Validation of Perfusion Index to Measure the Depth of General Anesthesia in Patients Undergoing Ophthalmic Surgery: Before-and-After- Study

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Abstract

Background: Intra-operative awareness is a large medico-Legal issue to the anesthesiologists and can lead to a postoperative psychosomatic dysfunction so it must be prevented under all possible settings by monitoring the depth of anaesthesia. Among multiple modalities of monitors.

Aim: our study compares between Bispectral index and perfusion index. the prediction probability of perfusion index compared to bispectral index, as a gold standard, in detecting different stages of anaesthesia using propofol for induction and sevoflurane for anaesthesia maintenance.

Methods: The study involved 50 adult patients of both sexes undergoing elective ophthalmic procedures under general anesthesia, This intervention before and after, clinical study was conducted in the Theatre of Ophthalmic Surgery - Kasr-Alainy Hospitals - Cairo University Hospitals. Diagnostic intervention using different concentrations of sevoflurane to have different degrees of depth of anaesthesia that were monitored using PI readings was compared to BIS readings.

Results: Our primary outcome showed significant changes in perfusion index values (PI) to changes in depth of anaesthesia while BIS values decreased from 70 to 60. The difference between baseline value (soon after intubation) and 10 minutes later (BIS reading of 60 compared to 70) with significant P value (0.006) and AUROC more than 0.62, sensitivity 78 % ,specificity 42 % and accuracy 60 %.Our secondary outcomes were The correlation between change in PI and BIS immediately after induction of general anesthesia When BIS reading is 70, 20 minutes after intubation when BIS reading is 40 and 30 minutes after intubation when BIS reading is 30.

Conclusion: compared with the BIS, the PI can track changes in the depth of anesthesia in adult patients undergoing ophthalmic surgeries under sevoflurane anesthesia with the surges and drops in the PI compared with its respective baseline are highly informative regardless of whatever this baseline value was.

Keywords: Depth of Anaesthesia - Bispectral Index - Perfusion Index

Introduction

One of the goals of modern anesthesia is to assess the depth of anesthesia in order to avoid awareness without giving the patient anesthetic overdose. So one of the achievements of modern anesthesia is the ability to monitor the depth of anesthesia using clinical signs and non clinical methods. The overall incidence of intraoperative recall is approximately 0.2–3%[(1)], which may be > 40% with high-risk patients such as multiple trauma, cesarean section, cardiac surgery, and hemodynamically unstable patients[(2)]. Intraoperative awareness is a large medico-Legal issue to the anesthesiologists and can lead to a postoperative psychosomatic dysfunction so it must be prevented under all possible settings[(3)].

There are approximately 1 to 2 cases of intraoperative awareness per 1000 administrations of general anaesthetic, and among those with intraoperative awareness with recall, 43% develop posttraumatic stress disorder[4,5]. The primary contributing factor for intra operative awareness is related to inadequate anaesthetic dosing for a given procedure. This can occur when

1. The anesthesia provider does not adequately dose the anesthetic
2. Patients have elevated anesthetic requirements, which are previously unknown.
3. Patients are too ill to tolerate adequate levels of anaesthesia (ie, American Society of Anesthesiologists class IlI-V patients or emergent surgery).
4. The anaesthesia delivery system malfunctions[5,6].

A successful GA is defined as a reversible triad of hypnosis, analgesia, and abolition of reflex activity. In a balanced anaesthetic technique that uses multiple drugs, the classical stages of anaesthesia are concealed.[7] An inadequate GA can lead on to intraoperative awareness with or without recall, while overdosage results in delayed recovery and possible postoperative complications.

Bhargava et al. [7] described a detailed classification of anaesthetic state based on the use of a sole inhalational anaesthetic agent diethyl ether. The signs of this classical Guedel's classification depended on the eyelash reflex, respiration, eyeball movements, pupillary size, and muscular movements among others.

Clinical monitoring of depth of anesthesia can be achieved via physiological parameters such as heart rate, blood pressure, and respiratory rate (autonomic reflexes) and patient movement (somatic reflex); these reflexes depend on acute changes in sympathetic tone for detection of light planes of anesthesia.

Beside clinical monitoring,there are other methods used in assessing the depth of anesthesia including; Isolated forearm technique, Spontaneous surface electromyogram, Lower oesophageal contractility (LOC), Heart rate variability, Brain electrical activity monitoring (including bispectral index) and Evoked brain electrical activity.

Signs of inadequate general anesthesia develop in response to painful stimuli are movement, increased breathing or heart rate or increased blood pressure [8]. During general anesthesia, the stress response is decreased by hypnotics and analgesics. The heart rate (HR) and the tone of the smooth vascular muscles are controlled by the sympathetic nervous system[9,10]. It is known that the autonomic fluctuations caused by pain and stressful stimuli reduce the plethysmographic amplitude of the peripheral finger[11]. Fast SNS reactions are mediated neuronally, Slower but more sustained sympathetic responses are due to circulating adrenaline and spilled noradrenaline from the nerve endings[12].

The degree to which vasomotor tone changes is reliant on many factors, including drug type, dosage, route, as well as type and severity of surgical stimulus and pain. The patient's own co-morbidities as well as natural physiological variance between patients also play a part.

The vasomotor tone can be quantified by the Perfusion Index (PI), a metric that becomes the pulse plethysmograph. The perfusion index is a ratio of the pulsatile to the non-pulsatile signal obtained from the pulse plethysmograph[13] and is obtained from future modern pulse oximetric relationships. The perception variable that rights the PI is the degree of emotional arterial vasodilation. This change is minimal in vasoconstriction, but also in vasodilation. Therefore, the perfusion index is that of vasoconstriction and vasodilation[14].

In the last several decades, the bispectral index (BIS), derived from electroencephalogram (EEG), has become one of several technologies often used to monitor the depth of anesthesia[15]. With a normalized score from 0 to 100, BIS is intended to replace or supplement the classic anesthesia-depth staging system and has been validated to monitor the anesthesia depth in adults and children older than 1 year[16]. BIS can be a very useful tool in guiding the anesthetic dose and implementing individualized anesthesia[17]. It helps to reduce risk of intraoperative awareness and to improve the safety of recovery from anesthesia[18].

However, BIS monitoring is not routinely used in all patients for its inconvenience to apply and the high cost of equipment and supplies[19].

The BIS monitor is the first quantitative electroenchephalogram (EEG) index used in clinical practice as a monitor to assess the depth of anesthesia. It consists of a sensor, a digital signal converter, and a monitor. The sensor is placed on the patient's forehead to pick up the electrical signals from the cerebral cortex and transfer them to the digital signal converter. A BIS score quantifies changes in the electrophysiologic state of the brain during anesthesia. In patients who are awake, a typical BIS score is 90 to 100. Complete suppression of cortical activity results in a BIS score of 0, known as a flat line and surgical anesthesia 40 to 60.

PATIENTS AND METHODS

This intervention before and after, clinical study was conducted in the Theatre of Ophthalmic Surgery - Kasr-Alainy Hospitals - Cairo University Hospitals.

The Research Committee of Cairo University's Anesthesiology Department and the Research Ethical Committee of Cairo University's Faculty of Medicine provided ethical permission for this work. The study involved 50 adult patients of both sexes undergoing elective ophthalmic procedures under general anesthesia.

Eligibility Criteria

a- Inclusion criteria:

1. ASA I and II.
2. Patients undergoing elective ophthalmic surgeries under general anesthesia.
3. Age (20-65) years.
4. Both sexes.

b- Exclusion criteria:

1. History of brain injury or cerebrovascular disease.
2. History of electroencephalographic abnormality (e.g., epilepsy or congenital low-voltage EEG.
3. Patient with peripheral vascular disease.

Study Procedures

Study Protocol

1. Preoperative preparation
2. Pre-operative assessment and evaluation as all patients were admitted for careful history taking, clinical examination and investigations that include complete blood picture, Liver function tests (ALT, AST, serum albumin and serum bilirubin)and kidney function tests (serum urea and creatinine),coagulation profile and ECG.
3. No premedication was administered before induction of anesthesia.

On arrival in the operating theater, intravenous cannulation was secured and routine monitoring of ECG, oxygen saturation and blood pressure were started. The BIS was recorded continuously by using an (Aspect Medical Systems, Inc., Mansfield, MA, USA). PI monitoring was done by using Radical 7™ Oximeter (Masimo Corp., Irvine, CA, USA). The oximeter probe which was used to monitor the perfusion index was attached to the middle finger tip of the hand contralateral to the site of BP monitoring and was wrapped in a towel to minimize heat loss and contamination by ambient light.

Anesthesia was induced with intravenous fentanyl 1ug/kg and 2.5mg/kg propofol until loss of the verbal contact, 0.5mg/kg atracurium was administered. Tracheal intubation was attempted after complete muscle relaxation, maintenance of anesthesia by sevoflurane 2% and atracurium 0.1mg/kg every 20 minutes.

The inspired and end-tidal concentrations of inhalational agents, were measured by using a Datex Capnomac monitor.

Starting from Immediately after induction of anesthesia BIS reading at 70 was taken while both readings of the end-tidal concentration of inhalational anesthetic and PI taken at this BIS reading.
10 minutes after induction of anesthesia, the end-tidal concentration of inhalational anesthetic was adjusted at 1-1.5 MAC for 10 min to keep BIS at 60. When BIS values are stabilized, the inspired concentrations of sevoflurane were increased at 0.5 MAC increment (1,1.5,2) till BIS decreased from 60 to 40 and then decreased to 1 MAC in same graded manner till BIS increase to 60 again. For increment or decrement, the concentration was kept constant for 10 min. The BIS and PI values were recorded at the end of 10 min interval at each end-tidal concentration.

Data collection

During the intraoperative period, heart rate, systolic, diastolic, mean arterial blood pressure, SpO_2, were continuously measured. PI and BIS were recorded at: baseline immediately after induction of anesthesia when BIS reading is 70 (T1), 10 minute after endotracheal intubation when BIS reading is 60 (T2), when BIS decreased from 60 to 40 (T3) and when BIS decreased from 40 to 30 (T4).

Intervention:

Diagnostic intervention using different concentrations of sevoflurane to have different degrees of depth of anaesthesia that were monitored using PI readings was compared to BIS readings.

Potential risks:

1. Awareness with light anaesthesia,
2. Hemodynamic instability with deep anaesthesia

Study outcomes

a- Primary outcome

The correlation between change in PI and BIS 10 minutes after tracheal intubation When BIS reading is 60.

b- Secondary outcome(s)

1. The correlation between change in PI and BIS immediately after induction of general anesthesia when BIS reading is 70.
2. The correlation between change in PI and BIS 20 minutes after intubation when BIS reading is 40.
3. The correlation between change in PI and BIS 30 minutes after intubation when BIS reading is 30.
4. Sensitivity and specificity of change of PI in predicting depth of anesthesia
5. The changes in SBP, DBP, MAP and HR.

Sample size

The Power Analysis and Sample Size software (PASS 13 software; NCSS, LLC, Kaysville, UT, USA) is used for sample size calculation before patient enrollment. No previous clinical trials have studied the correlation between PI and BIS during general anesthesia in adults listed for ophthalmic surgeries. The sample size is based on assuming a moderate correlation (r=0.4) between the change of PI and BIS. With a power of 0.8 and two-tailed α of 0.05, a sample size of 46 patients was required. The number was increased to 50 patients to compensate for possible dropouts.

Statistical analysis

Descriptive statistics were done and numerical variables were presented as median (interquartile range) or mean (standard deviation) according to normality. Categorical variables were presented as frequencies (percentages). Shapiro Wilk normality test was done. Comparison between different variables between varying time points was performed using the Wilcoxon matched-pairs rank-sum test due to the non-normal distribution of data. Spearman's rank correlation test was done to assess the correlation between PI and other parameters. ROC curves were constructed to evaluate the diagnostic ability of PI in detecting different levels of anaesthesia depth with the BIS serving as the gold standard. Best cut-offs, sensitivity and specificity were determined. values <0.05 were considered significant. STATA 15.1 was used for the analysis

RESULTS

A total of (60) patients were enlisted for our study and subjected to different levels of end tidal sevoflurane inhalational anaesthesia 10 of them showed haemodynamic instability at last step of increasing the depth of anaethesia so this 10 patients were excluded and our research was resumed with omitting this last step to correlate the changes in PI values to BIS readings during changing the depth of anaethesia by changing end tidal sevoflurane. Demographic data and ASA status are described in **(Table 1)** expressed using median and interquartile (IQR) values.

Descriptive statistics

Table (1): Baseline characteristics for the study population (n=50)

	Median (IQR)/ Number (%)	
Age:	**Range (20-65)**	
Median	57.5	
(IQR)	(45-61)	
Gender		
Male	21	42%
Female	29	58%
ASA		
I	19	38%
II	31	62%

Table (2): Revealing significant changes in median and interquartile values of Et Sevoflurane, PI, Systolic BP, Diastolic BP and Mean ABP at different BIS readings over the time extended from tracheal intubation till 30 minutes later while Heart rate changes were not significant to changes in depth of anaesthesia levels.

	Soon after	**10 minutes after**	**20 minutes after**	**30 minutes after**	**P***
BIS reading	70	60	40	60	-
End tidal					
Sevoflurane					<0.0001
Median	1.5	2	3.5	3	<0.0001
(IQR)	(1-1.5)	(2-2.5)	(3-4)	(2-3)	<0.0001
PI					<0.0001
Median	0.8	1.2	2.56	2.08	<0.0001
(IQR)	(0.27-2.64)	(0.45-4.1)	(0.81-6.51)	(0.58-4.72)	<0.0001
Systolic BP					<0.0001
Median	129	119	110	119	<0.0001
(IQR)	(120-134)	(115-126)	(105-119)	(112-125)	<0.0001
Diastolic BP					<0.0001
Median	83	76	70	74	<0.0001
(IQR)	(80-89)	(70-80)	(60-78)	(70-80)	<0.0001
Mean BP					<0.0001
Median	97	90	84	89	<0.0001
(IQR)	(93-103)	(85-96)	(77-92)	(85-95)	<0.0001
HR					0.01
Median	78.5	78	77	77	0.8
(IQR)	(70-83)	(70-81)	(70-81)	(70-82)	0.8

**1st p value is for values obtained immediately after tracheal intubation when compared to 10 minutes later,*
2nd p: 10 minutes when compared to 20 minutes and
3rd p: for 20 minutes when compared to 30 minutes after tracheal intubation.

The change in PI overtime after induction of anaesthesia

Table (3): Correlation between PI and other parameters at baseline measurements showing significant positive correlation with Et.sevoflurane level and negative correlation to age and mean arterial blood pressure with irrelevant correlation to heart rate.

Table (3): Correlation between PI and other parameters at baseline measurements

	Rho coefficient	**P**
Age	-0.69	<0.0001
Etsevo	0.51	0.0001
MBP	-0.57	<0.0001
HR	0.33	0.02

The diagnostic accuracy of the perfusion index (PI) in detecting different levels of anaesthesia depth using the BIS as the gold standard

Our primary outcome show significant changes in perfusion index values (PI) to changes in depth of anaesthesia while BIS values decreased from 70 to 60.

Table (4): The difference between baseline value (soon after intubation) and 10 minutes later (BIS reading of 60 compared to 70) , 20 minutes later (BIS reading of 40 vs 70) and 30 minutes after induction (BIS reading from 40 to 60)

PI difference between baseline and	**AUROC**	**Best cutoff**	**Sensitivity**	**Specificity**	**Accuracy**	**P value**
10 min	0.622	>=.41	78.00%	42.00%	60.00%	0.006
20 min	0.7	>=.81	76.00%	52.00%	64.00%	<0.0001
30 min	0.65	>=0.88	60.00%	54.00%	57.00%	0.006

Table (4): The difference between baseline value (soon after intubation) and each of; 10 minutes , 20 minutes and 30 minutes later.

DISCUSSION

In this study, we investigated the performance of the PI as a tool to assess the depth of anesthesia during different stages of anesthesia delivery in direct comparison with the BIS. Our results demonstrated that the PI significantly increased while deepening the planes of anaesthesia and decrease again significantly during recovery from anaesthesia, with an inverse relation with BIS. At whatever time the BIS decreases, the PI increases and vice versa. While the correlation testing between these two indices was significant to the investigated end tidal sevoflurane level and arterial blood pressure but insignificant to changes in heart rate, to this was non explained, the ROC analysis was informative, showing clear cut off values with their corresponding sensitivity, specificity and accuracy.

***Kanaya et al.* [20],** studied the differential effects of propofol and sevoflurane on heart rate variability and concluded that Administration of propofol during induction of anaesthesia resulted in a significant reduction in SBP, DBP and MBP in a BIS-dependent manner; however, there was no significant effect on HR. In the sevoflurane group, HR did not show any significant change throughout the study period.

The physical principles of the PI and the BIS are completely different. The BIS is derived from spontaneous EEG reflecting changes in cortical area, Meanwhile, the PI acts as an indicator of the plethysmographic pulse wave amplitude, reflecting changes in the peripheral vasomotor tone in response to changes in the sympathetic output (i.e., "subcortical zone") [21-23]. The PI increases with peripheral vasodilatation in response to decreased sympathetic output and decreases with peripheral vasoconstriction in response to increased sympathetic output [21-24].

Light anesthesia and inadequate analgesia both stimulate the sympathetic nervous system and decrease the PI [21]. ***Ezri et al.* [25],** in their study on adult females undergoing D&C procedures, reported that the PI decreased with cervical dilatation and during light anesthesia.

***Korhonen and Yli-Hankala* [21]**, in their study, also confirmed the relationship between nociception and the PI. They concluded that the quality of analgesia delivered, the type of surgery, and its perceived level of nociception would all affect the PI.

This could have confounded the results when we investigated the PI as a tool to assess the depth of anesthesia. However, many clinicians found that these observations make the PI a useful, non-expensive, available continuous tool forecasting the patients' needs for additional analgesia and for deeper planes of anesthesia in busy operating rooms with rapid turnover, thus increasing the patients' safety and reducing perioperative risks[24].

Also, this was financially reserve the specific depth of anesthesia monitors to special patients' categories and types of operations that are commonly associated with intraoperative awareness[26].

Correlation analysis showed a negative correlation between the PI and the BIS at the studied time points, with the significant p-value < 0.006, <0.0001 and < 0.006 when comparing changes in PI to changes in BIS at 10, 20 and 30 minutes after induction of anaesthesia, respectively.

In this study, we conducted a ROC analysis as an approach to quantify the PI performance in comparison to that of the BIS (as a specific monitor for the depth of anesthesia) for analysis at three different states: immediately after anaesthesia and intubation, then an adequate level of surgical anesthesia (BIS when 60) and (BIS when 40) and then toward recovery again when BIS reading is 60, extracting a clear cut-off value with its corresponding sensitivity, specificity and accuracy. In this study, the baseline preoperative immediately after induction of anaethesia median PI was 0.8 (range:0.27-2.64). At BIS 60, the best cut-off value for the PI was > =.41 (78.00%sensitivity, 42.00% specificity and 60.00% accuracy), and the best cut-off value for the PI at 20-min was > =.81 (76.00% sensitivity, 52.00% specificity and 64.00% accuracy).

During recovery from anesthesia at 30 minutes interval from baseline at BIS 60, the best cut off value for the PI was > = 0.88 (60.00%% sensitivity, 54% specificity and 57.00% accuracy) Compared with its preoperative value, it increased by 50% 10min after, 220% 20 min after with the rate of increase in PI from 10 to 20min (BIS from 60 to 40) was 113% compared to rate of decrease from 20min to

30min (BIS from 40 to 60) was 48%, that means nearly the rate of descent was half the rate of ascent of PI values while passing throw different planes of anaesthesia. These results are in accordance with those of studies that confirmed the sensitivity of PI for detecting changes in the depth of anesthesia [22,24,25,27] but differ from them in an added advantage of this study was that we defined clear cut off values for the PI at different stages of anesthesia delivery and during recovery.

Considering that the AUC was from (0.62 to 0.7) meaning < 0.7 at all the studied time points and the accuracy (57% to 64%) of the PI to differentiate the depth of anesthesia might be defined as low. Further studies are needed to support these findings.

In this study, we reported large inter-individual variations in the PI, ranging from 0.27 immediately after induction of anaethesia and up to 6.51at 20-min. intraoperatively. Similarly, Granelli and Ostman-Smith found a larger inter-individual variation of the PI that ranged from 0.02 to 20 in 10,000 healthy newborns recruited in their case-control study [28]. Despite these large inter-individual variations, we think that the PI is a useful tool when comparing the trend of changes in the value of PI in comparison to its baseline value. We conclude that the surges and drops in the PI compared with its respective baseline are highly informative regardless of whatever this value was.

A limitation of this study was that changes in the PI reflect both anesthetic and analgesic needs. In this study, we assumed that the changes in the PI are mainly due to changes in the depth of anesthesia because our patients received an adequate analgesic protocol that is suitable for such operations. In addition, we studied a homogenous sample as regards operative procedure and patient category. So, we can assume that this bias has been controlled. Possible effects of iv propofol on BIS should be considered and a second limitation to this study is that we used IV propofol as a supplementation to sevoflurane inhalational induction. The minimum propofol dose required for loss of consciousness was used and we did not use any anesthetic adjuvants afterward. We assume that this technique did not affect our results.

CONCLUSION

According to our study, compared with the BIS, the PI can track changes in the depth of anesthesia in adult patients undergoing ophthalmic surgeries under sevoflurane anesthesia with the surges and drops in the PI compared with its respective baseline are highly informative with this rate of change regardless of whatever this baseline value was.

Conflicts of Interest: The authors declare no conflict of interest.

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