Original Research

Can Bispectral Index Monitoring (EEG) be an Early Predictor of Respiratory Depression under Deep Sedation during Endoscopic Retrograde Cholangiopancreatography?

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Abstract

Objectives: The more often the endoscopy sedation is performed, the more the risk of adverse events, and therefore, advanced monitoring becomes more and more essential in endoscopy units. The present study aims to evaluate whether the Bispectral Index (BIS) monitoring is an early predictor of respiratory depression and to determine the compliance between commonly used clinical sedation score.

Methods: This study was approved by the ethics committee. The sample consisted of 60 patients aged 18 to 50 years with an American Society of Anesthesiologists (ASA) physical status of I scheduled for endoscopic retrograde cholangiopancreatography (ERCP). All patients received propofol mediated sedation. Ramsay sedation score (RSS) was used as a clinical sedation score to assess the depth of sedation. Participants were attached to a BIS monitor. Perioperative hemodynamics, BIS values, the mean dose of propofol, procedure duration, apnea, frequency of oxygen desaturation and airway-related interventions, as well as demographic parameters, were recorded. BIS scores were blinded to RSS data.

Results: The study sample consisted of 60 patients (36 females) aged 18 to 50 years (mean: 36.10±8.02). The mean procedure time and the dose of propofol were 32.70±1.79 min and 287.17±59.66 mg, respectively. The cut-off values for respiratory depression were as follows. At the 15th min of measurement, the BIS score of 60 had 96.2% sensitivity and 42.9% specificity. At the 20th min of measurement, the BIS score of 59.50 had 98.2% sensitivity and 100.0% specificity. At the 25th min of measurement, the BIS score of 59.00 had 98.3% sensitivity and 50.0% specificity. Regression analysis showed that the mean BIS score (p=0.000, 95%CI-0.110-0.043) increased by 0.076 with a unit increase in the RSS.

Conclusion: BIS was highly correlated with RSS, and therefore, can be used to avoid respiratory depression during sedation.

Keywords: Bispectral index; continuous monitoring; respiratory depression; sedation.

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Endoscopic retrograde cholangiopancreatography (ERCP) is widely used in the diagnosis and treatment of pancreaticobiliary diseases. It is important to maintain deep sedation due to the discomfort and pain and insufficient movement control associated with the cannulation stage of the procedure. However, patients with an increased risk of respiratory depression may easily progress from deep sedation to general anesthesia. Therefore, accurate and repetitive assessment of sedation level is critical for safety and completion of the procedure.[1, 2]

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It is always a challenge for anesthesiologists to plan adequate sedation. Patients' responses depend on the sedative agents administered according to a dosage algorithm. Several anesthetic drugs and combinations can be used to maintain adequate sedation. Propofol is a widely used sedative agent because it is safe and provides rapid onset, awakening and recovery. However, its infusion increases the risk of respiratory depression. Airway management is, therefore, vital to avoid airway obstruction and associated respiratory complications.[3]

Sedation scales, such as the Ramsay sedation scale (RSS) and/or the Observer's Assessment of Alertness and Sedation (OAAS), are widely used to measure the level of sedation by observing patients' responses to stimuli. The RSS developed by Ramsay (1974) is widely used to measure the levels of sedation in patients. It is an international evidence-based scale used in sedative-analgesic medications and also in intensive care units. In clinical routine practice, it is the most commonly used sedation scale due to its easy application and interpretation. RSS consists of six scores. The scores > 4 indicates deep sedation. However, its use is patient and researcher-dependent, assessments are made at intervals, and stimuli may have a disruptive effect during the assessment.[4]

BIS is a multiprocessor EEG parameter developed specially to measure the effects of anesthetics and sedatives on the brain hypnotic state, making it possible to measure the depth of anesthesia. In clinical practise, the introduction of BIS is a reliable method to assess brain function and allows the anesthesiologists to make the titration of hypnotics sedatives on cortical activity. Anesthesia may occur unpredictable responses at different times of procedures with variability among patients, and still, the exact dosage of sedatives to be administered remains a challenge so at this point, BIS can be a life-saving guide.

BIS is an easy-to-use, objective, continuous, and quantitative monitoring tool incorporating various electroencephalography (EEG) signals into a single dimension on a scale of 0 (no brain activity) to 100 (fully awake) A BIS score lower than 40 represents deep hypnosis and a score higher than 80 may be associated with the recall.[4]

The present study aims to determine whether the BIS index is an early predictor of respiratory depression in patients under sedation and whether it is correlated with clinical sedation scores.

Methods

This was a single-center cross-sectional and analytic study approved by the Institutional Review Board (B .10.1.TKH.4.3 4.H.G.P.0.01/2019). Written informed consent was obtained from participants. All procedures were performed according to the ethical principles for medical research outlined by the World Medical Association's Declaration of Helsinki. Electronic medical records were manually reviewed to evaluate the data.

The study sample consisted of 60 patients aged 18 to 50 years with an American Society of Anesthesiologists (ASA) physical status of I scheduled for ERCP (see Flow Chart Fig. 1). The exclusion criteria were as follows: (1) ASA II-V, (2) sleep apnea syndrome, (3) allergy to sedative drugs used for sedation, (4) anticipated difficult airway.

All participants received diclofenac sodium intravenously for analgesic 30 min before the procedure. No premedication was used. The standard intravenous fluid was administered at a rate of 10 mL/kg/h. Then, participants were laterally positioned and continuously monitored using electrocardiography, non-invasive blood pressure (NIBP), capnography and pulse oximetry. A BIS sensor was applied unilaterally to the forehead and connected to a BIS monitoring system (BISTM Complete 2 channel monitor, Covidien USA) according to the manufacturer's instruction. All baseline data were collected before induction. Supplemental oxygen was administered through a simple oxygen na-
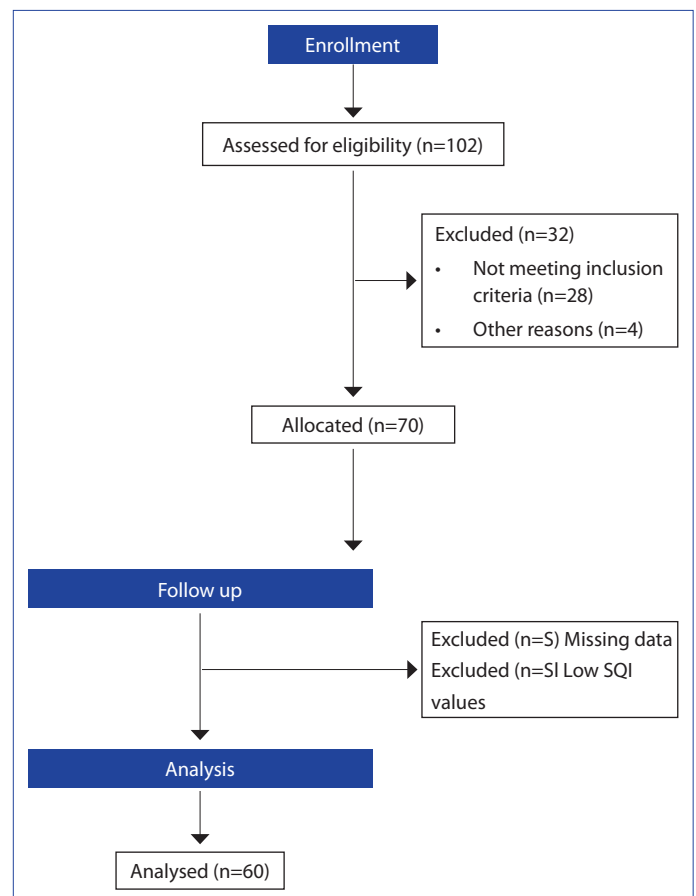

Figure 1. Flow Chart.

sal line at a flow rate of 4 L/min throughout the procedure. Respiratory rates per minute and continuous waveform of expired CO2 were used to monitor ventilation during sedation using a sampling line around a nostril connected to side-stream capnography.

For induction, the anesthesiologist intravenously administered 1 mg/kg propofol as a bolus over one min, followed by a continuous infusion at a rate of 5 mg/kg/h. Propofol infusion rate was increased by 1 mg/kg/h every one min, up to 10 mg/kg/h, until adequate sedation was achieved where 60 < BIS < 80 and RSS ≥ 4. Propofol infusion was terminated to perform an airway-related intervention in case of oxygen saturation < 90%, end-tidal carbon dioxide concentration > 50 mm Hg, apnea or a decrease in heart rate by 20% from baseline.

The anesthesiologist, who was blind to BIS scores, assessed RSS scores throughout the procedure, including induction and every five min during sedation. An assistant researcher recorded the BIS values, oxygen saturation, respiratory rate, non-invasive blood pressure and heart rate before each assessment of RSS scores. In addition, BIS values were recorded at the time when desaturation occurred. Deep sedation was defined as an RSS score >4 (Table 1). Oxygen desaturation was defined as SpO_2 <90%. Apnea was defined as the cessation of spontaneous ventilation for 20 sec. The rescue airway-related interventions were jaw thrust and head reposition maneuvers, oral airway usage, and bag-mask ventilation.

All EEG data (BIS) and signal quality indices were downloaded at 1-min intervals by the device. The BIS values with a signal quality index (SQI) >50 were accepted for analysis. The BIS values at the time each RSS was evaluated were recorded and averaged.

Table 1. Ramsey Sedation Scale

If Awake
Ramsey 1 Anxious, agitated, restless
Ramsey 2 Cooperative, oriented, tranquil
Ramsey 3 Responsive to commands only

If Asleep
Ramsey 4 Brisk response to a light glabellar tap or loud auditory stimulus
Ramsey 5 Sluggish response to a light glabellar tap or loud auditory stimulus
Ramsey 6 No response to a light glabellar tap or loud auditory stimulus

The procedures were performed by the same anesthesiologist and the same gastroenterologist team over 10 years of experience.

Statistical Analysis

Scale parameters were presented as mean and standard deviations. The Kolmogorov-Smirnov test was used for normality testing. The Receiver Operating Curve (ROC) was used to determine the diagnostic values of BIS scores at different measurement points. Binary logistic regression analysis was used for airway obstruction and RSS.

Results

The data of 102 patients who underwent procedural sedation were examined and 32 patients' data were excluded from this study for not meeting the inclusion criteria. Of the 70 patients included in this study, five patients were excluded due to the missing data, whereas five of them had low SQI. Totally 60 patients were included in the present study.

The mean age of participants was 36.10±8.02 years (Min: 18; Max: 50). The mean weight was 70.58±9.55 kg (Min: 50; Max: 100). The mean procedure time was 32.70±1.79 min. The mean dose of propofol was 287.17±59.66 mg (Table 2).

Table 3 shows the participants' BIS, SPO_2, ETCO2 and RSS mean values. Initial BIS scores decreased after the proce-

Table 2. Age, weight, procedure duration, mean dose of propofol

Parameter	Value
Sex, n (%)	
Female	36 (60.0)
Male	24 (40.0)
Age, mean±SD	36.10±8.02
Weight, mean±SD	70.58±9.55
Procedure duration, min, mean±SD	32.70±1.79
Propofol dose, mg/kg, mean±SD	287.17±59.66

Constant data are shown as frequency (percentage).

Table 3. Distribution of BIS, SPO_2, $ETCO_2$ and RSS values

Mean±SD	BIS	SPO_2	$ETCO_2$	RSS (median)
Initial	91.40±3.21	96.87±4.94	34.55±1.43	3.80±0.68 (4)
5th Min	68.05±4.66	95.52±5.31	34.95±1.70	3.95±0.81 (4)
10th Min	67.02±4.24	95.55±4.44	38.42±2.12	4.02±0.68 (4)
15th Min	66.22±4.71	95.23±2.64	38.13±2.06	4.05±0.53(4)
20th Min	65.65±4.62	95.17±3.32	38.37±1.86	4.15±0.68 (4)
25th Min	65.38±4.02	95.60±2.57	37.85±1.95	3.97±0.41 (4)
30th Min	65.77±3.77	96.02±1.84	37.63±2.12	3.82±0.47 (4)

Continuous data are shown as mean±SD.

dure and ranged from 91.40 to 65.77 whereas SPO_2 scores ranged from 96.87 to 96.02 and $ETCO_2$ 34.55 to 37.63 mmHg. RSS scores ranged from 3.80 to 3.82 at all measurement points. In the 10-25th min. of the procedures we recorded an increase in both $ETCO_2$ and RSS scores while decrease in BIS scores reversely.

All patients included in the analysis maintained stable non-invasive blood pressure and heart rate perioperatively as presented in Figure 2. None of the patients had bradycardia or hypotension and required any medical treatment during the procedures.

Table 4 shows the distribution of participants with an SPO_2 <90. After induction of anesthesia and at 5th min three patients had apnea. The infusion of anesthesia was interrupted and the patients were ventilated via the mask. During the procedure at 10-25th min under deep sedation, rapid oxygen desaturation was seen in seven patients and simple airway-related maneuvers were performed. No tracheal intubation was required. The procedures were completed.

From the initial point to the 25th min of measurement, except for the 15th min, three participants (5.0%) had an SPO_2 level <90. At the 15th min of measurement, seven participants (11.7%) had an SPO_2 level < 90. In ROC analysis, SPO_2 <90 was defined as respiratory depression. Table 5 shows the ROC curve results.
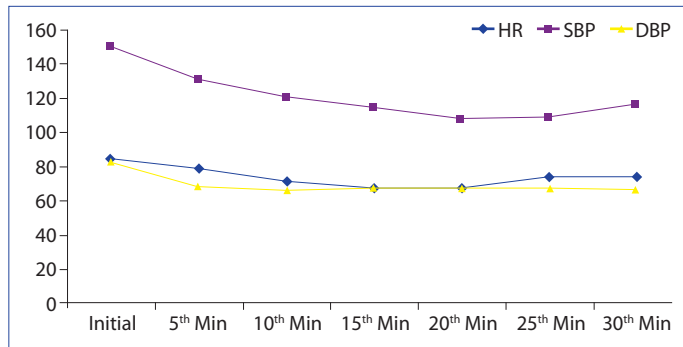

Figure 2. Distribution of vital parameters.

Table 4. Distribution of participants with an SPO_2 <90

n (%)	SPO_2<90
After induction	3 (5.0)
5th Min	3 (5.0)
10th Min	3 (5.0)
15th Min	7 (11.7)
20th Min	3 (5.0)
25th Min	3 (5.0)
30th Min	-

Constant data are shown as frequency (percentage).

According to the ROC curve results, 15th, 20th and 25th min BIS measurements had diagnostic value for respiratory depression (p<0.05). The values below the curve showed that 20th min BIS scores had the highest diagnostic value for respiratory depression with a rate of 99.7%.

At the 15th min of measurement, the BIS score of 60 had 96.2% sensitivity and 42.9% of specificity. At the 20th min of measurement, the BIS score of 59.50 had 98.2% sensitivity and 100.0% of specificity. At the 25th min of measurement, the BIS score of 59.00 had 98.3% sensitivity and 50.0% specificity.

Figure 3 ROC curve for initial, 5th and 10th min. mean BIS values and respiratory depression; SPO_2 <90. The area below the curve is 0.842 (95% confidence interval, 0.687 to 0.998; p<0.001) at the initial BIS score. The mean BIS is 89.0 (sensitivity, 0.825; specificity, 0.667) at initial. The area below the curve is 0.673 (95% confidence interval, 0.001 to 1.000; p>0.05) at 5th min BIS score. The area below the curve is 0.757 (95% confidence interval, 0.001 to 1.000; p>0.05) at 10th min BIS score.

Figure 4 ROC curve for 15th, 20th and 25th min mean BIS values, and respiratory depression; SPO_2 <90. The area below the curve is 0.778 (95% confidence interval, 0.591 to 0.964; p<0.05) at 15th min BIS score. The BIS cutoff value for deep sedation is 62.5 (sensitivity, 0.849; specificity, 0.571) at 15th min. The area below the curve is 0.997 (95% confidence interval, 0.001 to 1.00; p<0.01) at the 20th min BIS score. The BIS cutoff value for detecting deep sedation is 58.5 (sensitivity, 1.000; specificity, 0.667) at the 20th min. The area below the curve is 0.935 (95% confidence interval, 0.001 to 1.00; p<0.05) at the 25th min BIS score. The BIS cut-off value for detecting deep sedation is 59.0 (sensitivity, 0.983; specificity, 0.500) at the 25th min (Table 6).

Since the area below the curve had the highest value at 20th min, a binary logistic regression analysis was performed for BIS and RSS. The regression analysis showed that the mean BIS score (p=0.000, 95%CI -0.110-0.043) increased by 0.076 with a unit increase in RSS.

Discussion

The results show that continuous BIS monitoring can be a reliable and fast method for detecting deep sedation as it may avoid respiratory depression earlier in spontaneously breathing patients and the recorded BIS scores are in high compliance with the RSS scores observed clinically during propofol mediated sedation. In this respect, to our knowledge, this was one of the leading studies that determined a threshold score for the desired sedation level.

Ventilation monitoring during endoscopic sedation is contentious because the patient's mouth is open and both the

Table 5. ROC results for BIS Scores and SPO_2

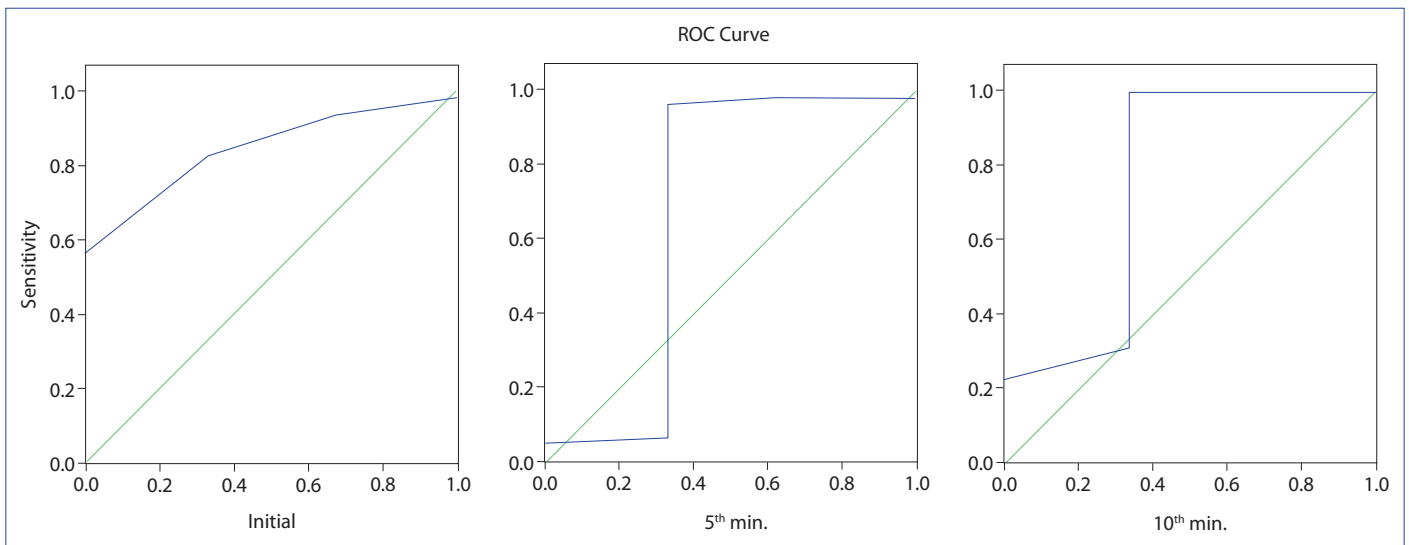| Test Result Variable(s)	Area	Std. Error	p	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Initial	0.842	0.079	0.047	0.687	0.998
5th Min	0.673	0.250	0.317	0.000	1.000
10th Min	0.757	0.200	0.136	0.000	1.000
15th Min	0.778	0.095	0.018	0.591	0.964
20th Min	0.997	0.006	0.004	0.000	1.000
25th Min	0.935	0.047	0.038	0.000	1.000

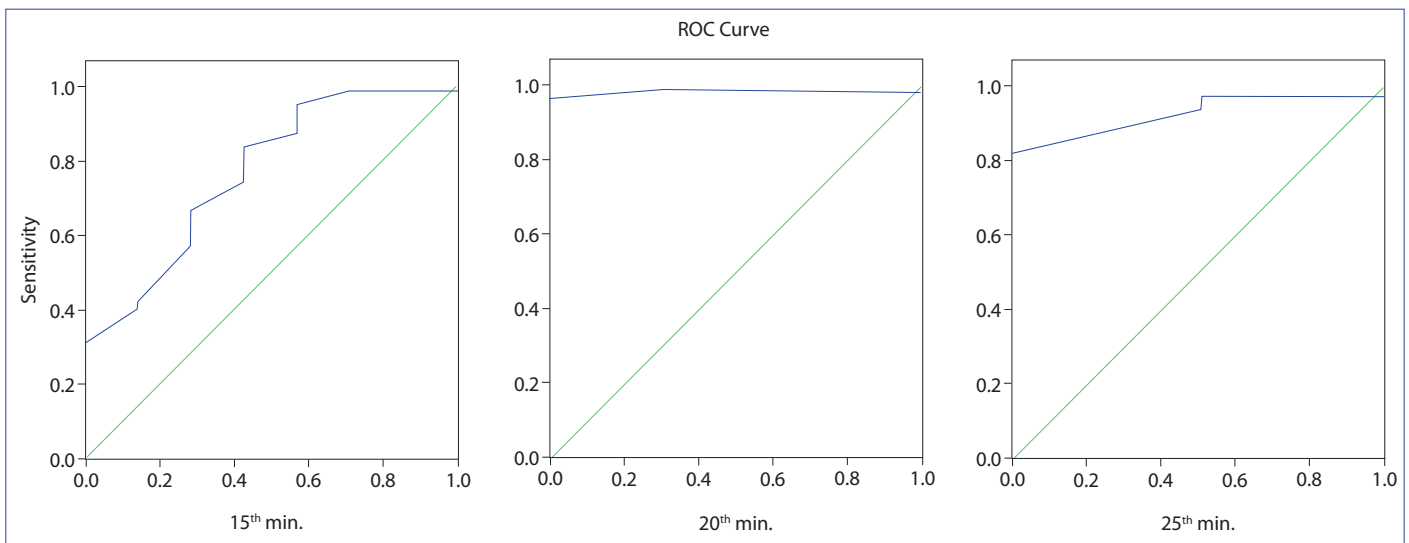**Figure 3.** ROC curve analysis for BIS initially, 5th and 10th min.

Figure 4. ROC curve analysis for BIS at 15th, 20th and 25th min.

anesthesiologist and endoscopist perform oral interventions. Under these circumstances, the standard monitoring and capnography cannot always fully present the patient's breathing patterns. Therefore, airway obstruction and asso-

ciated respiratory depression is usually clinically detected.[5-7] Providing airway potency is a major concern and dilemma for anesthesiologists. Airway obstruction and respiratory depression are potential complications that are frequently

Table 6. Linear regression results						
	Unstandardized Coefficients		**Standardized Coefficients**			**95.0% Confidence Interval for B**	
	B	**Std. Error**	**Beta**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
(Constant)	9.153	1.099		8.328	.000	6.953	11.353
BIS_20[th]	-.076	.017	-.514	-4.564	.000	-.110	-.043

observed during endoscopic sedation. Standardization or how to monitor it is also discussed in order for airway obstruction detection and early intervention. Endoscopic sedation, however, is not free from adverse events due to prolonged lateral prone position. Therefore, facilities and equipment should be monitored to prevent those events. New monitoring methods, as well as conventional clinical data, are warranted.[8, 9]

BIS monitoring is a modality developed to assess EEG more easily and accurately by digitizing the electrical activity of the brain. BIS values range from 0 (no brain activity) to 100 (fully awake). 40 < BIS < 60 indicates general anesthesia for surgery, while BIS < 40 indicates a deep hypnotic state. The use of BIS to assess the depth of anesthesia is recommended because it shows the electrical activity in the deep cortical layers of the brain. A recording device assesses EEG signals in the last 5 to 10 sec and updates the value every second, which allows for the detection of changes in the brain metabolism in 5-10 sec.[10]

Consistent with the results of Zheng's study recently, BIS monitoring can be helpful to the clinical sedation scores used routinely. BIS can assess the level of sedation objectively without interrupting the procedure and is highly correlated with observational sedation scales during non-invasive and invasive procedures. There is a growing interest in the objective assessment of sedation levels by electroencephalogram monitors during deep sedation. 60 < BIS < 80 indicates moderate sedation. In our study, BIS values ranged from 55 to 80.[11]

Depth of anesthesia monitors is becoming more and more common with advances in computerized regimens in endoscopic sedation based on propofol. A GABA agonist propofol is a potent often preferred general anesthetic as well as a sedative, depending on the dose. It dose-dependently depresses consciousness and increases the arousal threshold.[12] It significantly depresses both central and peripheral chemo-sensitivity.

It is reported that an increase in propofol concentration significantly reduces the rate of respiration and increases respiratory depression. Despite the respiratory failure, increased central and peripheral chemo-stimulation restore ventilation.[6]

Higher doses of propofol are definitely associated with increased severity of respiratory disturbances. When deep sedation is induced during advanced endoscopic procedures, patients begin to snore, and airway obstruction can become more severe than ever expected, resulting in rapid oxygen desaturation. However, propofol is considered safer than conventional sedation because it has a lower risk of rescue events and higher patient satisfaction and results in faster recovery. In a German study of gastroenterologists with propofol sedation (n=24441). The rate of cardiorespiratory complications was very low. Several studies have shown that propofol-based sedation for endoscopy is well tolerated.[6]

ERCP is a high-risk procedure not only due to prolonged prone position but also due to deep sedation-related adverse events that result in morbidity and mortality. In practice, patients are monitored for heart rate, oxygen saturation, non-invasive blood pressure and end-tidal CO_2, all of which deteriorate in case of a complication. There is no robust method available to predict complications before they occur. The participants with BIS scores < 60 had higher rates of complication while those with lower BIS scores improved without desaturation thanks to airway-related maneuvers and/or reducing the dose of sedative drug. Consistent with our results, Miner et al.[13] reported a significant difference in BIS scores between patients with and without complications while Yang[14] reported lower complication rates in the group monitored with BIS.

There are few studies on BIS Index, sedation depth and airway obstruction. Sabouri et al.[15] argue that BIS monitoring is an objective and reliable method for detecting airway obstruction in oral or dental surgery under intravenous sedation performed especially in office settings and that it increases the sensitivity of anesthesiologists to sedation depth and complications.

In this present study, we also used a capnograph for routine monitoring. Capnography is considered to be a superior method for the evaluation of ventilation and also more sensitive to alveolar hypoventilation than SPO_2.[16] A decrease in SpO_2 by just 1-2%, even if the value still remaining at 96-98%, should prompt the physician for immediate intervention due to the alveolar hypoventilation. SPO_2 with

capnography based monitoring for endoscopy procedures improve patient safety, but additional potential predictors of early respiratory compromise are still under investigation.[17] Deep sedation suppresses the patient's respiration strongly and causes upper airway obstruction and apnea, which requires airway-related interventions. Therefore, we conclude that adding BIS monitoring is indispensable for endoscopy which requires deep sedation.

This study has several limitations. First, the sample size is small. We, however, believe that respiratory disturbances were objectively assessed. We used RSS scores to assess the depth of sedation. RSS was first used, and is still commonly used, to assess the depth of sedation in patients in intensive care units. This is why it was the scale of choice in this study. Different scales and sedatives might yield different results. It is, therefore, recommended that future studies recruit larger samples from different patient populations to determine BIS scores suitable for sedation.

Conclusion

Target BIS score is useful for determining sedation levels and avoiding respiratory complications.

Disclosures

Ethics Committee Approval: Ümraniye Training and Research Hospital (B .10.1.TKH.4.3 4.H.G.P.0.01/2019).

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Conflict of Interest: None declared.

Authorship Contributions: Authorship Contributions: Concept – E.T.K.; Design – E.T.K.; Supervision – S.S.; Materials – E.T.K., S.S.; Data collection &/or processing – E.T.K.; Analysis and/or interpretation – E.T.K.; Literature search – E.T.K.; Writing – E.T.K.; Critical review – E.T.K., S.S.

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