Original Article

Correlation between bispectral index, end-tidal anaesthetic gas concentration and difference in inspired–end-tidal oxygen concentration as measures of anaesthetic depth in paediatric patients posted for short surgical procedures

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ABSTRACT

Background and Aims: Measurement of end-tidal anaesthetic gas concentrations (ETAG) is currently a pragmatic indicator for monitoring anaesthetic depth. We aimed to assess the performance of ETAG for sevoflurane (ETAG-sevo) with bispectral index (BIS) and difference between inspired and end-tidal oxygen concentration (Fi–Et)O_2% in measuring anaesthetic depth in toddlers and preschool children. Primary outcome was to correlate BIS with ETAG-sevo. Secondary outcome was to correlate (Fi–Et)O_2% with ETAG-sevo and to derive cut-off value of (Fi–Et)O_2%which corresponds with light planes of anaesthesia [minimum alveolar concentration (MAC <0.6)]. **Methods:** Thirty patients between 1 and 5 years of age undergoing short procedures were included. ETAG, MAC, BIS and (Fi–Et)O_2% were measured at intubation, maintenance phase, last 15 min of surgery, end of surgery, extubation, recovery. Pearson's correlation coefficient was used to measure correlation. Receiver operating characteristic (ROC) curves were used to derive cut-off value of (Fi–Et)O_2% which corresponded with MAC <0.6. **Results:** BIS correlated poorly with ETAG at all time intervals. Significant correlation was seen between (Fi–Et)O_2% and ETAG at intubation ($P = 0.042$), last 15 min of surgery ($P = 0.019$) and end of surgery ($P = 0.001$). Cut-off value >7 was obtained for (Fi–Et)O_2% corresponding to MAC <0.6 at extubation with area under ROC curve0.955 (95% confidence interval 0.811–0.997), with sensitivity 0.8571 and specificity 1.00. **Conclusion:** BIS was an unreliable measure of anaesthetic depth. (Fi–Et)O_2% values >7 corresponded with light planes of anaesthesia.

Key words: Anaesthesia, awareness, bispectral index, oxygen consumption, paediatric, sevoflurane

INTRODUCTION

Awareness during surgery is undesirable and has long-term behavioural and psychological effects. The incidence of awareness during anaesthesia in children has been reported to be four to eight times higher than in adults.[1] Moreover, preverbal children cannot express the intraoperative recall of events which may be well-elicited in adults. In December 2016, the Food and Drug Administration of USA issued a 'Drug Safety Communication' warning for administering of general anaesthetic and sedation drugs in children aged <3 years which can affect brain development.[2] This is a further justification for needing to know the level of anaesthetic depth in paediatric patients.

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Measurement of end-tidal anaesthetic gas concentrations (ETAGs) provides real-time feedback and facilitates target-controlled titration of volatile anaesthetic agent administration and is currently a pragmatic indicator for monitoring anaesthetic depth.[3] Bispectral index (BIS) monitoring, which is based on an algorithm developed from adult electroencephalogram (EEG) values, is being used to measure anaesthetic depth in adults. However, due to the rapidly developing infant and toddler brain and increased neuronal synaptic activity, its use in children is controversial.[4] We hypothesised that ETAG for sevoflurane (ETAG-sevo) would not correlate with values of BIS in very young children. Inhalational anaesthetics decrease the cerebral metabolic rate and cerebral oxygen consumption.[5] Hence, a deeply anaesthetised patient will have a decreased rate of oxygen consumption, whereas lighter planes of anaesthesia will increase the cerebral oxygen consumption.[6] This has been elicited in various studies using cerebral oximetry by the method of near-infrared spectroscopy (NIRS).[7,8] Under static anaesthetic conditions of immobility, fixed inspired oxygen concentration, fixed inspired anaesthetic agent concentration and use of muscle relaxation, oxygen consumption depends on other factors such as pain, age, temperature and haematocrit.[6]Thus, during short surgical procedures where these factors are under controlled conditions, fluctuations in end-tidal oxygen concentration (EtO_2%) under anaesthesia could be translated to increased cerebral oxygen consumption due to light plane of anaesthesia. A simple method to measure oxygen consumption during anaesthesia would be to measure the difference between inspired and end-tidal oxygen concentration (Fi−Et)O_2%.

We aimed to assess the performance of ETAG-sevo with BIS and (Fi−Et)O_2% in measuring anaesthetic depth in toddlers and preschool children receiving general anaesthesia for short paediatric surgical procedures.

METHODS

It was a prospective observational pilot study conducted over a period of 6 months. The study was approved by the Institutional Ethics Committee. The primary outcome measure was to correlate BIS with ETAG-sevo at various time intervals intraoperatively. Secondary outcome measures were to correlate difference in inspired–end-tidal oxygen concentration [(Fi−Et)O_2%] with ETAG-sevo and to derive cut-off value of ((Fi−Et)O_2%which corresponds with light planes of anaesthesia [minimum alveolar concentration (MAC <0.6)].

The study protocol was explained to the parents/legal guardians during the pre anaesthetic check and consent was obtained. A total of 30 children between 1 and 5 years of age, posted for general surgical procedures with expected duration of upto 90 min, were recruited from the preanaesthetic clinic. Surgeries included abdominal and urological procedures. All patients had an American Society of Anesthesiologists physical status of I or II. Syndromic children, those with dysmorphism, neurological disease, cerebral palsy, seizure disorders, on antiepileptic medications, febrile kids with temperature >38°C, those with attention deficit hyperactivity disorder, sepsis, anaemia with haematocrit less than 30, children posted for laparoscopic procedures and surgeries having major fluid shifts or expected blood loss >20% estimated blood volume were excluded.

After confirming adequate nil per oral (NPO) status, all children were premedicated with intravenous (IV) midazolam 0.1 mg/kg, 5 min prior to induction. Administration of premedication was under controlled conditions in the preoperative holding area. The children were then wheeled into the operating room, and monitors such as pulse oximeter, noninvasive blood pressure (NIBP), electrocardiography, skin temperature, capnometer (measured from Drager Perseus® A500 anaesthesia delivery system, Dragerwerk AG and Co. Lubeck, Germany) were attached. BIS sensor electrodes (Aspect Medical systems, Newton, MA, USA) were applied over the patient's forehead after cleaning the forehead thoroughly with an alcohol swab. This was connected to BIS-A-2000 monitor on the Drager Perseus® machine. Electrode impedances were found to be less than 2 kW before data acquisition started. Data were collected by the principal investigator. Hence, consistency was maintained. Baseline BIS, heart rate, NIBP and skin temperature values were noted at this time point, prior to the induction of anaesthesia. Patients were then preoxygenated with 100% oxygen for 5 min at flows of 4 L/min using circle absorber. Anaesthesia was induced with incremental sevoflurane upto 8% till MAC of 1–1.4 was achieved (MAC values were adjusted for age). All children received IV Inj. fentanyl 2 μg/kg and muscle relaxation was achieved with Inj. atracurium 0.6 mg/kg. Patients were then intubated with appropriately sized endotracheal tube. Following intubation, 5 min later, intubation values of MAC, BIS, ETAG-sevo concentration (%),

dial agent concentration (%), FiO_2(%) and EtO_2(%) were noted. Following this, all children received a caudal block with 1 ml/kg of 0.25% bupivacaine. In addition, IV analgesia (Inj. paracetamol 15 mg/kg) was also administered. Anaesthesia was maintained with O_2 + N_2O (50:50), sevoflurane using the circle absorber and controlled ventilation at flows of 0.5 L/min maintaining MAC between 0.9 and 1.4. Intermittent atracurium 0.2 mg/kg IV was given when required.Values of MAC, BIS, ETAG-sevo concentration (%), dial agent concentration (%), FiO_2(%) and EtO_2(%) were noted at the following time intervals thereafter: maintenance phase of anaesthesia (15 and 30 min after noting down intubation values of study parameters), last 15 min of surgery (start of skin closure), end of surgery (skin dressing), extubation and recovery. At least 15 min of equilibration time was allowed after each new ETAG-sevo or change in FiO_2(%) was made. At the start of skin closure (after noting down values of outcome measures at last 15 min of surgery), inhalational agent was shut off and slowly the MAC values tapered down to 0. At the time of skin dressing and after ensuring equilibration time was achieved, 'end of surgery' values of study parameters were noted. Fresh gas flow was then increased to 4L/min and FiO_2(%) was increased to 100%. After equilibration time, residual neuromuscular blockade was reversed with neostigmine 50 μg/kg and atropine 20 μg/kg IV and patients were extubated. 'Extubation' values of parameters were then noted. Recovery for the study was defined as coughing, eye opening and purposeful spontaneous movements. Here, 'recovery' values of outcome measures were noted. Adequate immediate recovery constituted the end of the study and patients were shifted to the postanaesthesia care unit as per routine OT protocol.

Sample size was estimated from a previous study[9] in which the correlation between steady-state end-tidal sevoflurane concentration of 3% with BIS values in 81 children between 6 months and 12 years of age was 0.518($P < 0.001$). With type 1 error at 5% level of significance and 80% power of study, sample size of 27 was obtained. To compensate for dropouts, we added 10% and hence got a sample size of 30.

Quantitative data such as age, weight, height, skin temperature, haematocrit, duration of surgery, heart rate, systolic BP, BIS, MAC, dial agent concentration (%), ETAG-sevo concentration (%) and (Fi−Et)O_2% were normally distributed and represented as mean ± standard deviation. Pearson's correlation coefficient was used to measure correlation between adjacent values of BIS, ETAG(%), MAC and (Fi−Et)O_2% at the previously specified eight different time intervals. $P < 0.05$ was required for statistical significance. Light planes of anaesthesia were defined *a priori* as MAC <0.6.[10] Davidson *et al.*[10] reported MAC- awake of sevoflurane in age group of 2 to <5 years of age to be 0.81 (0.61–1.01) [(95% confidence interval (CI)]. We selected a value of 0.6 based on the lower limit of 95% CI value to ensure all children in our study would be included when defining light planes. Receiver operating characteristic (ROC) curve analysis[11] was used to derive cut-off value of (Fi−Et)O_2% which corresponded with MAC <0.6 (end of surgery, extubation, recovery). Data were entered in Microsoft Excel and analysed using the statistical software SPSS version 19 (SPSS Inc., Chicago, IL, USA).

RESULTS

All 30 patients provided complete data and were included in the analysis. Patient characteristics and surgical procedures are listed in Table 1. Analgesia was adequate in all patients based on the clinical discretion of the attending anaesthesiologist, and all caudal blocks were successful based on lack of heart rate response to incision. Haemodynamic parameters, ETAG-sevo(%), MAC, BIS and (Fi−Et)O_2% values at various time points are depicted in Table 2. BIS correlated poorly with ETAG at all time intervals [Table 3]. (Fi−Et)O_2% correlated significantly with ETAG at intubation ($P = 0.042$), last 15 min ($P = 0.019$) and end of surgery ($P = 0.001$)

Table 1: Patient characteristics and surgical procedures

Variables	Values
Age (months)	30.6 (16.0)
Gender (male/female)	(16/14)
Weight (kg)	11.9 (3.1)
Duration of surgery (min)	70.8 (17.3)
Nasopharyngeal temperature (°C) after induction	36.3 (1.4)
Haematocrit (%)	34.6 (3.2)
Surgical procedures	*n*=30
Hernia repair	7
Orchiopexy	6
Cystoscopy	5
Hypospadias repair	4
Pyeloplasty	4
Epispadias repair	1
Ureteric reimplantation	1
Ventral hernia repair	1
Colostomy	1

Values expressed as mean (standard deviation) and numbers where applicable

Table 2: Heart rate, systolic blood pressure, end-tidal sevoflurane, MAC, BIS and (Fi−Et) O_2% values at various time points

Time points	HR	SBP	ETAG-sevo (%)	MAC	BIS	(Fi−Et) O_2(%)
Baseline	128.8 (22.1)	98.9 (20.1)	0 (0)	0 (0)	76.4 (7.1)	12.4 (5.8)
Intubation	122.9 (19.9)	96.7 (19.2)	2 (0.4)	0.8 (0.2)	42.4 (14.2)	4 (2.1)
Maintenance						
15 min	121.5 (20.3)	85 (8.8)	2 (0.3)	1 (0)	54.7 (9.8)	3.9 (1)
30 min	114.7 (19.2)	83.2 (11.7)	1.8 (0.5)	0.9 (0.1)	53.5 (8.5)	4.6 (0.9)
Last 15 min of surgery	111.4 (17.4)	86 (8.4)	1.1 (0.6)	0.6 (0.3)	65.7 (7.2)	7.4 (3.9)
End of surgery	114.3 (18.4)	88.3 (9.3)	0.8 (0.6)	0.4 (0.3)	67.9 (7.6)	8.8 (4.5)
Extubation	114.4 (23.7)	91 (11.3)	0.4 (0.4)	0.2 (0.1)	72.9 (4.3)	11.8 (5)
Recovery	115.0 (21.7)	95.6 (16.5)	0.2 (0.1)	0.1 (0)	77.3 (5.1)	13.8 (5.8)

HR – Heart rate; SBP – Systolic blood pressure; ETAG-sevo (%) – End-tidal anaesthetic concentration for sevoflurane; MAC – Minimum alveolar concentration; BIS – Bispectral index; (Fi−Et)O_2% – Difference in inspired–end-tidal O_2 concentration. [Values are mean (standard deviation)]

Table 3: Correlation between ETAG-sevo with BIS and ETAG-sevo with (Fi−Et) O_2% at various time intervals

ETAG-sevo(%)	BIS (R^2)	(Fi−Et) O_2% (R^2)
Intubation	0.273	0.372**
Maintenance		
15 min	0.285	0.306
30 min	0.017	0.087
Last 15 min of surgery	0.069	0.575*
End of surgery	0.286	0.561**
Extubation	0.235	0.296
Recovery	0.090	0.118

ETAG-sevo (%) – End-tidal anaesthetic concentration for sevoflurane; BIS – Bispectral index; (Fi−Et) O_2% – Difference in inspired-end-tidal O_2 concentration; R^2 – Pearson's correlation coefficient **Correlation is significant at the 0.01 level; *Correlation is significant at the 0.05 level

[Table 3]. Using ROC curves, a cut-off value of >6 was obtained for (Fi−Et)O_2% corresponding with MAC <0.6 (last 15 min of surgery) with area under curve (AUC) 0.995; 95% CI (0.875–1.000), $P < 0.0001$, with sensitivity 1.00 and specificity 0.9474 [Figure 1]. A cut-off value of >6 was obtained for (Fi−Et)O_2% corresponding with MAC <0.6 (end of surgery) with AUC 0.964; 95% CI (0.823–0.999), $P < 0.0001$, with sensitivity 1.00 and specificity 0.7692 [Figure 2]. A cut-off value of >7 was obtained for (Fi−Et)O_2% corresponding with MAC <0.6 (extubation) with AUC 0.955; 95% CI (0.811–0.997), $P < 0.0001$, with sensitivity 0.8571 and specificity 1.00 [Figure 3].

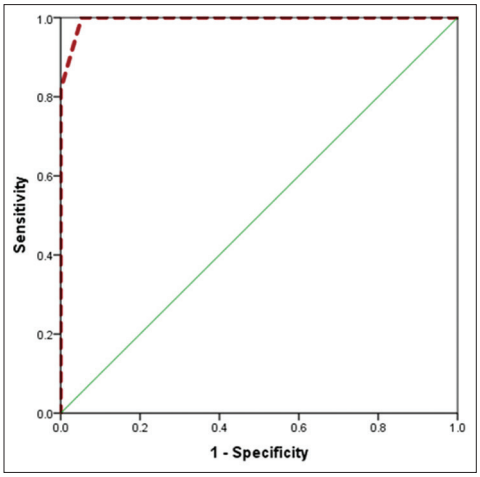

Figure 1: ROC curve for (Fi−Et)O_2% corresponding with MAC <0.6 at last 15 min of surgery. Sensitivity on *Y*-axis, 100 – specificity on *X*-axis. Sensitivity 1.00 and specificity 0.9474; area under curve = 0.995; 95% CI (0.875–1.000)

DISCUSSION

In this study, we chose children between 1 and 5 years of age as previous studies have shown younger age group to have wider variation in BIS values[4,9] and age-specific changes in MAC-awake.[10] In our study, BIS correlated poorly with ETAG-sevo at all time intervals and was not found to be reliable for monitoring the depth of anaesthesia. BIS values were higher (>60) even at MAC values of 0.9–1 (corresponding with ETAG-sevo 1.8%–2%). These results are in accordance with observations noted in previous studies where wide variations in BIS and poor correlation with vital and clinical signs have been reported.[12-15]

Multiple general anaesthetic exposures, especially at an early age, have been associated with long-term learning disabilities or delays.[16] Even brief exposures to the less mature neonatal and infant brain to anaesthetics may have neurotoxic effects.[17,18] On the other hand. there are complications associated with underdosing of general anaesthetics. A major complication of light planes of anaesthesia in children is laryngospasm. In a study to correlate BIS with airway reflexes, Davidson *et al.* reported BIS to be unreliable in preventing unwanted airway reflexes when using sevoflurane in children between 1 and 15 years of age.[19] Thus, measuring awareness in infants and toddlers is important to avoid under- or overdosing these patients to allow providers to deliver anaesthesia with more precision.

Current brain monitors in clinical anaesthesia use EEG-based indices that are graded on a scale of

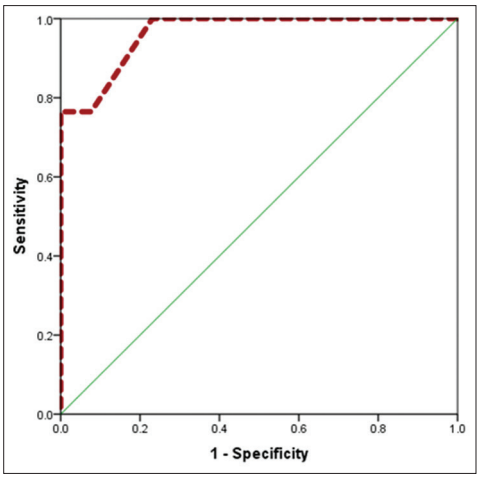

Figure 2: ROC curve for (Fi–Et)O_2% corresponding with MAC <0.6 at end of surgery. Sensitivity on *Y*-axis, 100 – specificity on *X*-axis. Sensitivity 1.00 and specificity 0.7692; area under curve = 0.964; 95% CI (0.823–0.999)

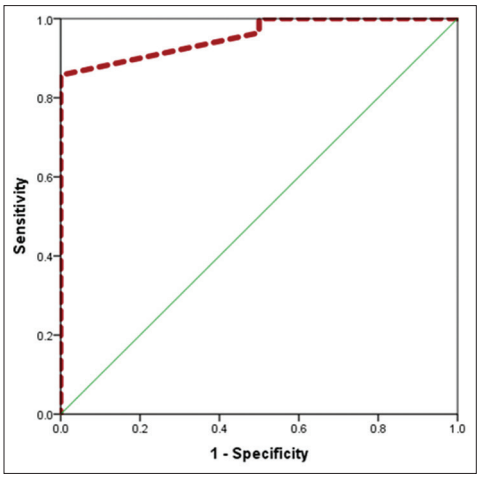

Figure 3: ROC curve for (Fi–Et)O_2% corresponding with MAC <0.6 at extubation. Sensitivity on *Y*-axis, 100 – specificity on *X*-axis. Sensitivity 0.8571 and specificity 1.00; area under curve = 0.955; 95% CI (0.811–0.997)

0 (isoelectric EEG) to 100 (fully awake and alert). These indices may show variable readings depending on three main factors, namely the general anaesthetic agent used, dose dependency of the EEG and patient age.[20] BIS monitoring is a reliable and validated method for measuring the depth of anaesthesia in adults. However, its use in children, especially infants and toddlers, has shown confounding results.[9,12,13,21,22] In a recent review,[4] authors assessed studies on the various commercially available EEG-derived devices for monitoring anaesthetic depth in children and found that the devices had reasonable correlations with doses of anaesthetic agents in older children. However, these devices were not adequately studied in infants and younger children. Although BIS was the most widely studied device, they concluded that there was no evidence to suggest that BIS was substantially superior to other devices like ETAG% or MAC in infants and younger children. EEG signals, auditory evoked potential (AEP) and facial electromyography signals as possible monitors of depth of anaesthesia are under investigation.[23] However, a recent study suggested that the AEP monitor is a poor predictor of sevoflurane concentration in infants and children.[23]

(Fi−Et)O_2% showed significant correlation with ETAG-sevo only at certain time points (intubation, last 15 min and end of surgery). This could be because this study was not powered to detect this. Hence, the robustness of this method for measuring anaesthetic depth needs further validation with a larger sample size. Using the criterion of (Fi−Et)O_2%>7, excellent sensitivity and specificity are achievable corresponding to (MAC <0.6) using ROC curves. This method had good AUC and was highly significant ($P < 0.001$). However, this difference in inspired and end-tidal oxygen is reflective of global (whole body) and not just cerebral oxygen consumption. It is known that the oxygen consumption index depends on the depth of sedation.[24] As anaesthetics reduce the oxygen consumption, patients in lighter planes or awake patients will have a higher oxygen consumption and this difference in (Fi−Et)O_2% will increase steadily. The more challenging aspect, however, are all the different variables that go into determining oxygen consumption beyond anaesthetic depth. This includes age of patient, weight, pain, cardiac output, temperature, sympathetic stimulation, stress and so on. In our study, all patients received a caudal block in addition to IV analgesia. Adequacy of analgesia was judged by lack of heart rate response to incision and the clinical discretion of the anaesthesiologist. The impact of regional anaesthesia and analgesia further reduces global oxygen consumption by excluding the confounding factor of pain, stress and sympathetic stimulation. None of the patients in the study was anaemic or hyper- or hypothermic. All these factors strengthen our hypothesis of inspired–expired oxygen concentration as a measure of cerebral oxygenation under controlled anaesthetic conditions.

This (Fi−Et)O_2% difference is a simple method to deduce oxygen consumption. Measuring oxygen consumption may need sophisticated anaesthesia workstations, may not be feasible in routine practice and does not provide real-time values. Anaesthesia delivery in poor resource settings may not have the facilities for monitoring MAC and ETAG. However,

most multipara monitors in use today even in these settings provide values of inspired and end-tidal oxygen concentration. Hence, as the difference between (Fi−Et)O_2% increases to values above 7, it may alert the anaesthesiologist that the patient may be in lighter planes. We maintained MAC between 0.9 and 1.4 during maintenance phase. This range was chosen to study the corresponding (Fi−Et)O_2%values as this MAC range is indicative of adequate depth of anaesthesia based on the study by Davidson *et al*.[10] In deeper planes of anaesthesia, the (Fi−Et)O_2% values remained below 6 and decreased proportionally corresponding to the increased anaesthetic depth [Table 2]. However, this method will not be reliable in patients having other factors complicating anaesthetic management like sepsis, anaemia, hypo- or hyperthermia, low or high cardiac output states where the oxygen consumption is likely to be variable. This method may have questionable efficacy in laparoscopic and thoracoscopic procedures where carbon dioxide insufflation affects gas exchange and oxygenation. A drawback of using (Fi−Et)O_2% values for measuring anaesthetic depth is in situations where inspired oxygen concentrations are changed like after induction, where FiO_2% is usually decreased, during recovery where FiO_2% is increased or during maintenance phase if concentrations are changed. It is recommended to wait till steady-state inspired oxygen concentrations are achieved after any change in FiO_2%. We waited for 15 min to achieve this equilibrium. However this would depend on the flows one is using at that time and thus the time interval would be far more variable. One should be cautious while interpreting (Fi−Et)O_2% values in these circumstances. Due to the lag period, real-time monitoring of (Fi−Et)O_2% values will not be possible in these phases. In a study done by Kim *et al*.[9] in 81 children between 6 months and 12 years of age, BIS values were correlated with three steady-state end-tidal sevoflurane concentrations (ETAG-sevo) of 2%, 3% and 4%. The average of the consecutive 5-min average BIS values was recorded at each ETAG-sevo. BIS decreased significantly when ETAG-sevo increased from 2.0% to 3.0%, but there was a paradoxical increase in BIS values when ETAG-sevo increased from 3.0% to 4.0%. BIS values showed a wide variation in the same ETAG-sevo and the age itself was considered to be a factor affecting the BIS values. In our study, the time points did not include fixed steady-state ETAG-sevo concentrations and we obtained a single BIS value after equilibration. Our age group (1–5 years) was more homogeneous compared with Kim *et al*.'s study.

The use of this method in neonates and infants was not studied. Considering their high oxygen consumption, it is our anecdotal opinion that this method may not be reliable for monitoring anaesthetic depth in this age group.

More recently, NIRS has been evaluated as a safe and noninvasive method for measuring the effects of anaesthetics on the suppression of awareness. It has been reported to be sensitive to different anaesthetics such as propofol, sevoflurane and desflurane at sedation and surgical doses and is an attractive subject for further research in the field of depth of anaesthesia monitoring.[8]

New research in the laboratories of Drs. Purdon and Brown have recently discovered unique, highly structured oscillations in the EEG that arise abruptly at the onset of loss of consciousness (LOC) and persist with patient unconsciousness during general anaesthesia.[25] Since then, the laboratory has characterised these abrupt changes in brain states for a variety of general anaesthetics, over a range of patient ages.[26] These spectral anaesthetic signature (SAS) patterns, which are unique to each general anaesthetic, may serve as objective neurophysiological endpoints that can be used to guide drug administration. These concepts are directives for future research. They are currently being applied to patient care through development of a closed-loop anaesthetic monitor with real-time power spectrum biofeedback that helps drive anaesthetic dosing based on maintenance of the biomarkers of LOC (i.e., the SAS).

CONCLUSION

BIS was unreliable in measuring the depth of anaesthesia in toddlers and preschoolers. (Fi−Et) O_2 values >7 corresponded with light planes of anaesthesia. This is a simple and economical tool and provides real-time data which can be used to avoid light planes although it has its limitations. Further studies to support this observation are warranted.

Disclosure

None.

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Conflicts of interest

There are no conflicts of interest.

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