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Review

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Spectral edge frequency during general anaesthesia: A narrative literature review

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Abstract

Previous studies have attempted to determine the depth of anaesthesia with different anaesthetic agents using electroencephalogram (EEG) measurements with variable success. Measuring depth of anaesthesia is confounded by the complexity of the EEG and the fact that different agents create different pattens. A narrative review was undertaken to examine the available research evidence on the effect and reliability of spectral edge frequency (SEF) for assessing the depth of anaesthesia in adult patients under general anaesthesia. A systematic search of the PubMed®, Scopus®, CINAHL and Cochrane databases identified six randomized controlled trials and five observational studies. The findings of these studies suggest that SEF varies according to the anaesthetic drugs used. Remifentanil and age are two factors that can affect SEF, while other opioids and benzodiazepine (administered separately) seem to have no effect. No patients experienced intraoperative awareness. However, this does not indicate that SEF can provide full protection against it and the number of articles in which intraoperative awareness was studied was too small to afford any certainty. None of the studies demonstrated a reliable SEF interval associated with adequate general anaesthesia. SEF must be adapted to the anaesthetic drug used, the patient's age and state while under general anaesthesia.

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Introduction

Anaesthesia is an essential tool to facilitate surgery. It comprises a combination of hypnotics and pain relief. Nevertheless, many anaesthetists still rely on parameters of the autonomic nervous system, such as blood pressure and heart rate, to determine whether a patient is sufficiently anaesthetized. An electroencephalogram (EEG) is deemed to provide further information on anaesthetic state.[1]

Recent studies suggest that the depth of anaesthesia needs to be monitored continuously and adapted to the individual patient and the surgery.[1,2] Patients' reactions to anaesthesia vary and it is important to tailor the depth of anaesthesia depth to the individual pateint.[3] Examples of commercial EEG monitors for fine-tuning the depth of anaesthesia are Bispectral Index™ (BIS™), Entropy™ and Cerebral State Index™. These similar, potentially helpful tools for assessing the patient's anaesthetic state, work by obtaining signals from the frontal lobe of the cortex by means of skin sensor electrodes attached to the patient's forehead. The monitor calculates the signals using a statistical multivariate model with nonlinear functions of electroencephalography-based subparameters.[4–6]

Since 2017, European Society of Anaesthesiology (ESA) guidelines have advised the use of commercial EEG-based anaesthetic-state monitors only as a supplementary means of assessing anaesthetic depth, to prevent anaesthetic overdose or underdose.[7] Today's anaesthetic-state monitors are designed to be simple and convenient to use for interpreting the level of the anaesthetic's effects (one of the ESA guidelines). An optimal anaesthetic-state monitor can distinguish between a waking and an unconscious state without reference to the physical haemodynamic conditions caused by anaesthesia and surgery.[8]

A previous report states that anaesthetic-state monitors have been in use for over two decades, but still have limitations.[9] For example, they cannot rule out anaesthesia awareness with certainty; nor can they show, in real time, exactly how and where the anaesthetics act on the cortex.[9] However, recent studies have proposed another commercial anaesthetic-state monitoring system that uses a spectrogram with spectral edge frequency (SEF), such as the Masimo SedLine® Sedation Monitor, as a possible alternative.[10,11] This monitor updates values faster (~1 s), facilitating more individualized EEGs, which provides superior precision in detecting an individual's anaesthetic state than a multivariate model as used by the BIS index.[4–6,9] However, the reliability of BIS index monitoring has been questioned.[12,13] It is known that BIS levels in already anaesthetized patients decrease with reduced electromyography activity associated with the use of neuromuscular-blocking drugs and this has been interpreted as electromyography noise affecting BIS algorithms.[13] A previous study demonstrated BIS values as low as 44 and 47 in fully conscious, paralyzed patients, values that only returned to normal with the return of motor function.[13]

Cortex activity, shown by oscillations on the spectrogram, is affected by hypnotics used to obtain adequate depth of anaesthesia.[9] This spectrogram uses four frequency bands: alpha, beta, delta and theta, representing 8–12 Hz, 12–30 Hz, 0.5–4 Hz and 4–8 Hz, respectively. The SEF value and the effect (dB) in every frequency band can be calculated from these frequencies. It also involves calculating the frequency in which the effect is greatest, by determining the frequency in which 90% or 95% of brain activity takes place.[14]

Figure 1 presents a typical screenshot showing a two-dimensional spectrogram where the y-axis represents frequency in Hz and the x-axis represents time. The area below the white line represents SEF90 or SEF95, where 90% or 95% of brain activity, respectively, is located.[9] In a previous study, SEF was used for reference to determine an adequate depth of anaesthesia; and the authors used the frequency band of 8–13 Hz, which is alpha activity.[14] The authors suggested that there was risk of beta activity (>13 Hz) in addition to the alpha activity, which is equivalent to lighter sedation.[14] The authors also took the view that a SEF value < 8 Hz was associated with a higher overdose risk.[14] This narrative review was undertaken to examine the available research evidence on the effect and reliability of SEF for assessing the depth of anaesthesia in adult patients under general anaesthesia.

Narrative review methodology

A narrative literature review was undertaken using the PICOT (patient, intervention, comparison, outcome and [sometimes] time) format. Inclusion and exclusion criteria were used to impose search limits (Table 1). A systematic search of the PubMed®, Scopus®, CINAHL and Cochrane databases was undertaken to identify articles published between 2010 and February 2021 (the latest 11-year period) that investigated the impact of anaesthesia method on SEF and depth of anaesthesia. Quantitative and qualitative English-language studies confined to adults were searched. The search strategy used the following Medical Subject Headings and/or keywords combined: Spectral Edge Frequency, Anesthesia, General Anesthesia, Reliability, and Depth of Anesthesia (see supplementary materials, Appendix 1).

The results were then analysed by two of the authors (A.B. and K.H.) and the initial studies retrieved were searched for secondary papers. Study selection was based on a preliminary screening of the titles and abstracts, followed by reading of the final

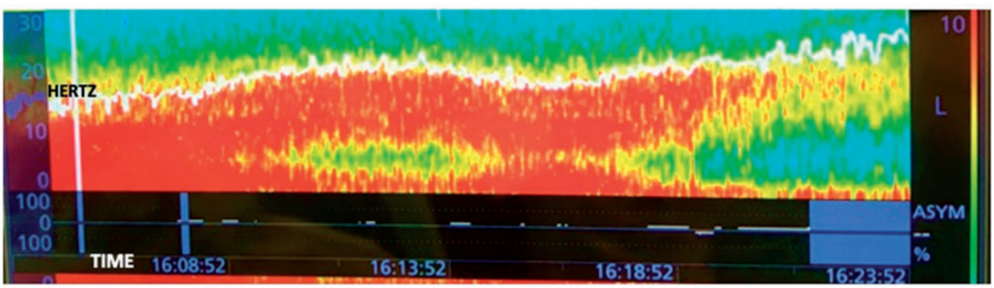

Figure 1. Representative image of a spectrogram showing the density spectral array including the spectral edge frequency (SEF) value. The area below the upper white line shows the SEF and it also represents the SEF value. The y-axis represents the frequency (Hz) and the x-axis shows the time (h:min:s). The colour version of this figure is available at: http://imr.sagepub.com.

Table 1. Inclusion and exclusion criteria for this narrative literature review.

Inclusion criteria	Exclusion criteria
Research participants $\geq$18 years	Research participants $<$18 years
Randomized controlled trials and observational studies	Full text of articles not available
Articles $\leq$11 years old	Articles $>$11 years old
Quantitative studies	Qualitative studies
Approval from an ethics committee	Focus on intensive care
General anaesthesia	Sedation
Written in English	Studies performed on animals

articles identified. Papers where SEF techniques were used to assess clinical intraoperative effects were included. Selection of papers and subsequent data extraction were performed independently by two authors (A.B. and K.H.). Consensus was reached on final article inclusion and data extraction by discussion among all of the authors. A standard data extraction matrix was compiled manually for study information, which included references, year of publication, author, depth of anaesthesia method and anaesthetics used.

This narrative review included six randomized controlled trials (RCTs) and five observational studies (see supplementary materials, Appendix 2) in which SEF was measured intraoperatively.[15–25] The studies covered various types of surgery performed under general anaesthesia, which was induced and maintained in numerous ways. In two studies, to achieve adequate depth of anaesthesia, anaesthesia was induced with midazolam. Other studies selected propofol or inhalational anaesthetic agents. Two studies covered the impact of Remifentanil on the value of SEF and compared different age groups. Table 2 presents the type of study, number of participants, anaesthetic agents and SEF values for the 11 studies.[15–25]

SEF and different anaesthetic agents

Desflurane, sevoflurane and isoflurane. Two RCTs aimed to investigate SEF in various age groups when inhalational anaesthetic agents were administered at 1 minimum alveolar concentration (MAC).[16,17] One study compared the value of SEF among young, middle-aged and elderly patients.[16] The results showed that 1 MAC desflurane affords a lower SEF value than 1 MAC sevoflurane (12.53 Hz versus 14.42 Hz).[16] Younger participants generally had lower SEF values regardless of whether desflurane or sevoflurane was administered (Table 3).[16] From the results obtained by the other study,[17] the value of SEF for desflurane and isoflurane appeared to have been higher in elderly patients (69.5–83.5 years) than in younger adult and middle-aged patients (26.9–53.9 years). However, the SEF value was higher in the group of elderly patients when sevoflurane was administered.[17] This result emerged at a lower frequency for 1 MAC desflurane than for 1 MAC sevoflurane or isoflurane.[17] SEF values increased with patient age (40–90 years) for all inhalational anaesthetic agents.[17] The previous showed that if the value of MAC was kept at 1 for sevoflurane and desflurane, no burst suppression or epileptiform discharge occurred.[16]

In an observational study,[18] 70% nitrous oxide (N_2O) was added to general anaesthesia with isoflurane to see if it had any impact on the SEF values. SEF values were observed for 1 h from induction of anaesthesia to administration of N_2O and values of 13.1 ± 1.1 Hz were observed.[18]

Table 2. Summary of the 11 studies included in this narrative review of the evidence of the effect and reliability of spectral edge frequency (SEF) for assessing the depth of anaesthesia in adult patients under general anaesthesia.[15–25]

Author	Article	Study type	Participants	Anaesthesia	Value of SEF, Hz
Liu et al. 2016[25]	A comparison of five different algorithms for EEG signal analysis in artifacts rejection for monitoring depth of anaesthesia	Comparative observational study	10	General anaesthesia	Unclear
Tsukamoto et al. 2020[17]	Age-related effects of three inhalational anaesthetics at one MAC on electroencephalogram waveform	RCT	60 (40 adults included)	General anaesthesia with isoflurane, desflurane or sevoflurane	Mean $\pm$ SD for adults: 12.2 ± 1.3 Elderly participants (69.5–83.5 years): 13 ± 1.6
Fan et al. 2011[23]	Comparison of EEG approximate entropy and complexity measures of depth of anaesthesia during inhalational general anaesthesia	Comparative observational study	23	General anaesthesia with isoflurane and fentanyl	0.5 Hz = 0 30 Hz = 100 Mean (of three values): 53.3–69.7
Miyake et al. 2010[19]	Effect of remifentanil on cardiovascular and bispectral index responses following the induction of anaesthesia with midazolam and subsequent tracheal intubation	RCT	60	General anaesthesia with midazolam and remifentanil	12–23 Hz after intubation
Hayashi et al. 2010[24]	Electroencephalographic changes in the late cardiopulmonary bypass period are not reflected in the bispectral index	Comparative observational study	11	General anaesthesia with propofol and remifentanil	10.5 ± 1.8–14.5 ± 1.0
Kanazawa et al. 2017[16]	Electroencephalographic effect of age-adjusted 1 MAC desflurane and sevoflurane	RCT	116	General anaesthesia with desflurane or sevoflurane	10–17 Hz at 1 MAC

(continued)

Table 2. Continued.

Author	Article	Study type	Participants	Anaesthesia	Value of SEF, Hz
	in young, middle-aged and elderly patients				
Miyake et al. 2010[21]	Electroencephalographic response following midazolam-induced general anaesthesia: relationship to plasma and effect-site midazolam concentrations	RCT	40	General anaesthesia with midazolam	13–25 Hz
Linstedt et al. 2012[22]	Light levels of anaesthesia after relaxation for tracheal intubation – comparison of succinylcholine and cis-atracurium	RCT	65	General anaesthesia with fentanyl and propofol	7–24 Hz
Touchard et al. 2020[15]	Propofol requirement and EEG alpha band power during general anaesthesia provide complementary views on preoperative cognitive decline	Cohort study	42	TIVA/TCI of propofol and remifentanil or sufentanil	8–13 Hz
Kuizenga et al. 2018[20]	Test of neural inertia in humans during general anaesthesia	RCT	36	General anaesthesia with sevoflurane or propofol with/without remifentanil	Propofol: 9–22.5 Hz Sevoflurane: 10–23 Hz
Hagihira et al. 2012[18]	The impact of nitrous oxide on electroencephalographic bicoherence during isoflurane anaesthesia	Comparative observational study	20	Isoflurane, nitrous oxide and fentanyl with 70% nitrous oxide added 1 h after induction of anaesthesia	6.8 ± 2.0–14.2

EEG, electroencephalogram; MAC, minimum alveolar concentration; RCT, randomized controlled trial; TIVA, total intravenous anaesthesia; TCI, target-controlled infusion.

Table 3. Spectral edge frequency (SEF) values in different age groups at 1 minimum alveolar concentration desflurane or sevoflurane.[16]

SEF values obtained with:	Young (22–28 years)	Middle-aged (53–65 years)	Elderly (66–80 years)
Desflurane	≈12 Hz	≈13 Hz	≈12.5 Hz
Sevoflurane	≈14 Hz	≈16 Hz	≈15 Hz

Thereafter, N_2O was added and 10 min later the SEF value had fallen to 6.8 ± 2.0 Hz.[18] Over 30 min, the value of SEF increased slowly and when administration of N_2O stopped, it then rose to the same levels as before the N_2O was supplied.[18]

Remifentanil and midazolam. A previous study examined whether remifentanil had any effect on SEF values in general anaesthesia using midazolam.[19] The patients were divided into three groups based on how much remifentanil was administered (group S: 0.1 μg/kg per min; group M: 0.2 μg/kg per min; group L: 0.5 μg/kg per min).[19] Five minutes after induction, the remifentanil infusion was started and immediately before this, SEF values between 17.9 and 22.6 Hz were observed.[19] SEF values barely changed in the groups after induction with midazolam (0.2 mg/kg), the mean being 19.2 Hz (range, 15.6–21.5 Hz) during the 10 min in which SEF values were recorded.[19] All the patients lost consciousness and when their level of consciousness was assessed using the Observer Assessment of Alertness/Sedation Scale, every patient scored one point out of five.[19] The SEF value decreased more in group L before laryngoscopy, as well as 1–3 min after intubation.[19] There were no differences among the groups after 4–10 min. After intubation, the remifentanil infusion was reduced to 0.05 μg/kg/min in all three groups.[19]

An RCT studied whether remifentanil administered at varying dosages had any impact on SEF values during general anaesthesia with propofol and sevoflurane.[20] The study showed that SEF values decreased when remifentanil was used (target control infusion).[20]

Another RCT studied changes in SEF resulting from different concentrations of midazolam.[21] The patients were divided into two groups and were given 0.2 mg/kg or 0.3 mg/kg midazolam.[21] The study shows that, in the first measurement, SEF was in the range of 15–25 Hz. This barely changed for 60 min, remaining within a range of 17–24 Hz in both groups. During anaesthesia, concentrations of protein-bound and non-protein-bound midazolam were measured seven times (after 5, 10, 15, 20, 30, 45 and 60 min) and compared with the EEG.[21] No association between SEF and midazolam concentrations was found.[21]

Depolarizing and non-depolarizing muscle relaxants. An RCT compared succinylcholine (SUC) and cisatracurium (CIS) in terms of their effect on inappropriate light levels of anaesthesia (ILLA) by monitoring the SEF values of patients.[22] To assess ILLA, one of the patient's arms was isolated with a tourniquet to prevent SUC and CIS from reaching the arm.[22] ILLA was assessed as 'no response', 'spontaneous movement' or 'hand squeeze requested'.[22] In the waking state, the SUC group showed values of 20 ± 4 Hz and CIS group 21 ± 3 Hz.[22] After induction with 2 mg/kg of propofol, the SEF value decreased.[22] When the corneal reflex ceased, the frequency decreased to 12 ± 4 Hz (from 14 ± 4 Hz).[22] After muscle relaxation, the group receiving SUC had lower SEF values (10 ± 3 Hz) than the CIS group (13 ± 4 Hz).[22] The authors found that in the SUC group, eight of 30 patients (27%) had 11 episodes of ILLA, while in the CIS group, 24 of 35 patients (69%) had 31 episodes of ILLA.[22] The same RCT also measured the reliability of SEF (Table 4).[22] Reliability was assessed in terms of specificity and sensitivity and the study calculated that SEF had a specificity of 47–68% and sensitivity of 80–92% (Table 5).[22]

Level of complications related to anaesthesia depth

Four of the 11 articles had no patients that experienced intraoperative awareness. All four studies involved either interviews or using questionnaires to investigate patients' awareness.[16,19,21,22] In one of the studies, two patients appeared to have been dreaming during surgery and conveyed this information immediately afterwards in the postanaesthetic care unit.[19] These dreams were pleasant ones and appeared to be unrelated to the surgery or anaesthesia.[19] The other articles did not investigate awareness.[15,17,18,20,23–25]

Only one article studied how propofol affected a patient with cognitive impairment during surgery.[15] The study described patients with cognitive impairment that needed a lower dosage than patients with good cognitive function when target-controlled infusion was used.[15] A SEF range of 8–13 Hz was found to be preferable.[15] However, the study did not include all patients with cognitive impairment because they did not manage to maintain a stable SEF value.[15] There was also a risk of various stages of surgery affecting the SEF value, as described by a previous study that investigated how cardiopulmonary bypass can affect the value of SEF in various depth-of-anaesthesia monitors.[24] It emerged that at the stage when a cardiopulmonary bypass was being carried out, the SEF value fell by 4 Hz.[24] This stage was associated with hypothermia.[24]

Anaesthesia stage and SEF

A comparative observational study that compared the distinct stages involved in general anaesthesia (preanaesthesia, maintenance and recovery) using isoflurane concluded that SEF was able to indicate the transition from anaesthesia and conscious condition, but not vice versa.[23] Another observational study described how SEF

Table 4. Spectral edge frequency values for patients with or without inappropriate light levels of anaesthesia (ILLA).[22]

Time for testing of ILLA	Patients with ILLA, Hz	Patients without ILLA, Hz
Complete relaxation (hand squeeze)	13–21 (17 ± 4)	7–13 (10 ± 3)
During intubation (spontaneous movement)	11–15 (13 ± 2)	9–15 (12 ± 3)
After intubation (hand squeeze)	12–20 (16 ± 4)	9–15 (12 ± 3)

Data presented as range (mean $\pm$ SD).

Table 5. Measurement of specificity and sensitivity of a spectral edge frequency (SEF) of 12 Hz to identify inappropriate light levels of anaesthesia (ILLA).[22]

Time for testing ILLA	Specificity, %	Sensitivity, %
Complete relaxation (hand squeeze): SEF 12 Hz	68	89
During intubation (spontaneous movement): SEF 12 Hz	47	80
After intubation (hand squeeze): SEF 12 Hz	48	92

affects activities in various parts of the body by creating 'artifacts'.[25] The study performed an EEG in ten patients that underwent surgery under general anaesthesia.[25] After the artifacts were eliminated from the primary EEG, they were exchanged by computer-generated artifacts.[25] Accordingly, although all the monitoring and registration of the depth of anaesthesia were affected by the artifacts, SEF was the variable least affected.[25]

Discussion

The evidence described in this narrative review suggests that SEF varies according to which anaesthetic drugs are used. Remifentanil and the patient's age are two factors that can affect the value of SEF, while other opioids and benzodiazepine (administered separately) seem to have no effect on SEF. No patients experienced intraoperative awareness. However, this does not indicate that SEF can provide full protection against it and the number of articles in which intraoperative awareness was studied was too small to afford any certainty.

Based on the definition of reliability used in this narrative literature review, a correlation was found in only one RCT.[22] This study demonstrated that if the patient was affected by ILLA when SEF was 12 Hz, there was between 80% and 92% sensitivity of assessment and determination during full muscle relaxation under intubation and at 1 min after intubation, respectively.[22] The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) concluded that commercial devices, such as BIS™ or Entropy™, are sensitive enough to detect ILLA.[26] SBU relies on a specificity for SEF of 12 Hz between 47% and 68%,[22] which indicates a lower accepted percentage. However, this shows that SEF is not specific during ILLA. The sensitivity and specificity shown by the SEF as calculated previously indicated a coherence of spontaneous movements during surgery.[27] The previous study compared propofol with isoflurane at a higher value of SEF (14 Hz) and demonstrated a lower sensitivity (70%), but a higher specificity (88%).[27] However, most of the articles included in this narrative review presented SEF values that were similar.[15,16,19–24] None of the studies included in this narrative review identified any patients that underwent awareness during anaesthesia and surgery. Surprisingly, only the two articles written by the same research team showed a slightly higher SEF value than the other studies.[19,21] However, this may be due to several aspects of their data collection, such as somewhat differing inclusion criteria and maintenance of anaesthesia method.[19,21] Disturbances from artifacts, such as skin tonus and brain trauma, are another factor known to affect the reliability of SEF.[25]

With regard to age being a factor, two demonstrated that elderly patients appeared to have higher SEF values than adult patients $\leq$67 years of age for 1 MAC desflurane or sevoflurane.[16,17] These findings suggest that that older patients do not require as low SEF values as younger patients.[16,17] A similar result was observed by a study of propofol administered using target-controlled infusion.[15] The results demonstrated that patients with a preoperative cognitive dysfunction required a lower dosage of propofol to maintain a value of SEF between 8 and 13 Hz (a frequency interval they found optimal for general anaesthesia).[15] Two previous studies suggested that lighter anaesthesia can reduce the frequency of postoperative cognitive dysfunction.[28,29] None of the studies point to postoperative cognitive dysfunction being a negative aspect of anaesthesia; the only complication that they mention is awareness. A previous web-based study reported that the greatest fear of anaesthesia nurses was to anesthetize patients too little rather than too much.[30]

In terms of optimal frequency, none of the studies included in this narrative review demonstrated a correct interval for SEF. Previous studies used 8–13 Hz and regarded it as the optimal SEF to achieve adequate general anaesthesia.[15,31] This range was not substantiated by the other studies, most of which indicate that a majority of patients should have a higher SEF value and that it should be adapted to the patient, but also to the hypnotics used.[14,17,28] It should be noted that only one study described in this narrative review reported on the reliability and correlation regarding SEF and depth of anaesthesia.[22]

In conclusion, none of the studies included in this narrative review demonstrated a reliable SEF interval associated with adequate general anaesthesia. SEF must be adapted to the anaesthetic drug used, the individual patient's age and the patient's state while under general anaesthesia. It is clear that more research is required.

Author contributions

Study concept and design: Pether Jildenstål, Amanda Bäckström and Klara Hedman. Analysis and interpretation of data: Pether Jildenstål, Amanda Bäckström, Klara Hedman and Margareta Warren-Stomberg Drafting of the manuscript: Pether Jildenstål, Amanda Bäckström, Klara Hedman and Margareta Warren-Stomberg. Critical revision of the manuscript for important intellectual content: Pether Jildenstål, Amanda Bäckström, Klara Hedman and Margareta Warren-Stomberg. Obtained funding: NA. Study supervision: Pether Jildenstål, Amanda Bäckström and Klara Hedman.

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Supplemental material

Supplemental material for this article is available online.

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