Comparison of Sedation Complications and Salivary Alpha-Amylase (sAA) Levels in Gastrointestinal Endoscopy Patients Under Total Intravenous Anesthesia (TIVA) Using Bispectral Index (BIS)

Wahyu Wiswa Wardhana, dr.[1,2], Dr. Bambang Pujo Semedi, dr., Sp.An-TI., Subsp.TI(K)., Subsp.An.Ped (K)[1,2], Dr. Hamzah, dr. Sp.An-TI., Subsp.NA.(K)., Subsp.TI(K)[1,2], Dr. Prananda Surya Airlangga, dr., M.Kes., Sp.An-TI., Subsp.TI(K) [1,2], Dr. Prihatma Kriswidyatomo, dr., Sp.An-TI[1,2]

[1]*Departement of Anesthesiology and Intensive Care, Dr Soetomo General Academic Hospital, Surabaya*

[2]*Departement of Anesthesiology and Intensive Care, Faculty of Medicine – UNIVERSITAS AIRLANGGA, Surabaya*

KEYWORDS

Bispectral Index (BIS), gastrointestinal endoscopy, sedation complications, salivary Alpha Amylase (sAA)

ABSTRACT:

Introduction: Gastrointestinal endoscopy procedures are becoming increasingly common worldwide. These procedures require the assistance of anesthesiologists to ensure adequate sedation, reducing complications caused by patient movement during the procedure. However, sedation administration is not without risks. Additionally, gastrointestinal endoscopy falls under the category of Non-Operating Room Anesthesia (NORA) and is performed on patients across nearly all age groups, presenting unique challenges alongside potential complications due to underdosing or overdosing of sedation.

Objectives: This study compares sedation-related complications in respiratory, hemodynamic, anesthesia awareness, and salivary alpha-amylase (sAA) levels in patients monitored for anesthesia depth using either the Bispectral Index (BIS) or clinical parameters via the PRST score.

Methods: This quasy experimental study used a randomized allocation design. A total of 24 subjects, aged 22–65 years, were divided into two groups: BIS and non-BIS. Non-BIS group was monitored by using PRST score objective instrument to assure depth of sedation. Patients meeting the inclusion and exclusion criteria provided saliva samples before and after the procedure. Intraoperative events, such as sedation-related complications involving respiration, hemodynamics, and awareness, were recorded during the procedure.

Results: There were no respiratory complications in either group. However, there was a significant difference p=0.037 between the BIS and non-BIS groups towards hemodynamic complications that occurred more in the BIS group. Meanwhile, there was no difference in anesthesia awareness with a p=0.249. Likewise, no difference was found in sAA levels in both groups with p=0.679.

Conclusions: There was no difference in the incidence of awareness, and the level of sAA in the BIS and non-BIS groups. There was a significant difference in complications hemodynamic complications in the BIS group.

1. Introduction

Gastrointestinal endoscopy procedures are now widely performed worldwide. These procedures require anesthesia services to enhance the comfort of both patients and operators[1,2]. Such procedures fall under Non-Operating Room Anesthesia (NORA) services, which come with various limitations and a highly heterogeneous patient age range, from infants to geriatric patients. Furthermore, complications from endoscopic procedures can increase if the patient moves during the procedure[3]. Therefore, adequate anesthesia or sedation is essential to maintain the patient's condition during the procedure. Upper or lower gastrointestinal endoscopy is often performed on both outpatient and inpatient cases. The most commonly used anesthesia technique is Total Intravenous Anesthesia (TIVA), administered via intermittent boluses. The anesthetic drugs most frequently used include propofol for sedation and fentanyl for analgesia[6]. Endoscopic procedures are conducted with standard monitoring of vital signs and pulse oximetry saturation.

The administration of sedation in gastrointestinal endoscopy patients is not without risks. These risks may arise from either underdosing or overdosing of sedatives or analgesics, as the actual requirements of each patient are often unknown. A mismatch between the required and administered dosage increases the likelihood of complications related to underdosing or overdosing of anesthetic drugs[1]. Therefore, appropriate monitoring tools are essential to accurately measure the depth of sedation in patients receiving anesthetic agents (Figure 1). Overdosing can lead to respiratory or hemodynamic complications, while underdosing may result in anesthesia awareness and, in more severe cases, Post-Traumatic Stress Disorder (PTSD)[4,5]. Such complications trigger the sympathetic pathway via the Sympatho-Adrenal Medullary (SAM) axis, leading to the release of catecholamines, including adrenaline and noradrenaline, as a physiological response to stress. Salivary Alpha-Amylase (sAA) is an enzyme secreted by the salivary glands in response to stress, which correlates with increased levels of adrenaline and norepinephrine[7,8].

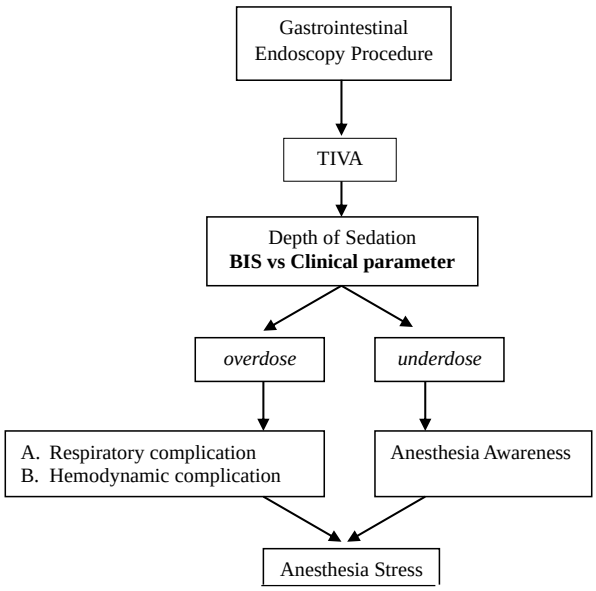

Figure 1 Conceptual framework

Salivary Alpha-Amylase (sAA) is an enzyme that has recently gained attention in research as a potential biomarker for stress. This enzyme responds rapidly to stress, making it a useful indicator. Previous studies have linked increased sAA levels to stress, pain, and psychological conditions[8,9]. For monitoring sedation depth, the recommended approach is the use of the Bispectral Index (BIS), which provides a quantifiable numerical index representing the depth of anesthesia[10,11]. According to the literature, a BIS index value of 40–60 is suggested for general surgical procedures to prevent awareness during anesthesia[12]. Currently, sedation or anesthesia depth is often monitored using clinical parameters, such as the PRST score. This score evaluates anesthesia depth based on parameters like blood pressure, heart rate, sweating, and crying[13,14].

2. Objectives

This study aims to examine the differences between groups monitored using clinical parameters and those monitored using BIS for sedation depth to sedation complication and sAA level as surrogate marker of stress hormone.

3. Methods

This study is a quasy experimental research with a comparative method to evaluate two groups using a random allocation sampling technique. The total number of patients included in this study, calculated based on the sample size formula, was 24, divided into two groups: BIS and non-BIS, with 12 patients in each group. Patients meeting the inclusion and exclusion criteria were randomly allocated to one of the groups. The inclusion criteria for this study were as follows: patients aged 18–65 years, the use of total intravenous anesthesia (TIVA), and patients who agreed to participate in the study.

Meanwhile, the exclusion criteria included parotid tumors, psychological disorders, a Glasgow Coma Scale (GCS) score of less than 15, severe heart disease, severe hemodynamic instability (requiring inotropic or vasopressor support), severe pulmonary disease (P/F ratio < 200), difficult airway management (difficult to ventilate or intubate), alcohol consumption, a history of radiotherapy, use of beta-blocker medications, ASA physical status classification III or IV, and refusal to participate in the study.

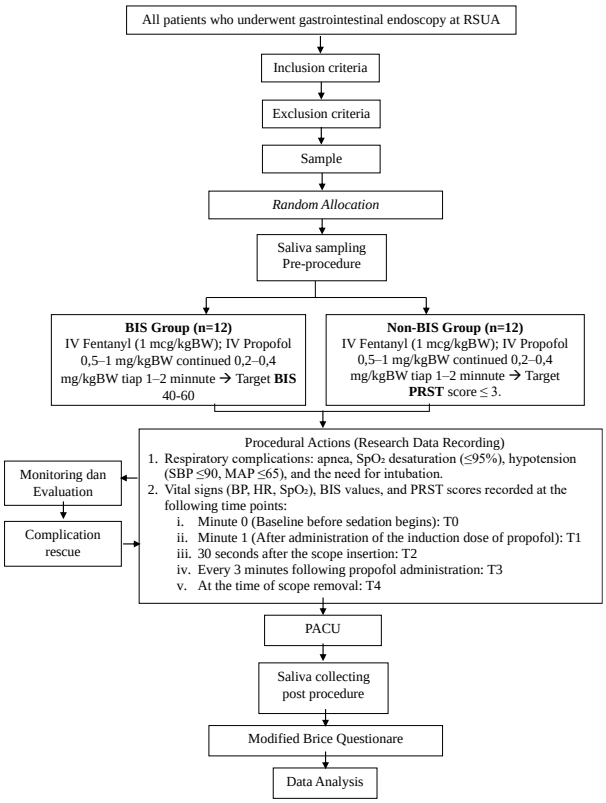

Figure 2 Research protocol flowchart

Saliva samples were collected from each patient before the procedure. In the BIS group, patients were equipped with BIS electrodes and administered intravenous fentanyl at a dose of 1 mcg/kg and propofol at 0.5–1 mcg/kg during induction. Maintenance was performed using intermittent bolus doses of propofol at half the loading dose, targeting a BIS index of 40–60 for anesthesia depth. In the non-BIS group, patients received the same induction drugs and doses, with maintenance targeting a PRST score of ≤3 (Figure 2).

Drug administration was titrated based on the response to sedation depth, monitored using either BIS or PRST scores. In the post-anesthesia care unit, patients were observed, and once fully conscious, they were asked to complete a modified Brice questionnaire. Additionally, a second saliva sample was collected as an indicator of the post-sedation state. The samples were then analyzed using the ELISA (Enzyme-Linked Immunosorbent Assay) method.

4. Results

In this study, 20 patients (83%) were female, and 4 patients (17%) were male, with an average age of 43 years, an average body weight of 59.8 kilograms, and a BMI of 23.75 kg/m². Six patients (25%) were classified as ASA PS 1, and 18 patients (75%) as ASA PS 2. Esophagogastroduodenoscopy (EGD) was performed on 16 patients (67%), while colonoscopy was performed on 8 patients (33%) (Table 1). Before sedation, the characteristics of vital sign did not show difference in each group (table 2). It means, two groups with the same characteristic so researcher can analyse more. Regarding respiratory complications, none of the patients experienced any respiratory issues. Similarly, no cases

of awareness were reported. However, hemodynamic complications were more frequently observed in the BIS group, affecting 5 patients.

Table 1 Demographic characteristics of study subjects

Category	Total (n=24) f (%) Mean±SD	BIS Group (n=12) f (%) Mean±SD	Non-BIS Group (n=12) f (%) Mean±SD
Sex			
Female	20 (83,3%)	10 (50, 0%)	10 (50,0%)
Male	4 (16,7%	2 (50, 0%)	2 (50,0%)
Age (y.o)	43,17±13,22	46.67±11.44	39,67±14,41
Body weight (kg)	59,88±10,40	62,50±9,80	57,25±10,73
Height (cm)	158,67±5,35	158,42±4,98	158,92±5,92
BMI (kg/m²)	23,75±3,75	24,90±3,64	22,60±3,65
Physical state			
1	6 (25%)	3 (50, 0%)	3 (50,0%)
2	18 (75%)	9 (50, 0%)	9 (50,0%)
Procedure			
EGD	16 (66,7)	8 (50,0%)	8 (50,0%)
Colonoscopy	8 (33,3)	4 (50, 0%)	4 (50,0%)

The salivary alpha-amylase (sAA) levels showed a significant difference ($p < 0.05$) between pre- and post-procedure conditions, with lower post-procedure levels. However, the post-procedure sAA levels between the BIS and non-BIS groups did not show a significant difference ($p > 0.05$) (Table 5). Observation of patients' vital signs during sedation procedures showed no significant differences between the BIS group and the Non-BIS group, as indicated by a p-value > 0.05. Similarly, the bar chart below illustrates that the vital sign values at T1, T2, T3, and T4 do not exhibit any significant differences (Figure 3). In the group not using BIS, the depth of anesthesia was measured using the PRST score, with a PRST score of less than 3 achieved at T1, T2, and T3.

Tabel 2 Vital sign characteristics of patients before sedation procedure

Category	Total (n=24)	BIS (n=12)	Non-BIS (n=12)	p value
SBP (mmHg)	120,8±12,8	120,4±8,7	121,3±16,4	0,977
DBP (mmHg)	76,7±10,5	76,7±8,4	76,9±12,7	0,949
MAP (mmHg)	91,5±10,8	91,3±8,1	91,7±13,5	0,960
HR (times/min)	87,8±7,0	86,6±7,9	89,1±6,3	0,370
RR (times/min)	17,7±1,4 18 (16-20)	17,7±1,4 18 (20-16)	17,8±1,6 18 (20-16)	0,790

This was comparable to the BIS group, where blood pressure decreased during measurements at T1, T2, and T3. However, blood pressure and MAP remained above 65, indicating no episodes of hypotension during the monitoring period. The average MAP of patients in the non-BIS group was relatively high, exceeding 80. In both groups, there were no extreme respiratory rates causing shortness of breath, desaturation, or the need for airway management. Patients' pulse oxygen saturation remained above 95%, even with the use of a nasal cannula.

(Figure 3) Vital signs observation chart during sedation procedure

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, HR: Heart Rate, RR: Respiratory Rate, B: BIS, NB: Non-BIS

Table 3 Distribution of the incidence of complications for anesthesia measures

Category	Total (n=24) f (%)	BIS Group (n=12) f (%)	Non-BIS Group (n=12) f (%)	P value
Hemodynamic Complication				0,037
Yes	5 (20,8%)	5 (100%)	0 (0%)	
No	19 (79,1%)	7 (36,8%)	12 (63,2%)	
***Awareness anesthesia* (BMQ)**				0,249
Possible awareness	4 (16,7%)	1 (25%)	3 (75%)	
Unlikely awareness	7 (29,2%)	2 (28,6%)	5 (71,4%)	
No awareness	13 (54,2%)	9 (69,2%)	4 (30,8%)	

BMQ: Brice Modified Questionare

Recording anesthesia complications during endoscopy procedures performed with the intermittent bolus TIVA technique revealed that none of the patients experienced respiratory complications, such as apnea or desaturation requiring airway support like Laryngeal Mask Airway (LMA) or intubation. This finding was consistent across both groups. However, hemodynamic complications occurred more frequently in the BIS group, where 5 out of 12 patients experienced episodes of hypotension and received treatment according to the protocol. In contrast, no episodes of hypotension were observed in the non-BIS group.

The study also categorized awareness into four levels, with no cases of definite awareness reported. The results showed that 4 patients (16.67%) experienced possible awareness, 7 patients (29.17%) experienced unlikely awareness, and the majority, 13 patients (54.17%), experienced no awareness. The study found that the BIS group experienced hypotension (a hemodynamic complication) more frequently than the non-BIS group, requiring ephedrine administration, with a significant p-value of 0.037 ($p < 0.05$). Fisher's exact test was used for statistical analysis, as the chi-square test was not applicable due to more than 50% of expected values being less than 5, necessitating the use of an alternative test.

Table 4 Difference test of pre and post sedation sAA levels (Pair t test)

	n	Mean±SD	Mean Difference ± SE	CI 95%	p value
sAA pre procedure	24	1,08±0,31	-8,84±5,48	-11,15 - -6,52	<0,001
sAA post procedure	24	9,92±5,48			

Observation of ELISA test results for salivary alpha-amylase (sAA) levels showed that sAA levels were higher pre-procedure compared to post-procedure in both the BIS and non-BIS groups. Paired t-test analysis of pre- and post-procedure sAA levels in this study demonstrated a significant difference, with a p-value of <0.001, indicating a statistically significant difference between the pre-procedure and post-procedure conditions (table 4).

Table 5 Profile and difference test of post-sedation sAA levels (Independent t test)

Category	Total (n=24) (ng/ml) Mean±SD	BIS (n=12) (ng/ml) Mean±SD	Non-BIS (n=12) (ng/ml) Mean±SD	p value
sAA Pre	16,08±15,21	16,22±17,45	15,94±13,40	0,747
sAA Post	9,92±5.48	10,40±5,25	9,45±5,90	0,679

The results of the analysis on the effect of BIS use during endoscopy on post-procedure sAA levels showed no significant difference, with a p-value of 0.670 ($p > 0.05$). This analysis was conducted using an independent t-test, preceded by a normality test for post-procedure sAA levels. The Shapiro-Wilk normality test yielded a p-value of >0.05, indicating that the data were normally distributed and thus suitable for further analysis.

5. Discussion

Cardiopulmonary complications caused by sedation and analgesic drugs account for approximately 50–60% of morbidity and mortality[15]. The target level of sedation using the TIVA technique for gastrointestinal endoscopic procedures is moderate sedation. At this level, the patient's spontaneous ventilation remains adequate, cardiovascular function is stable, and airway intervention is often unnecessary[16]. To guarantee safety, comfort, and the success of the process, titration is used to provide the intended depth of sedation, which varies depending on the patient and the procedure. Deeper sedation is frequently needed for therapeutic endoscopic interventions or lengthy endoscopic procedures[15].

In this study, no respiratory complications, such as desaturation or the need for advanced airway management, were observed in either group. Since continuous BIS monitoring allows for the early prevention of respiratory depression in individuals with spontaneous breathing, it can be a dependable and quick way to identify deep sedation. However, because the patient's mouth is open and both anesthesiologists and endoscopists conduct oral interventions at the same time, breathing monitoring during endoscopic sedation is still up for dispute[17].

Hypoxia, apnea, and coughing were considerably less common in the BIS group than in the non-BIS group (p-values of 0.001, 0.002, and 0.017, respectively)[18]. Propofol sedation by non-anesthesiologist staff has been the subject of studies. Only 9% of individuals experience severe hypoxemia, the most frequent sedation-related consequence, which affects 11–37% of patients. With or without oxygen supplementation, the incidence of hypoxemia was shown to be greater under sedation administered by non-anesthesiologist staff (22.4% and 37%, respectively). These results are consistent with earlier research, showing that anesthesiologists' sedation is safer when hypoxemia occurs. The superior capacity of anesthesiologists to properly manage sedation-related problems may also be responsible for this outcome[19,20].

The biggest obstacle to guaranteeing appropriate oxygenation for high-risk patients receiving endoscopic sedation is the incapacity to generate sufficient positive airway pressure. This is because HFNC gas escapes as the mouth opens during the surgery, lowering the positive airway pressure to 1.7 cmH_2O. The usefulness of such low airway pressure in avoiding hypoxemia is limited[21]. Therefore, as this study showed, Conventional Oxygen Therapy (COT), which was regularly used as a common technique, is very helpful for patients having gastrointestinal endoscopy with anesthesia. Examples of this include nasal cannulas or basic masks.

Respiratory complications often precede hemodynamic complications. This aligns with research suggesting that BIS values should be maintained above 75 to prevent respiratory complications[22]. According to Imagawa et al[31], the target BIS level for sedation during endoscopy and colonoscopy can range between moderate and deep sedation, with a BIS index of 60–80. However, in the context of

preventing awareness, it has been stated that a BIS value of 40–60 is sufficiently effective in preventing patients from awareness[12]. As a result, respiratory or hemodynamic complications may be more likely to occur.

In this study, respiratory complications were defined as the occurrence of apnea or desaturation. These conditions did not result from airway obstruction or hypoventilation that required advanced intervention. Instead, they were managed using simple airway-opening techniques, such as the chin lift or jaw thrust, in accordance with standard initial airway management procedures[30].

While anesthesia underdosing may result in consciousness during operation, anesthesia overdose is linked to postoperative problems. 40–60 is the BIS range to avoid awareness. To avoid hypoxia and airway blockage, it is advised that the BIS index be kept above 75 while using propofol. According to a study by Myles and Leslie that looked at the effect of BIS monitoring on perioperative awareness and involved 2,503 patients, BIS monitoring lowers the risk of intraoperative awareness by 82%[22,23]. Another study found no significant differences in the final memories of patients prior to surgery (p-value = 0.1724). In this study, unpleasant dreams occurred in only 2% of the participants[13]. Preventing awareness requires premedication and close observation of responses that suggest a lower level of anesthesia[24]. However, some authors contend that prevention is the most effective way to regulate intraoperative awareness[25].

It is true that the Bispectral Index (BIS) is a useful instrument for tracking the depth of anesthesia. However, because BIS ratings might be misunderstood in some circumstances, there is ongoing discussion regarding the accuracy and practical usefulness of BIS in endoscopic sedation. The real-time processing of the analog EEG input is another problem with BIS use. This implies that the monitor shows an index value that is about 25 seconds behind the real signal, depending on how users manage artifacts and settings. Additionally, BIS values vary during endoscope insertion and in response to different stimuli. This could be the reason why the displayed index occasionally exhibits poor accuracy[26].

In this study, a significant difference was found between pre-procedure and post-procedure sAA levels, with a p-value of <0.001. This indicates that in endoscopic procedures performed using the TIVA technique with intermittent bolus, either with or without BIS monitoring, the results were the same, showing a decrease in sAA levels at the end of the procedure. These results are similar to a study which reported that sAA levels decreased post-procedure compared to pre-procedure levels[27]. Patients scheduled for spinal surgeries had higher sAA levels in the operating room prior to the surgery, while the group that took midazolam as an anxiolytic had lower sAA levels after the procedure. Setting a baseline for initial sAA activity in this study was challenging because it differs from patient to patient. Therefore, progressive and sequential measurements of the patient at various time periods prior to the surgery are required since each step of the treatment causes a quick stress reaction that is reflected in sAA levels. Furthermore, sAA reacts to changes in stress very rapidly[28].

In the other study, monitoring techniques using sAA levels and BIS were employed. This was due to the observation of high sAA levels in patients undergoing endoscopy, even though the average BIS values remained stable. In that study, examinations were conducted more frequently using the dry test method which the results of which were immediately available at the time[8]. Currently, there is no

scientific evidence regarding the ideal method for measuring the depth of anesthesia in terms of clinical assessment or EEG-derived parameters. Unlike other studies, some have instead focused on evaluating anesthesiologists' ability to predict the Bispectral Index. These studies found that clinical assessments of anesthesia depth during stable anesthetic conditions were reasonably accurate compared to EEG-based assessments in 58% of cases[29].

Some limitations of this study include the sAA measurement was conducted only at the beginning and after the procedure, whereas endoscopic maneuvers and administered anesthetic interventions can trigger the release of sAA as a stress hormone that responds rapidly to stress conditions. In this study, invasive blood pressure monitoring was not utilized, which resulted in delayed evaluation of the response to sedative administration. Additionally, the relatively short duration of the colonoscopy procedure made the differences in sAA levels less apparent. The use of invasive blood pressure monitoring and capnography can provide real-time information regarding hemodynamic and respiratory complications in the context of research.

There were no significant differences in the incidence of awareness and sAA levels between the BIS and non-BIS groups. However, there were significant differences in hemodynamic complications within the BIS group. The researchers recommend, in clinical practice, that the use of instruments measuring anesthesia depth based on EEG-derived techniques alone may not be entirely appropriate. Therefore, a combination with clinical assessment is necessary. Similarly, stress biomarkers with rapid catecholamine response times require prompt evaluation.

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