on the situation and the person involved. Finally, psychological symptoms after the event may develop.

The most challenging part in studies of general consequences of awareness is how to collect a representative patient material. Different ways trying to overcome this problem have been used in the seven major studies conducted in adults (42, 52-56, II), and may in part explain the differences in results. Some findings are general, and consequences of awareness can be divided into immediate symptoms and late psychological symptoms. Another convenient way to put headlines on consequences, connecting to the chain reaction described above, is: Acute mental distress, pain and late psychological symptoms (57). These three variables are documented, in slightly different form, in the seven studies. A summarised view of the results is obtained from the figure below.

- Mental distress (fear, panic, and helplessness) is experienced by 2/3.
- Pain by 1/3.
- Late psychological symptoms (anxiety, chronic fear, nightmares, flashbacks, indifference, loneliness, and/or lack of confidence in future life (54, II)) by approximately 1/2.



Pain and mental distress are quite straight forward, but late psychological symptoms involve several symptoms with a very variable degree of suffering and persistence. The quality and severity of these later symptoms decide the possibility of diagnosing a posttraumatic stress disorder (PTSD). The notation PTSD originates from non-medical situations, but awareness can definitely be a distressing event outside the normal range of human experience, a prerequisite for a PTSD diagnosis.

PTSD

PTSD is a more common condition than often believed. The lifetime prevalence is 5-10%, but most persons with PTSD recover spontaneously whereas about 25% become chronic (58, 59).

The criteria for a diagnosis of PTSD can be summarised as follows:
PTSD is triggered by a traumatic event with a high degree of severity (e.g. torture, war, major accidents, rape, and awareness), that elicits a response of severe fear or helplessness. The symptoms must persist for at least one month and impair function of daily life, and they consist of three key features:

1. Re-experiencing the trauma, with flashbacks or nightmares.
2. Avoidance of things or situations related to the trauma, also including emotional numbing.
3. Hyper-arousal, which may increase sleep disturbance, irritability and fear.

Depending on methodological differences in recruiting patients and divergent reluctance or capacity to diagnose PTSD, very different risk-figures for PTSD development after awareness are presented in four of the seven studies on consequences of awareness (42, 54, 56, II). The incidence-range for PTSD after awareness is 2% to 56%. Based on these studies, an estimation of risk for PTSD after awareness in general has been made, stating probably below 10% risk (57).

When it comes to children, the problem with late psychological symptoms seems to be much smaller, and in the three available papers dealing with this question no long term sequelae was found (43, 44, 60).

Dreaming during anaesthesia

The last two papers in this thesis deal with dreaming in relation to anaesthesia and awareness (III, IV). They are recently published and will not be mentioned in this introduction.

The main cause for an anaesthetist to study this topic is to illuminate the relationship between dreaming during anaesthesia on the one hand, and awareness and depth of anaesthesia on the other hand.

Definition

Defining dreaming during anaesthesia is not easy, but anyhow not as intricate as the definitions of general anaesthesia or awareness. A good comprehensible definition for dreaming during anaesthesia is: Any recalled experience, excluding awareness, which occurred between induction of anaesthesia and the first moment of consciousness upon emergence (61). Often the expression intraoperative dream is used, meaning exactly the same.

Incidence

There is a tremendous variation in reported incidence of dreaming during anaesthesia, with a range from 1% to 57% in cohorts given mixed forms of anaesthesia (14-17, 20, 23, 24, 62-64). The highest incidence (over 80%) is, not surprisingly, reported after ketamine based anaesthesia (65). Many studies states incidences about 5% (16, 17, 19), meaning that dreaming is much more common than awareness, and is experienced by millions of patients every year. Some factors may influence dream-incidence and deserve further comments.

Patient factors

Gender, age, health, and home dream recall are factors that have been discussed to impinge on the incidence of reported dreams after anaesthesia.

Women have reported higher incidence than men in some earlier studies (17, 20, 63). Speculations to explain this finding include faster emergence from anaesthesia in women (39-41, 66), and a tendency for women to recall dreams in general more often than men (67). These explanations may lead to more dreams not forgotten and hence, more dreams reported. However, other studies do not find women to be overrepresented as dreamers during anaesthesia (64, 65).

Young and healthy is something to be. These two factors may cooperate in increasing intraoperative dreaming (16, 63, 64), that is, they may share the same mechanism. Older and unwell people have more daily problems falling to sleep and also more difficulty with rapid eye movement (REM) sleep cycling (68, 69). If dreaming during anaesthesia and normal dreaming are related, this can be an explanation.

There are wide differences in ordinary home dream recall (16). If this is a factor influencing dreaming during anaesthesia remains to be proven. Some older studies do not find any connection (70-73), but a recent very ambitious study shows a significant relation between high home dream recall and reported dreams during anaesthesia (64). These findings may also indicate a relation between ordinary dreaming and dreaming during anaesthesia.

Overall, the discussion above indicates that there is no identified patient factor that definitely can predict a higher incidence of intra-operative dreaming.

Interview timing

Most dreaming patients do not report this spontaneously. Reasons for this may be: They find it unremarkable, easily forgotten, embarrassing or they are sidetracked by more resolute problems like pain and nausea (61). The modified Brice-interview, used to detect awareness, is also used in identifying dreamers after anaesthesia. Emerging from anaesthesia is a much slower procedure than the opposite. The state of the brain goes from fully anaesthetised to awake in a continuous process. Since many anaesthetic drugs also affect memory function, the timing of the post-operative interview may be of importance.

In some studies a decreased capacity to remember intraoperative dreaming was found in later interviews compared with earlier. Two studies (73, 76) found this phenomenon comparing interviews in the post anaesthesia care unit (PACU) with immediate post-operative interviews, and another (16) comparing later interviews with PACU-interviews. This is also indicated by a high incidence of dream recall (21%-34%) in four studies in which the interviews were conducted immediately after emergence (64, 70, 71, 76). Thus, the effect of interview timing on dream-incidence seems to indicate a different time-dependency compared to the effect on awareness-incidence.

Drugs

Different hypnotic agents may generate diverse incidences of reported dreams after anaesthesia. This has been shown for ketamine, with very high figures. Anaesthesia care providers have known for a long time that ketamine produces dreams with different character than other anaesthetics. Dreams are often bizarre, dramatic and sometimes nasty, especially with high doses, but this problem is markedly reduced with lower doses and concomitant benzodiazepines (65, 74). Maybe the specific site of action via the N-methyl D-aspartate (NMDA) receptor is responsible for both the character and the high incidence of recall, concerning ketamine-induced dreaming.

Propofol-based anaesthesia has in some, but not all, studies shown higher dream incidences than volatile anaesthetics (70-73). This can not be explained by the amnesic properties, since propofol is a very potent drug in that aspect (49). Explanation has been sought in faster recovery, which may suffice for comparing with older volatiles (70-73). When comparing propofol with newer volatile agents sevoflurane and desflurane in a recent study (64), some other factor remains to be found responsible for the difference.

High dose opioids as a basis for anaesthesia is nowadays neither common nor up-to date, since opioids are not potent hypnotics. Two older studies found high incidences of dreaming using opioid based anaesthesia (24, 62), and the high incidences of dreams may be related to lack of potent anaesthetic agents (62). This is an exciting hypothesis that puts the next headline in high-light.

Depth of anaesthesia

Many studies over many years have created a large and somewhat diversifying amount of findings dealing with depth of anaesthesia and dreaming.

Some of these findings point in the direction that dreaming during anaesthesia may be related to light or insufficient anaesthesia. Distinct examples are cases where dream content relates to intra-operative events, directly or in-directly (14, 17, 29, 62-64, 75), and clinical signs of light anaesthesia in dreamers (24, 62). Most of these cases are from older studies were the use of potent hypnotic agents was sparse, and it may well be that this kind of cases in fact are near-awareness due to insufficient anaesthesia. There is also one case where a dream subsequently merged into awareness with time (19). Other indications implicating light anaesthesia as cause of dreaming are much more speculative, including more dreams in patients with fast recovery, short procedures or Caesarean sections.

On the other hand findings exist suggesting that dreaming during anaesthesia is independent of anaesthetic depth. The best support for this hypothesis is two studies using BIS. One study was not designed for this purpose, and includes only patients at high risk for awareness who were randomised to BIS-monitoring or not. There were no major differences in dreaming incidence, except at the very first interview where more dreamers were found in the group without BIS guidance (63). The other study is designed for dream evaluation, is carefully done, but includes only 300 patients. No differences in BIS-values, as a surrogate for anaesthetic depth, were found between dreamers and non-dreamers (64).

The two different hypotheses about dreaming as being dependent of anaesthetic depth or not, do not necessary need to contradict each other. It may be so that they apply to two different situations:

- Near awareness dreams, dependent of anaesthetic depth.
- Ordinary dreams, independent of anaesthetic depth, probably taking place during recovery.

Content and form

The content of dreams during anaesthesia can be roughly classified as unpleasant or pleasant without detailed description, or they can be more or less carefully described. Three major groups can be discerned:

- Pleasant dreams with ordinary content of daily life.
- Dreams were the content can not be remembered, although the patients "know" they have been dreaming.
- Dreams containing drugs, surgery, trauma and pain.

The form of intra-operative dreams is only described in one study (64), where comparison with dreams during sleeping is made. These authors conclude that most dreams during anaesthesia closely resemble the dreams of sleep onset.

Consequences

The outcome of dreaming during anaesthesia is diverse. This may correspond to the assumption that different types of dreams have different aetiology, and hence, various descriptions of consequences are not surprising.

Improved postoperative mood among dreaming patients have been described (70, 71). If it is the dreaming per se or the overrepresentation of propofol based anaesthesia in dreamers that is responsible can not be determined.

Equal outcome concerning postoperative anxiety and satisfaction between dreamers and non-dreamers have been presented (64, 70), but also worse outcome among dreamers for these parameters (63).

Some patients find dreaming during anaesthesia distressing. The degree of distress can be severe and has been described as the worst part of the hospital visit (62). If the patients confuse their dreams with awareness it is easy to understand distress and dissatisfaction, and if this is the case, consequences of awareness may apply also to some dreamers.

Generally, the overall impression is that consequences of dreaming during anaesthesia seem to be small and of minor importance to the majority of patients.

AIMS

The overall aim of this thesis was to investigate the incidence and importance of awareness and dreaming during anaesthesia. More specified aims for the separate papers were:

I. To prospectively assess the incidence of awareness in a large cohort, including the impact from follow-up time and neuromuscular blocking drugs.
II. To assess the incidence and general severity of immediate and delayed problems due to awareness using a consecutive inclusion design.
III. To test the hypothesis that dreaming during anaesthesia should not be regarded as near-awareness that may develop into explicit recall of real events.
IV. To investigate if dreaming during anaesthesia is associated with insufficient anaesthesia, as indicated by high BIS levels. A secondary goal was to investigate whether earlier results identifying subgroups with a higher incidence of dreaming could be reproduced.

MATERIAL AND METHODS

Patients

In all four studies inclusion of patients was preceded by informed consent from the patients and approval by the local ethical committee at Linköping University.

Paper I

Patients were enrolled between 1997 and 1998 in two Swedish Hospitals, Kalmar County Hospital and Norrköping County Hospital. Inclusion criteria were as follows: general anaesthesia with laryngeal mask airway, endotracheal intubation or jet ventilation; age of minimum 16 years; ability to communicate in Swedish or English; no overt psychiatric disorder thought to interfere with the reliability of the interview; ability to attend at least one of the last two interviews; and agreement to participate. All patients who fulfilled the inclusion criteria were entered into the study. Planned and emergency surgeries were included. Of 12 179 eligible patients, 394 were not included because they could not be contacted for either of the last two interviews, leaving 11 785 patients to be assessed.

Paper II

Two thousand six hundred eighty-one consecutive patients, from January 2001 to May 2002, who had undergone general anesthesia 1–3 days earlier, were interviewed according to the modified Brice-interview (15). One additional question was added to the interview: whether they had experienced awareness earlier in life. Ninety-eight patients (3.7%) considered themselves as having been aware during previous general anesthesia. These patients were considered eligible for further exploration of long-term consequences of

awareness. Six patients died before inclusion. A letter with information, including content and arrangement of the interview, was sent to the remaining 92 patients. Of these, 4 were excluded because of stroke or dementia, 7 declined to participate, and 2 patients could not be reached. Therefore, 79 patients were interviewed via telephone.

Paper III

This paper is based on the one-centre data from Kalmar County Hospital on intraoperative dreams obtained in connection with a previous two-centre study on awareness only (I), and the same inclusion criteria were thus used. 6991 consecutive patients above the age of 16 years, given inhalational anaesthesia were included in the analysis.

Paper IV

2681 consecutive patients older than 16 years, scheduled for surgery from January 2001 to May 2002, including use of muscle relaxants and/or intubation, were consecutively included. They comprise the one-center (Kalmar) part from an earlier two-center study on BIS and awareness, where further details can be found (48). Exclusion criteria were surgery precluding the use of BIS sensors on the forehead, cases where BIS data were unreliable for technical reasons and failure to conduct any of the two last interviews for awareness and dreams. 2653 patients fulfilled all the criteria, and were analysed in this study.

Interviews and classification

Paper I

Clinical routine at the two hospitals included an interview for awareness on discharge from the post-anaesthesia care unit in all patients older than 15 years who had undergone general anaesthesia. This modified Brice-interview was given by the nurses who attended the patients, and was recorded in the anaesthesia record. Nursing staff designated for the study recorded data from the routine interview in the post-anaesthesia care unit and repeated the interview 1–3 days and 7–14 days after anaesthesia. Inpatients were interviewed face-to-face, whereas patients who had left the hospital were contacted by telephone. Patients with possible memories of intraoperative events at any of the three interviews were given an additional interview to obtain data on awareness. All four investigators were involved in the interviewing of patients, and together they classified cases into one of three categories according to the likelihood of true recall: definite cases required that the recalled event was confirmed by attending personnel; for probable cases, the investigators were convinced that the memory was real, but no confirmation could be obtained; and possible cases, who were unable to recall any event definitely indicative of true awareness. A reported dream alone was not classified as awareness. Neurophysiological monitoring was not allowed in any patient, since our aim was to assess the present situation and the possible need for additional monitoring.

We assessed the cases of awareness or awake paralysis with reference to whether additional monitoring, education, or increased vigilance could have prevented awareness.

Paper II

The duration of each telephone interview was approximately 45 min. A structured protocol divided into seven sections, similar to that of Schwender et al. was used (54). The different sections were personal data, detailed own

description of the awareness episode, sensory perception, acute emotions and cognition during the awareness episode, late psychological symptoms afterward, and handling of the knowledge of having been aware. Each section was subdivided. In uncertain cases, medical records were obtained, if possible, and checked. Three co-workers with experience from awareness studies independently assessed the interviews for awareness classification. The outcome measures for all parameters were either yes or no responses, except for the following parameters, which were more thoroughly explored. The three parameters measuring acute emotions, the seven measuring late psychological symptoms, and the pain parameter were also semi quantified: 0 = none, 1 = light to moderate and 2 = severe.

Paper III

The three modified Brice-interviews are described above in paper I. Apart from awareness, we also asked about dreams during anaesthesia. Reported dreams were classified, in accordance with the patient's own opinion, as unpleasant (U-dreams) or neutral/pleasant (NP-dreams). No further attempt was made to evaluate the dream content. Only patients who considered themselves definitely able to distinguish between a dream and real events were classified as having experienced both. No neurophysiological device for monitoring depth of anaesthesia was used.

We describe the interrelationships between intraoperative dreams reported after surgery, awareness and case-specific variables such as demographic data (gender, age, body mass index, etc.) as well as type and duration of the anaesthesia.

Paper IV

The patients were interviewed on three occasions using the modified Brice interview: before they left the Post Anaesthesia Care Unit, 1–3 days, and 7–14 days after the operation. The dreams reported were classified, in accordance with the patient's own opinion, as unpleasant or pleasant/neutral, but no further analysis of the dream content was performed. Any patient who claimed they had been dreaming during anaesthesia, at any of our three interviews, was classified as a dreamer.

Bispectral index (BIS)

Staff members, anaesthesiologists and nurses were instructed to maintain BIS values between 40 and 60, and to avoid values >60 during induction and maintenance. BIS A-2000 monitors (Aspect Medical Systems, Norwood, MA, USA; BIS index version 3.4) were used, and the smoothing time of the BIS monitors was set to 30 seconds. In the analyses, separate mean BIS values for every minute during induction and maintenance were used. Data were analyzed according to BIS levels and durations:

BIS variables (Induction + Maintenance)
Mean BIS (Maintenance only)
Total time BIS>60 Total time BIS>70 Total time BIS<40
Number of episodes BIS>60 at least 1 min long Number of episodes BIS>60 at least 2 min long Number of episodes BIS>60 at least 4 min long Number of episodes BIS>60 at least 6 min long Number of episodes BIS>70 at least 1 min long Number of episodes BIS>70 at least 2 min long Number of episodes BIS>70 at least 4 min long Number of episodes BIS>70 at least 6 min long Number of episodes BIS<40 at least 1 min long Number of episodes BIS<40 at least 2 min long Number of episodes BIS<40 at least 4 min long Number of episodes BIS<40 at least 6 min long

Statistics

Paper I

The material is presented using descriptive statistics only.

Paper II

Because of the small numbers, logistic regression was not considered appropriate. The Fisher exact test (two-tailed) was used on parameters considered as interesting in advance, namely: sex, relaxant anesthesia, pain during surgery, acute emotions during the awareness episode, and late psychological symptoms.

Paper III

Multiple logistic regressions were used to analyse the coupling between dreams (NP and U, respectively) on the one hand and, on the other hand all case-specific parameters, except awareness. Induction with ketamine was only used in 10 cases and sevoflurane in 19 cases. Both these were omitted from the logistic regression analyses. The coupling between awareness and dreams (NP and U put together) was analysed by Univariate logistic regression. Because of low numbers, Fisher's exact test was used in one instance.

Paper IV

Statistical analyses were performed to assess whether dreams (yes vs. no or pleasant/neutral vs. unpleasant) could be related to the BIS levels using the chi-square test. We also tested whether dreams were related to case-specific parameters, using chi-square test or logistic regression. Total times with BIS

below 40, above 60 or above 70 were analyzed using the Mann–Whitney U-test and the mean BIS between the three groups (no dreams, neutral/pleasant dreams and unpleasant dreams) was analyzed using Kruskal–Wallis ANOVA. P-levels <0.05 were considered to be statistically significant.

RESULTS

Paper I

Anaesthesia details of the 11 785 patients included in the study:

Premedication	Opioid	11440	97.1%
	Benzodiazepine	2084	17.7%
Induction	Propofol	6473	54.9%
	Thiopentone	5248	44.5%
	Sevoflurane	36	0.31%
	Ketamine	28	0.24%
Maintenance	Sevo- /Iso- /Des-flurane	11454	97.2%
	-with N_2O supplement	11034	93.6%
	Propofol	325	2.8%
	-without N_2O supplement	288	89.2%
Monitoring	ETAGC	9528	83.2%
Airway	Intubation	7796	66.2%
	Laryngeal mask	3977	33.8%
	Jet ventilation	12	0.1%
Neuromuscular block	Total	7753	65.8%
	Suxamethonium only	672	5.7%

Incidence of awareness

18 patients (11 [0.16%] women and seven [0.15%] men) reported awareness, and one further woman had awake paralysis (pat. 4, in the table below). Neuromuscular block was used in 14 of the 18 patients who reported awareness. None of the patients anaesthetised with a total intravenous technique reported awareness during surgery. There was no difference in the incidence of awareness among patients who had been given a benzodiazepine before anaesthesia and those who had not. The incidence of awareness was also similar for men and women. Overall incidence was 0.18% when neuromuscular block was used, and 0.10% in the absence of relaxant drugs.

Detection interview

Six patients recalled awareness at the first interview, 12 patients had recall at the second interview, including five of the six patients who had memories at the first interview. 17 of 18 patients with awareness had recall of events at the third interview. Five of those patients had not previously been identified as having been aware. One patient who had no recall at the first interview, but remembered intraoperative events at the second, had once again forgotten 12 days after surgery, although 24 days after surgery she had detailed memories. One patient thought he would not have remembered at all had he not been questioned. The patient who had awake paralysis remembered at all three interviews about being paralysed before anaesthesia.

Movement

Eleven patients with awareness were convinced that they had tried to move, but only one realised he was able to do so. Two patients who were unable to move had received no neuromuscular block, although one of these patients had restrained arms. Three patients denied making any attempt to move despite their comprehension of the situation.

Comprehension, anxiety and delayed symptoms

Of the 14 patients with recall who had received neuromuscular block, nine immediately realised their situation, and five of these were anxious. Totally nine patients felt anxious. The patient who had awake paralysis did not realise the situation, felt anxiety, and experienced delayed symptoms. No one of the 4 patients who was aware during non-relaxant anaesthesia felt anxiety. Three of these patients understood their situation, and all four were free from delayed symptoms.

All patients who experienced awareness or awake paralysis were offered repeated discussion and explanation according to their own desire, and within 3 weeks all patients declared that they were satisfied with the explanations, that they did not need any further contact, and that all their delayed symptoms had disappeared.

Pain

Pain was reported by seven patients, two of whom reported severe pain. Among the six paralysed patients who reported pain, only one patient had delayed symptoms, and this patient was also among those who felt anxiety and was unable to understand the situation.

Pat. Number	Relaxant Drugs	Pain	Immediate Comprehension	Immediate Anxiety	Delayed symptoms	Probability	Detection Interview
3	0	0	+	0	0	Definite	2, 3
8	0	0	+	0	0	Probable	2, 3
14	0	0	0	0	0	Probable	3
15	0	+	+	0	0	Probable	3
1	+	0	+	+	0	Definite	1, 2, 3
2	+	0	+	0	0	Definite	1, 2, 3
4	+	0	0	+	+	Definite	1, 2, 3
5	+	0	+	+	+	Definite	3
6	+	+	+	+	0	Definite	1, 2, 3
7	+	+	+	0	0	Definite	3
9	+	+	+	0	0	Probable	3
10	+	+	0	0	?	Probable	1, 2, 3
11	+	+	+	+	0	Probable	2, 3
12	+	0	0	+	0	Probable	1, 3
13	+	0	+	+	0	Probable	2
16	+	0	0	+	+	Possible	1, 2, 3
17	+	+	0	+	+	Possible	2, 3
18	+	0	0	0	0	Possible	2, 3
19	+	0	+	0	0	Possible	2, 3
Sum		7+	12+	9+	4+		

Probable reasons for awareness and monitoring

The anaesthetist's insufficient knowledge and lack of vigilance contributed in four cases. Five of the 14 intubated patient's awareness occurred during intubation, and two of these intubations were difficult. In the remaining

patients, no obvious independent reason for awareness could be identified. The incidence of awareness among patients with neuromuscular block was similar irrespective of whether ETAGC was measured or not. Monitoring of ETAGC was used in 15 patients with awareness.

Paper II

Patient characteristics

Four of the 79 possible awareness cases were performed using regional anesthesia. Another 29 patient stories were not considered as awareness by the three assessors. These experiences included perioperative nightmares, memories before or after surgery, and recollections too diffuse for awareness classification. Therefore, the final analysis included 46 awareness cases.

There were 14 men and 32 women. The mean age when the awareness episode occurred was 31 years (range 6–62). Five patients were children at the time of awareness (age <18 yr). The median awareness year was 1980 (range, 1935–2001). Three patients had experienced awareness on more than one occasion. Muscle relaxants had been used in at least 35 cases (76%).

Sensory perception during the awareness episode

Auditory (n = 33; 70%) and tactile (n = 32; 72%) perceptions were the most common. Twenty patients (46%) had experienced pain, and 14 scored their pain as severe. Seventeen patients had felt paralyzed, and another 12 were not able to tell because they had not tried to move.

Acute emotions during the awareness episode

In total, 30 patients (65%) stated they had experienced an acute emotional reaction.

Cognition during the awareness episode

Thirty-seven patients claimed that they had understood what was going on, and 31 had tried to communicate.

Late psychological symptoms

Thirty-one patients denied any late symptom at all (total score 0). In the remaining 15 cases (33%), three of the seven classified late symptoms dominated. These were nightmares (n = 11), anxiety (n = 10), and flashbacks (n = 9). The median total severity score was 4 (range, 1–12; possible maximum 14). Only 8 patients (17%) had a total score above 2. Nightmares and flashbacks accounted for 34 of totally 59 points from late symptoms. In 6 patients, the symptoms persisted for years, albeit in 4 of those patients, the symptoms were restricted to nightmares and flashbacks. The remaining 2 patients had more severe mental problems (total scores of 12, and 10, respectively) and underwent psychiatric care.

Handling of the knowledge of having been aware

Thirteen of the 39 patients who described their awareness experiences were greeted with scepticism. During subsequent surgeries, 19 patients (41%) reported a lack of trust in medical staff, but only 4 (9%) had kept this attitude before their most recent surgery. Four patients had contacted medical help because of mental illness. One had a diagnosis of PTSD. She had also been exposed to other extreme mental stress earlier in her life.

Relations between outcome parameters

Acute emotions during the awareness episode, but not sex, pain, or relaxant anesthesia, were significantly related to late psychological symptoms ($p < 0.05$).

Paper III

Dreams were reported at any of the three interviews by 232 (3.3 %) of the 6991 patients and 10 (0.14 %) cases of awareness were identified. Awareness was

significantly more common among patients reporting a dream (4/232 = 1.7%) compared to those who did not (6/6759 = 0.09%; OR 18.7 (5.2-67); p=0.000007).

An intraoperative dream did not precede memories of awareness in any of the 232 patients reporting dreams within the two weeks follow up period. This means that neither did a dream reported merge into an episode of awareness in any patient, nor did a dream come first followed by memories of awareness in the four cases who experienced both. In the very exclusive group of four patients with both dreams and awareness, all four recalled the dream and the real event at the same interview, which in two cases were at the first interview and in two cases at the second interview.

Unpleasant dreams (U-Dreams) were associated with thiopentone induction as compared with propofol, with an odds ratio of 2.22 (1.28-3.86; p=0.005).

Neutral or pleasant dreams (NP-Dreams) were associated with female gender, low body mass index (BMI) and short duration of anaesthesia. Increasing BMI quartiles nicely follow a decreased odds ratio for dreaming.

Paper IV

In this study the total incidence of intraoperative dreams, defined as what the patients could remember at any interview, and claimed had occurred during anesthesia, was 8.0%. The dream incidences at each of the three interviews were 6.1%, 5.5% and 4.6% respectively. Of the 211 dreamers, 22 (10%) considered their dream unpleasant.

BIS levels

Mean BIS (maintenance) was just below 40, which was a little bit lower than intended. There were no statistical differences in mean BIS between the subgroups of dreamers and non-dreamers. Total time with BIS below 40, above 60 or above 70 did not differ between dreamers and non-dreamers (p-values; 0.56, 0.48 and 0.26 (Mann-Whitney U Test)). Numbers of episodes with high or low BIS for a continuous time of 1, 2, 4 and 6 minutes were similar between dreamers and non-dreamers. The figures in the table refer to percentage of patients in each group. Note the similar frequencies in each row for non-dreamers and dreamers. No significant difference was found.

Number of episodes	Non-dreamers (n=2442) 0	1-2	3-5	>5	Dreamers (n=211) 0	1-2	3-5	>5	p
BIS>60 1 min	43%	46%	8%	3%	42%	44%	9%	6%	0.254
BIS>60 2 min	58%	36%	4%	2%	55%	38%	5%	2%	0.869
BIS>60 4 min	78%	20%	2%	0.2%	78%	19%	2%	0.5%	0.892*
BIS>60 6 min	88%	11%	1%	0.1%	88%	11%	1%	0.5%	0.978*
BIS>70 1 min	74%	24%	2%	0.4%	70%	27%	3%	0.5%	0.368
BIS>70 2 min	85%	14%	0.5%	0.1%	82%	18%	0.5%		0.170*
BIS>70 4 min	96%	4%	0.04%	0.04%	94%	5%	0.5%		0.575*
BIS>70 6 min	98%	2%		0.04%	97%	2%	0.5%		0.506*

* Number of episodes 0 and 1-2 only, statistically analyzed
p-values: Chi-square

Case-specific parameters

We selected 11 parameters to analyze for possible relations to dreaming during anesthesia (gender, age, body mass index, ASA group, induction agent, suxamethonium for intubation, relaxant for maintenance, propofol for maintenance, N_2O supplement to sevoflurane for maintenance, epidural complement, and duration of anesthesia). Pleasant/neutral and unpleasant dreams were tested separately, except for propofol maintenance and N_2O supplement to sevoflurane, where all dreams were analyzed as one group due to the low numbers. We did not find any statistical significant correlation between any of the tested variables on the one hand and dreaming during anesthesia on the other hand, neither for the two dream types separately nor for dreamers as one single group.

DISCUSSION

Since general anaesthesia is a very frequent procedure, awareness and dreaming during anaesthesia also become numerous and involves thousands of patients and anaesthetists every year. The significant clinical aspect of this fact was the starting point of my research and this thesis. Contribution to bring clarity about awareness, consequences of awareness and the relationship between intraoperative dreaming and awareness, which might help both patients and health care providers in the daily work, was the main goal.

Incidence, details, and prevention of awareness

At the time of including patients to paper I, the knowledge of awareness-incidence was fairly good but some important details were missing. It was known that recall of intraoperative events in patients under general anaesthesia was rare (0.1–0.7%), although few prospective studies had assessed the incidence of awareness during surgical procedures (15, 19-21). Up to 54% of patients worry about the possibility of pain, paralysis, and mental distress during surgery (77). Previous studies had not recorded important background data, such as whether neuromuscular-blocking drugs were used or whether end-tidal anaesthetic gas concentration (ETAGC) was monitored. Also, memory for awareness may be delayed (19) and follow-up may have been too short to identify all cases.

In paper I we found awareness cases both among patients who had received neuromuscular blocking drugs (0.2%), and among those who had not (0.1%). Our inability to find non-paralysed patients who had unpleasant effects during or after awareness suggest that awareness among patients without neuromuscular block is not equally important, as long as conversation between operating-room staff remains respectful to the patient. Auditory perception is the most common awareness-perception, found both in paper I and paper II.

Ability for the patient to move during awareness is one reason to avoid unnecessary use of neuromuscular blocking drugs. This sign of awareness is, however, not as reliable as some colleagues tend to believe (78). Interestingly, in papers I and II we found both patients who did not even try to move

despite their comprehension of the awareness-situation, and non-relaxed patients who stated that they were unable to move.

There were some indications (19) that repeated interviews over time might be needed to include all awareness cases, when we designed study I. We found that the first interview was not at all sufficient, whereas the follow up time of 7-14 days seemed more satisfactory. However, in our study, patients' memories did not always remain constant or improve with time. In two patients, a reported memory of intraoperative events was temporarily forgotten at the next interview. A similar case was reported in a study in which one patient had recall soon after anaesthesia, but later forgot about his experiences (20). Obviously, there is no time when all cases of awareness will be detected reliably, but most previous studies may have underestimated the true number of patients with recall.

Improved knowledge and vigilance by the anaesthetist may have prevented some of the cases of awareness and also the case of awake paralysis, in paper I. However, in this type of study, it is not possible to detect less obvious cases of poor anaesthetic performance, and improved education may be of greater importance to prevent awareness than indicated by the situations we identified. One spin of from our and other studies is the recommendation by the Joint Commission on Accreditation of Health Care Organizations in USA, advocating teaching clinicians about awareness and its risk factors (51).

Benzodiazepines are, in many cases, valuable for relieving anxiety before surgery, but to give them as prophylactic prevention of awareness is doubtful. In paper I we found no difference in the incidence of awareness among patients who had been given a benzodiazepine before anaesthesia and those who had not. More importantly, we believe that giving anaesthesia in a way that would require deliberate pre-emptive amnesia for intraoperative experiences is ethically unsound. Our finding might modify the trust in the recommendation to use benzodiazepines in cases when low doses of anaesthetics are unavoidable (8), although one study showing some preventive effect recently has been published (23).

In paper I we found no awareness prevention by using ETAGC monitoring. Monitoring of ETAGC was used in 15 patients with recall, and did not help in these cases. We believe that monitoring would have been helpful in only one of the three cases of awareness among the 1928 patients without ETAGC. A weakness in this finding is that the patients were not randomised by whether ETAGC was used or not. Clearly, if the accepted ETAGC is too low, this technique will be of no value in the prevention of awareness. Five cases of awareness in our study occurred during intubation, that is, before

ETAGC monitoring might be useful. We do not believe that a general use of low concentrations of anaesthetic gas at the two departments in our study is the reason for the inability of ETAGC monitoring to prevent awareness, since the overall incidence of recall is one of the lowest ever reported. Our assumption that factors other than an inability to measure ETAGC are responsible for cases of awareness in current anaesthetic practice is strengthened by the fact that a similar incidence of 0.2% was found with total intravenous anaesthesia during which monitoring of ETAGC is of no value (19). As mentioned in the introduction another study was published this year comparing a BIS protocol with an ETAGC protocol (50). Due to weaknesses in that study, mentioned before, there is still no firm evidence for ETAGC monitors in awareness prevention.

When the cases of awareness found in paper I were scrutinised, we assumed that a neurophysiological monitoring technique with 100% sensitivity could have been helpful to avoid at most 12 of the 14 cases that occurred during relaxant anaesthesia. Nine of those 12 patients suffered in one or more ways from their experience. This means that at least 861 patients must be monitored to avoid one case of suffering due to awareness in relaxant anaesthesia, provided that the sensitivity of that particular technique is 100%, including human performance. Since then other investigations have made clear that neither sensitivity of BIS-monitors nor human performance using them are perfect (48), meaning that the number needed to treat in paper I is underestimated.

In order to provide definite information on the possible benefit from BIS and similar devices concerning awareness prevention, it has been calculated that over 40,000 patients will be needed to be included in a randomised study to show a 50% reduction in awareness incidence, using such monitoring (79). As mentioned in the introduction two studies with alternative and differing designs have now pointed out an awareness-incidence reduction around 80% using BIS (29, 48). Another perspective to the debate of BIS monitoring is that only 34% of patients in general were willing to pay for a proven awareness monitor, rising to 50% if they were at high risk, and awareness experience was a significant factor predicting willingness to pay (80). Yet another view is that anaesthetists generally rated awareness as only a moderate problem. Increasing age of the anaesthetist accompanied less importance of awareness and less use of awareness monitoring. But anaesthetists would use depth of anaesthesia monitors more if the monitor could be shown to prevent most awareness cases (81).

Consequences of awareness

In paper II, evaluating consecutive patients undergoing surgery, we found a smaller proportion of patients with late psychological symptoms after awareness as compared to previous investigations using other methods for inclusion (42, 53, 54, 56). Thirty-three percent of our patients scored at least one point in late symptoms. In 9 of those 15 cases, the symptoms disappeared within 2 months, whereas the remaining 6 patients had symptoms for years, which is worth taking into consideration. In 4 of these 6 patients, nightmares and flashbacks were the only remaining symptoms. These were insufficient for a diagnosis of PTSD. Two patients with persistent symptoms had contacted psychiatric care. One of these patients had been diagnosed with PTSD.

Among the patients with awareness in paper I, we found a tendency towards that emotional reactions during awareness were common among those who had delayed symptoms. Even though all awareness patients in paper I denied persisting symptoms one month later, this was not true. A follow up study two years later on these patients showed that four patients still suffered from severe mental sequelae. Only one of these patients experienced pain during awareness, but all four had intraoperative anxiety (55). In paper II, sixty-five percent of the patients had reacted emotionally in the operating room. Among the examined parameters in our study, only acute emotional reactions were statistically related to late psychological symptoms. Apart from the results in our two studies, this finding is in line with the definition of PTSD were the trauma must elicit a response of severe fear or helplessness, and also with a study on violent crime were the initial emotional response predicted later risk for PTSD (82).

Because our incidence of immediate emotional reactions in paper II is at least at the same level as in previous studies, this cannot explain our lower incidence of late psychological symptoms. With the exception of the very small prospective study from our own group (55), previous investigations are retrospective and have used advertisement, referral, and closed claims analysis for assessing late psychological symptoms (42, 53, 54, 56). All these methods for including patients bring along a high risk for selection bias. This is illustrated by figure A.

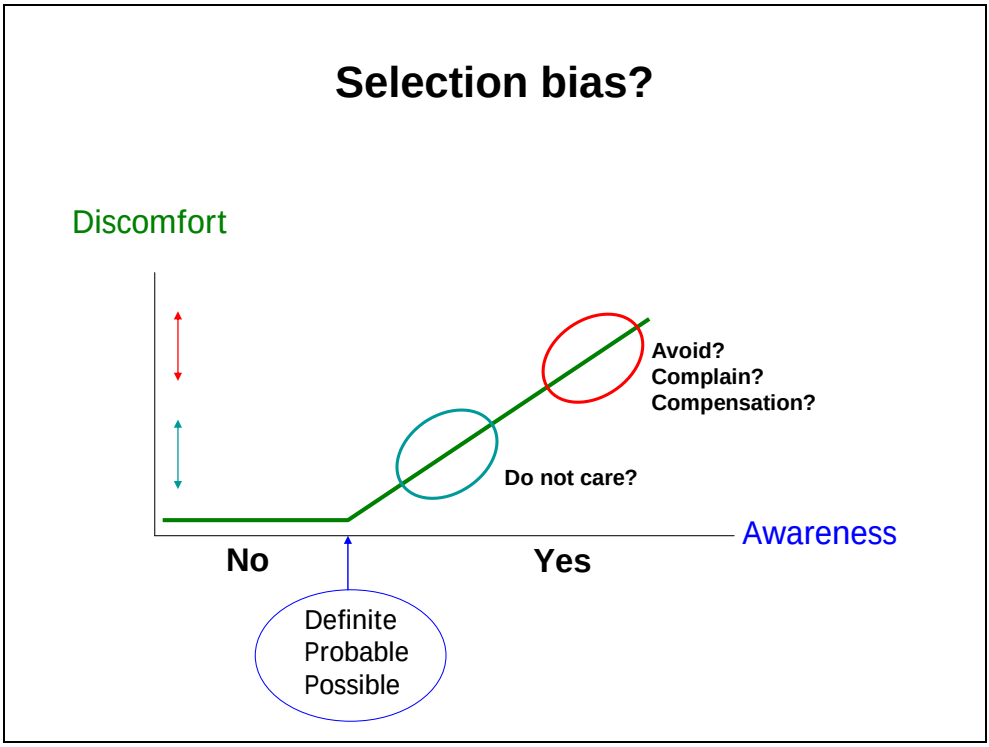


Figure A.

The most probable explanation for our lower incidence of late psychological symptoms, and the relatively less pronounced severity, is the method by which we identified our study population. Our inclusion method may have allowed for recruiting patients irrespective of where they are found on the sloping part of the green line in figure A.

Although we found awareness in general to less often be followed by PTSD compared to earlier studies, it is obvious from all seven studies on consequences of awareness that this complication exists. There are no sharp limits or borders in this kind of research, neither for inclusion and categorisation nor for labelling results. In addition to possible selection bias, also different methods for questioning and analysis have been used to find late psychological symptoms. This has probably affected the result in different studies regarding late psychological consequences and is illustrated in figure B below, where the sharp angle on the green line may have different locations in different studies.

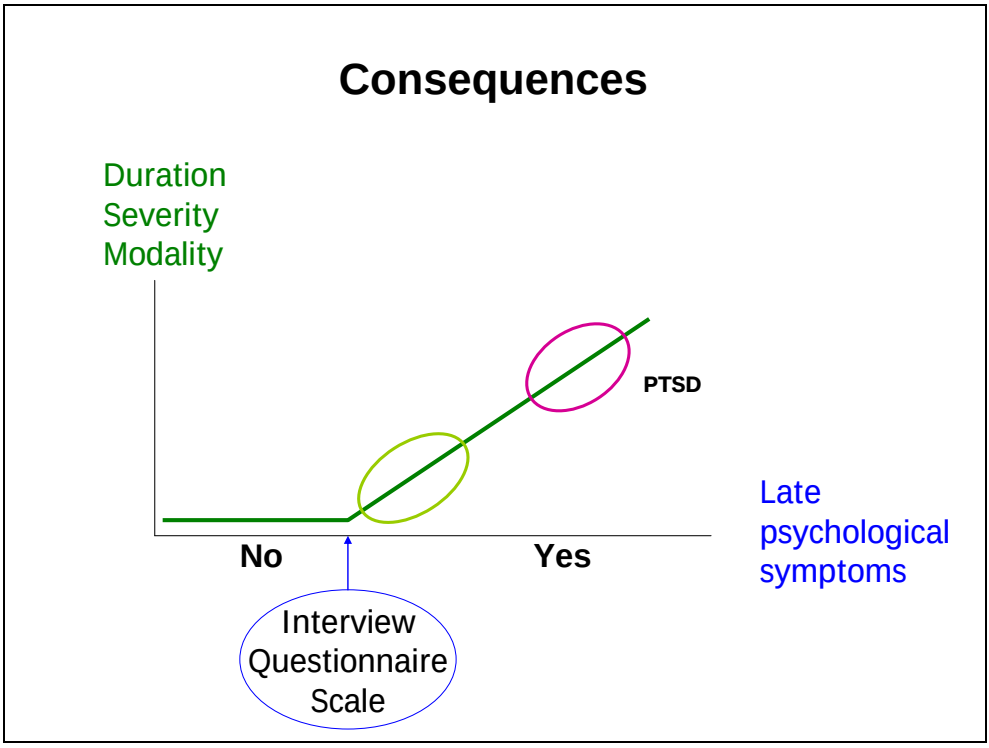


Figure B.

Our goal was to cover the whole green line in figure B. We used the same interview as used in the largest previous study (54) to be able to at least partly compare the results. Although the risk for PTSD after awareness might be overestimated in some earlier studies, it exists and has been estimated to less than 10% based on all available studies (57). Together with all other common suffering in connection with awareness (pain, anxiety, nightmares…) anaesthetists should handle this issue seriously.

Because awareness often leads to dissatisfaction and concern before subsequent anaesthetics, it is not surprising that 41% reported that they were uncomfortable in anticipation of their next anaesthesia, the one after being aware. With time and additional personal experience of successful anaesthesia, this attitude faded, and before their most recent operation, only 9% maintained similar negative feelings, indicating reversibility.

It is interesting to notice that 33 (42%) of 79 patients being interviewed in study II falsely considered themselves to be awareness victims before the interview. Perhaps the newfound knowledge of awareness among patients, media, and medical staff has created a new situation where the earlier risk for not being believed has totally disappeared. This was expressed in a recent

review as; "it may be time to tip the scale a little bit in the opposite direction" (26).

Dreaming during anaesthesia

In paper III we found 232 (3.3%) dreamers. During the study period of two weeks, memories of an intraoperative dream did not merge into, or preceded, memories of awareness in any patient, despite the fact that awareness was delayed several days or even weeks after the operation in 50 % of the cases (I). Thus, even if a dream reported after surgery may be due to insufficient anaesthesia, the dream is very unlikely to constitute a predecessor of explicit recall.

Four of the 232 dreaming patients experienced awareness as well. Great care was taken to ascertain that these patients regarded the dream and the real events as separate phenomena. Awareness was 19 times as frequent among patients who also reported a dream compared with patients who did not remember any dream (p=0.000007). Even if the association is highly significant, we are not sure that there is a true general bilateral relationship between dreams and awareness. No dream blended into an episode of awareness in any of the 232 cases, and it might be that the awareness episode triggered dreaming during the same anaesthesia in the exclusive four cases that experienced both. Leslie et al. (64) discussed the possibility that a small subgroup of intraoperative dreams in fact are related to awareness and insufficient anaesthesia, and in these cases the dream content also often involves surgery or related procedures. Since we did not analyze dream content in this study, we do not know if that was the case in our patients, but these four patients without doubt received insufficient anaesthesia, thus confining them to this subgroup. The highly significant association between intraoperative dreams and awareness in this study may be explained by a common denominator in these four patients - insufficient anaesthetic drug action to prevent cognitive processes.

In paper III we also found that thiopentone increased the risk for unpleasant dreams compared to propofol (OR 2.22; p=0.005). It cannot be determined whether this was due to fewer NMB treated patients in the propofol group, the amnesic properties of propofol or a genuine difference between the two agents. Neutral/pleasant dreams, three times as frequent as unpleasant dreams, were not related to NMB or induction agent, but significantly associated with female gender, lower BMI and shorter procedure.

To further evaluate the relationship between dreaming during anaesthesia and awareness we used BIS monitors in study IV. No correlation between BIS values and intraoperative dreaming was found in this large study in which 8.0% of patients reported intraoperative dreaming. BIS probably must be high enough over a long enough continuous time to create a persisting memory. Although we could detect high BIS for long periods, we did not find any significant relationship between dreams and any of the BIS variables. This finding is also in accordance with Leslie et al. (64), whose study was smaller but more detailed. Explanations to the differing results between our own two studies regarding dream incidence may be that in paper IV we used lighter premedication, all patients were intubated, and the use of BIS-monitors.

Regarding case-specific parameters and their association to dreams, earlier studies present a wide range of results. In paper IV we tested 11 parameters but did not find any statistically significant relationship between dreams and any of these parameters, underlining the inconsistent results in previous studies. The significance of case-specific parameters and dream incidence during anaesthesia has diminished for two reasons. First, findings are hard to reproduce in different studies. Second, in BIS monitoring we now have a more direct tool to examine the relationship between dreaming and awareness, with regard to anaesthetic depth.

Our two studies on dreaming during anaesthesia (III, IV) are large, albeit with limited analyses of dream content. This means that our data complement the earlier study on BIS and dreams, planned in the opposite way (64). In that study they stated that "most dreams were pleasant, unpleasant dreams were unusual, and dreams that included surgical themes or events occurring during anaesthesia were rare". They also stated that many dreaming patients felt that they woke up directly from the dream. Together these three studies support each other, stating that dreaming during anaesthesia in almost all cases is unrelated to depth of anaesthesia, and possibly occur in the recovery phase. A minor fraction of dreams are likely to be near-awareness dreams presumably occurring during light anaesthesia.

CONCLUSIONS

I. The incidence of awareness is approximately 0.2% when neuromuscular blocking drugs are used and awareness also exists without these drugs, albeit to a lesser extent. These findings represent standard practice in an adult population at normal risk. 50% of awareness cases may have delayed recall of awareness.

II. The method for recruiting patients in studies on late psychological symptoms after awareness probably affects the apparent severity significantly. Using a consecutive inclusion design we found initial awareness suffering comparable to previous studies, but a lower incidence and less pronounced severity of late psychological symptoms. The incidences found among the awareness-victims in our study were; experience of pain 46%, immediate mental distress 65%, any late psychological symptom 33%, and PTSD below 10%. Successful further anaesthesia improves trust in medical staff among patients with previous awareness.

III. A memory of an intraoperative dream after general anaesthesia is not an early interpretation of delayed awareness, indicating that no routine follow up of dreaming-only patients is indicated.

IV. Dreams reported after anesthesia are generally not related to insufficient anesthesia defined as high BIS, and should not be regarded as near awareness. Significant case-specific parameters related to intraoperative dreams remains to be identified.

SUMMARY IN SWEDISH (SVENSK SAMMANFATTNING)

Awareness har ingen bra svensk översättning. Den definition av awareness som används konsekvent i den här avhandlingen är: Explicit minne av händelse som inträffat under generell narkos. Eftersom det inte finns någon objektiv metod att påvisa awareness, så måste patienterna intervjuas efter narkosen. När och hur intervjuerna utförs är viktigt, och det duger inte att nöja sig med spontana berättelser. Även om det kan tyckas att risken för att drabbas är väldigt liten, så blir det totalt sett många patienter som upplever och minns något från sin narkos. Flera av dessa tycker att awareness episoden är det värsta de varit med om, och lidandet kan innefatta smärta, hjälplöshet, panik och kvarstående psykiska symptom. Upplevelsen av awareness är dock väldigt olika, och långt ifrån alla patienter lider.

Drömmar under generell narkos är mycket vanligare än awareness. En del tidigare studier har visat att drömmar eventuellt beror på för ytlig narkos, precis som awareness, medan andra undersökningar betvivlar detta samband. En del patienter upplever drömmarna som obehagliga, men generellt tycks betydelsen av drömmar under narkos vara mycket begränsad för de allra flesta.

I den här avhandlingen har jag funnit följande:

Förekomsten av awareness är cirka 0.2% när muskelrelaxerande läkemedel används men förekommer också utan sådana läkemedel, dock mera sällan. Detta gäller standard narkoser hos vuxna normalrisk patienter. Hälften av fallen kan ha fördröjd hågkomst av sin awareness.

Genom att använda fortlöpande insamling av patienter i en studie om konsekvenser av awareness fann vi färre och mindre allvarliga sena psykiska symptom än tidigare undersökningar funnit, trots minst likvärdigt lidande under awareness episoden. Förekomsterna i vår studie var; upplevelse av smärta 46%, omedelbart psykiskt obehag 65%, något kvarstående psykiskt symptom 33% och post-traumatiskt stress syndrom mindre än 10%.

Ett minne av en dröm under narkos är inte ett förebud om sent hågkommen awareness. Detta talar mot att rutinmässigt följa upp patienter med endast minnen av drömmar.

Minnen av drömmar efter narkos är generellt inte relaterade till ytlig narkos, definierat som höga BIS-värden, och skall inte klassas som nästan awareness.

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