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The Relationship Between Administered Midazolam Dosage as Premedication and Cortisol Levels in Gastrointestinal Endoscopy Patients

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ABSTRACT

Gastrointestinal endoscopy is crucial for diagnosis and treatment, but patients often experience anxiety as a result. This anxiety affects the outcome of the procedure and recovery. Midazolam, an effective premedication, reduces anxiety without disrupting vital functions. This study investigated how Midazolam correlates with physiological indicators and stress responses during endoscopy, focusing on cortisol levels and the Bispectral Index Score (BIS). This study was aimed to evaluate the relationship between Midazolam administration and cortisol levels as well as the Bispectral Index Score (BIS) in patients undergoing endoscopy with Total Intravenous Anesthesia (TIVA). This study employed a comparative experimental design to compare BIS and cortisol levels in patients received three different doses of Midazolam for gastrointestinal endoscopy. Participants were randomly selected from patients at RSUA Surabaya. Data analysis was performed using parametric and non- parametric statistical tests based on distribution. This quasi-experimental study compared the effects of Midazolam dose as premedication on cortisol levels and sedation depth monitoring via BIS. Thirty gastrointestinal endoscopy subjects at RSUA were randomly selected. Results showed a significant decrease in blood pressure and BIS in the Midazolam group with 0.06 mg/kg, but still within safe limits. The Kruskal-Wallis test indicated no significant difference in pre- and post-procedure cortisol levels (p=0.382). This study confirmed Midazolam's effectiveness in maintaining sedation without affecting hemodynamics or respiratory functions. There is no significant relationship between the administration of midazolam as premedication and cortisol levels in patient undergoing gastrointestinal endoscopy.

Keywords: *Endoscopy, Midazolam, Propofol, Cortisol, TIVA.*

1. INTRODUCTION

Gastrointestinal endoscopic examination is a pillar in the management of gastrointestinal diseases. Endoscopy is not only used for diagnosis, but also for therapeutic interventions such as removal of polyps, evaluation of bleeding, and management of inflammatory diseases [1]. Endoscopic procedures often cause anxiety in patients, which can affect comfort during the procedure and the outcome of the procedure [2].

Anxiety before endoscopy is common and varies in the extent of the disease [3]. Some of the factors that contribute to anxiety before endoscopy include uncertainty about the procedure, fear of pain, and concerns about the results of the examination [2]. Anxiety may occur due to unfamiliar surroundings and new experiences. Preoperative stress or anxiety has a negative impact on postoperative recovery [4].

High anxiety before endoscopy is associated with an increased risk of complications, technical difficulties during the procedure, and decreased patient compliance during treatment [5]. The mortality and morbidity effects of anxiety are enormous and it is described that the population-distributable risk of excess mortality due to anxiety is 4.3%, even higher than the risk of psychosis (0.63%) [6].

To reduce patient anxiety and increase tolerance to the procedure, the use of premedication agents [8] has become a common practice in endoscopic procedures [7]. One of the frequently used premedication agents is Midazolam, a Benzodiazepine with sedative, anxiolytic, and amnesic effects [9]. Midazolam has been shown to be effective in reducing anxiety and increasing tolerance to endoscopic procedures without impairing cardiorespiratory function [7].

Although the benefits of administering Midazolam as a premedication have been widely recognized, there is still a lack of clarity on the effect on physiological parameters during endoscopic procedures. Bispectral Index Score (BIS), a parameter used to monitor depth of anesthesia and level of consciousness, has become an important tool in anesthesia procedures [10]. The use of BIS is proven to help doctors in regulating the dose of anesthetic drugs and minimizing the risk of intraoperative awareness [11]. However, the effect of Midazolam administration on BIS during endoscopy is still not fully understood.

In addition, hormonal responses to stress can also affect patient comfort during endoscopic procedures [2]. Cortisol, the main stress hormone in the body, has been used as a biomarker to assess the physiological response to stress [12]. Measurement of cortisol levels before and after endoscopy may provide insight into the level of stress the patient experiences during the procedure. Therefore, this study aimed to explore the relationship between the administration of Midazolam as premedication and cortisol levels in patients undergoing gastrointestinal endoscopy.

2. METHODS

This study used a Quasi-experimental research design. This design allows researchers to compare certain parameters between three different groups of patients, namely groups receiving Midazolam as premedication dose (0.03 mg/kgBW, 0.06 mg/kgBW, and placebo). In this study, the main focus was the relationship between midazolam dose and cortisol levels between the three groups. Using this research design can evaluate differences in these parameters by intervening directly on the patient.

The population of this study includes all patients who will undergo gastrointestinal endoscopy with Midazolam as premedication at Airlangga University Hospital Surabaya. The study subjects consisted of patients who would undergo gastrointestinal endoscopy at Airlangga University Hospital Surabaya in a certain period who met the inclusion criteria. The specific sampling technique was randomized using a lottery technique for the selection of Midazolam dose. The process and drawing were done by anesthesia nurses with three Midazolam groups. Patients who fit the exclusion criteria will be excluded in this study. The researcher determined a type 1 error of 5% two-way hypothesis so that. Type 2 error of 10% so that the minimum difference is considered meaningful and the combined standard deviation of cortisol levels. Researchers determined type 1 error of 5% two-way hypothesis (α) to be ($Z\alpha = 1.96$), type 2 error of 10% (β) to be ($Z_\beta = 1.28$), the minimum difference that is considered meaningful (X1-X0) = 30, where X1 is 53.8 and X0 is 23.9 combined standard deviation (S) is 29.7. Thus, the minimum sample size for each group was 9 samples. The groups given Midazolam 0.03 mg/kgBW, Midazolam 0.06 mg/kgBW and Placebo were 10 samples per group.

The sampling technique will be carried out by taking into account the exclusion and inclusion criteria and for group placement is carried out by random allocation. The study will divide all patients undergoing gastrointestinal endoscopy into three groups, namely the group given Midazolam 0.03 mg/kgBW, Midazolam 0.06 mg/kgBW, and Placebo. Each patient will be randomly assigned to a different dose of Midazolam, with the consideration that all patients have an equal chance of being included in one of the groups. The use of random allocation method will help reduce bias in the study, because each patient has the same chance to be included in the group that receives Midazolam every dose. Thus, the relationship between midazolam administration and cortisol levels between the three groups will be more valid and reliable.

The inclusion criteria in this study included (1) Patients who underwent gastrointestinal endoscopic procedures and received Midazolam as premedication at Airlangga University Hospital Surabaya. (2) Age greater than and equal to 17 years and above and less than equal to 65 years of age. (3) Patients with PS ASA 1-2. (4) The patient and the patient's family signed the informed consent. (5) Patients had complete examination data. Exclusion criteria included (1) Patients with a history of severe psychiatric illness that may affect the response to Midazolam. (2) Patients with confirmed allergy to Midazolam. (3) Patients with a history of drug use that may affect BIS or cortisol levels, such as systemic steroid use in the preceding 1 week.

Table 1. Operational definition of research variables

Variable	Operational Definition	Data Scale	Unit
Dependent Variable Cortisol Levels	A hormone produced by the body in response to stress stimuli. Cortisol levels are measured through saliva samples taken before the administration of Midazolam premedication and after the patient has been transferred to the recovery room.	Numerical (Ratio)	Picomoles per liter (pmol/L)

Independent Variable Midazolam Dosage	A premedication drug used to provide anxiolytic effects in patients. Midazolam is administered intravenously in the premedication room (15–30 minutes before the procedure) before gastrointestinal endoscopy. PatientsCategorical are randomly assigned into groups through a lottery(Ordinal) system, resulting in an ordinal categorical classification. In the placebo group, 5cc of 0.9% NaCl is administered, and patients are aware of the injection.		Milligrams/kgBW Dosage 0,03 Dosage 0,06 Placebo

The research instruments to be used are data collection form, Bispectral Index Score (BIS) monitor, ELISA kit / measurement of cortisol levels, and observation sheet. After data collection, a normality test using Shapiro wilk was performed because the sample size calculation was <50. If the data is normally distributed between the variables of Midazolam administration and cortisol levels, it is tested using numerical comparative analysis of 3 unpaired groups, namely the parametric test, One Way Anova test. If the data test is not normally distributed, then use the nonparametric test, namely Kruskal wallis. This analysis aims to understand the relationship between the independent variable (Midazolam dose) and the dependent variable (cortisol levels) in the context of this study.

3. RESULTS

This study is quasi-experimental research designed to compare different doses of Midazolam as premedication on cortisol levels, with sedation depth monitored using BIS, conducted randomly on gastrointestinal endoscopy patients at Universitas Airlangga Hospital. A minimum sample size of 27 was determined using sample size calculation formulas, with data collection taking place from October to November 2024. This study has received ethical approval from the Ethics Committee of Universitas Airlangga Hospital, with approval number 178/KEP/2024. Cortisol level examination was conducted using the ELISA method in the research laboratory of Universitas Airlangga Hospital.

Characteristics of Research Subjects

Demographic characteristics of study subjects

The demographic characteristics of the subjects of this study were categorized based on gender, age, weight, height, BMI, PS ASA, and actions. In this study, data with demographic characteristics were obtained, namely the number of men was more, namely 23 patients (76.6%). While the average age is 45 years with the largest age range difference of 13 years in the three groups. The average weight of the entire study sample was 59 kg, height 158 cm, and BMI 23.50 kg/m2. Patients with PS ASA 2 were more numerous in this study with a proportion of 21 patients (70%) while PS ASA 1 was 9 patients (30%). In addition, EGD was the most commonly performed procedure in this study, namely 16 procedures (53.0%) while colonoscopy was 14 procedures (47.0%).

Table 2. Demographic characteristics of study subjects

Categories	**Total (n=30)** **f (%)** **Mean±SD**	**(n=10)** **f (%)** **Mean±SD M0**	**(n=10)** **f (%)** **Mean±SD M1**	**(n=10)** **f (%)** **Mean±SD M2**
Gender				
Female	7 (23,3%)	2 (28,5%)	2(28,5%)	3(42,8%)
Male	23 (76,7%)	8 (34,7%)	8(34,7%)	7(30,0%)
Age (year)	45,5 ±13	48,4 ±13	36,9 ±16,3	51,2 ±11
Weight (kg)	59,4 ±11,9	62,5 ± 11,9	56,6 ±17,9	59 ±11,7
Height (cm)	158,8 ±5,2	158,1 ±5,2	159,6 ± 6,9	158,6 ±3,2
BMI (kg/m^2)	23,5 ±3,9	25 ±3,9	22 ±6,5	23,4 ±4,1
PS ASA				
1	9(30,0%)	2(22,2%)	6(66,7%)	1(11,1%)

2	21(70,0%)	8(38,1%)	4(19,0%)	9(42,9%)
Procedure				
EGD	16(53,0%)	7(43,8%)	5(31,2%)	4(25,0%)
Colonoscopy	14(47,0%)	3(38,1%)	5(35,7%)	6(42,9%)

Vital sign monitoring characteristics

Observation of the patient's vital signs before sedation (after giving premedication) showed results that were not significantly different in recording TDS, HR, RR, but indeed in the Kruskal Wallis test conducted showed that TDD, MAP, and BIS showed significantly different results in the three groups in recording T0. The normality test results showed no normal distribution so the non-parametric test was used.

Table 3. Vital sign characteristics of patients before sedation procedure

Categories	**(n=30)**	**(n=10)**	**(n=10)**	**(n=10)**	**P Value**
	Median	**Median**	**Median**	**Median**	
	(Min-Max)	**(Min- Max)**	**(min-max)**	**(min-max)**	
	Total	**M0**	**M1**	**M2**	
TDS	119	120	122	118	0,765
(mmHg)	(105-140)	(110-140)	(105-132)	(105-129)	
TDD	64	74	74,5	62	0,000
(mmHg)	(56,0-90,0)	(60,0-90,0)	(60,0-90,0)	(58,0-76,0)	
MAP	83,3	89	81,8	81	0,008
(mmHg)	(76,0-106,0)	(76,3-106)	(76,3-92,3)	(72,0-92,0)	
HR	83,5	85	79,5	84	0,307
(times/minute)	(72,0-98,0)	(75,3-98,0)	(72,0-92,0)	(72,0-92,0)	
RR	18	18	18	18	0,548
(times/minute)	(16,0-20,0)	(16,0-20,0)	(16,0-20,0)	(16,0-20,0)	
BIS	BIS 82,0	87	81,5	78	0,000
	(74,0-95,0)	(82,0-95,0)	(78,0-85,0)	(74,0-82,0)	

Abbreviations: TDS (Systole Blood Pressure), TDD (Diastole Blood Pressure), MAP (Mean Arterial Pressure), HR (Heart Rate), RR (Respiratory Rate), BIS (Bispectral Index), M0: placebo M1 dose of Midazolam 0.03 mg/kgBW, and M2: dose of Midazolam 0.06 mg/kgBW.

Intraoperative monitoring was recorded for observation of vital signs, and depth of sedation (BIS). This was recorded five times including T0, T1, T2, T3, T4 where T0 is minute 0 (Baseline before starting sedation), T1 is minute 1 (after entering the induction dose of Propofol), T2 is 30 seconds after the scope enters, T3 is 3 minutes after each Propofol administration and T4 is when the scope comes out. In this study, it was found that blood pressure dropped at T1, T2, and T3 in the placebo group (M0). While the respiratory rate did not change significantly, it was maintained from 14-20 times per minute. There was no period of desaturation that required intubation or LMA. Likewise, the value of BIS can decrease at T1, T2, and T3 where the patient is maintained the depth of anesthesia with a BIS target of 40-60. For recording at T0, the M2 group obtained the lowest period of MAP decrease was 81.5 mmHg but still with MAP> 65. The decrease in blood pressure was found more in the M2 group, requiring the administration of 5 mg ephedrine if the MAP target was not met.

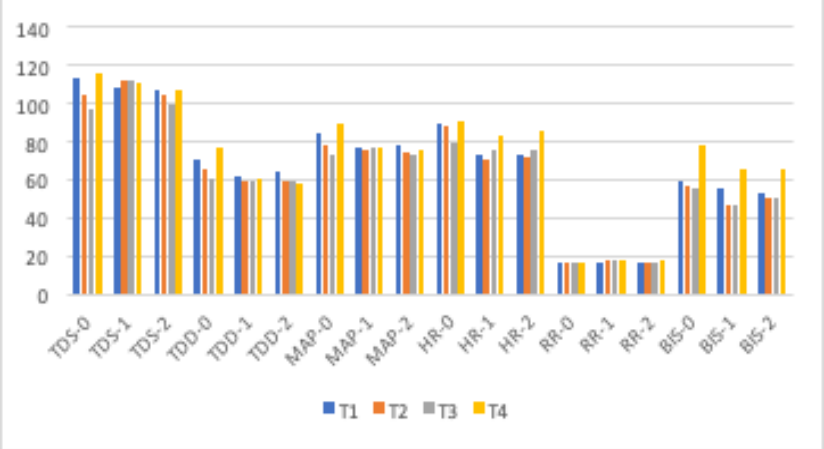

Figure 1. Characteristics of vital signs and BIS during the procedure in the three groups

In the bar chart, the values of TDS and TDD of the M0, M1, and M2 groups had no significant changes including complications such as hemodynamic or respiratory disorders (hypertension, hypotension, bradycardia, tachycardia, tachypnea, or bradypnea).

Table 4. Characteristics of BIS values at each time point in the three groups

BIS	M0(n=10)	M1 (n=10)	M2(n=10)	P Value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
T1	58	55	53	0,107
	(46,0-72,0)	(49,0-58,0)	(47,0-58,0)	
T2	58	47	50	<0,001
	(50,0-62,0)	(44,0-52,0)	(44,0-56,0)	
T3	58	46	49	0,003
	(42,0-62,0)	(44,0-52,0)	(46,0-54,0)	
T4	76	66	65	<0,001
	(72,0-85,0)	(62,0-68,0)	(58,0-68,0)	

Recording BIS values on endoscopic measures performed from T1 to T4 in the three groups, it was found that there were significant changes at T2, T3, and T4 with a p value <0.05 in the Kruskal Wallis test. Where at T2 the p value was <0.001, T3 the p value was 0.003 and T4 the p value was <0.001. While the BIS value at T1 p value is 0.107 which means it is not significantly different.

Table 5. Test results of differences in cortisol values of the sedation group

Categories		n	Median (Min-Max)	P Value
Pre-Cortisol	Placebo	10	103,2(35,8-304,2)	0,394
	Midazolam Dose 1	10	100,3(35,1-228,7)	
	Midazolam Dose 2	10	73,0(15,5-128,1)	
Post-Cortisol	Placebo	10	67,2(36,5-140,5)	0,962
	Midazolam Dose 1	10	89,0(34,7-119,9)	
	Midazolam Dose 2	10	88,1(30,1-108,4)	

Kruskal Wallis Test

The same thing was found in the analysis of the effect of Midazolam premedication dose on cortisol levels. In this study, the results of pre-procedure cortisol levels were different but the Kruskal Wallis test showed a p value of 0.394. Likewise, the results of post-procedure cortisol levels were different when the group with group M2 (81.6 ± 25.6) was compared to group M0 (182.8 ± 140.5) and M1 (85.3 ± 29.4). The Kruskal Wallis test showed a p value of 0.962 for the three groups. The one-way anova test was not carried out because the normality test found that the data was not normally distributed so that the nonparametric test was carried out, namely the Kruskal Wallis test.

Table 6. Comparative analysis results between cortisol before and after procedure

Categories	n	Median (Min-Max)	P Value
Pre-Procedure Cortisol	30	91,6(15,5-304,2)	0,382
Post-Procedure Cortisol	30	82,3(30,1-682,1)	

Wilcoxon Text

Cortisol levels were taken before procedure and after procedure in each placebo group, Midazolam dose 1 and Midazolam dose 2. In this study, it was found that cortisol levels were higher after the procedure, with an average of 116.6 ng/ml compared to the average cortisol levels before the procedure of 91.6 ng/ml. The independent t test was not carried out because the normality test showed that the data was not normally distributed so that the nonparametric test was carried out (Wilcoxon test) in this study on pre and post procedure cortisol levels did not show a significant difference where p 0.382.

Discussion

Effects of Midazolam on cortisol levels in patients with gastro intestinal endoscopy

This study shows that there is a decrease in BIS value at T1 (first 1 minute after Propofol induction dose), T2 (30 seconds after scope entry), and T3 (3 minutes after Propofol administration). This study also showed that there were significant changes in the BIS values of groups M0, M1, and M2 at T2 ($p<0.001$), T3 ($p=0.003$), and T4 ($p<0.001$). However, the BIS value at T1 was not significantly different with $p=0.107$. A study conducted by Ulusoy et al., 2016 which aims to determine the effectiveness of Midazolam and Tramadol as premedication conducted on 40 endoscopic retrograde cholangiopancreatography (ERCP) patients using Midazolam 0.015 mg/kgBB as premedication showed a decrease in BIS scores at T1, T2, and T5. BIS scores decreased significantly in subjects given with Midazolam compared to subjects given with placebo at 60-90 minutes after premedication. In line with the results of this study, no significant changes were observed in sedation scores. Inconsistency could be detected between BIS and sedation scores but the reason was not clear [13].

Midazolam is widely used in endoscopic procedures because it is easy to handle and has an antidote, Flumazenil, which can reverse its procedure in about 1 minute [14]. Midazolam is lipophilic, which redistributes rapidly to the central nervous system immediately after intravenous administration. The redistribution half-life is between 1 and 2 hours in normal patients such that the sedative effect disappears substantially within 2 hours. The duration of action of Midazolam is longer in elderly people. Factors that amplify the effects of Midazolam and its pharmacologically active metabolites include hypoalbuminemia, advanced age, decreased hepatic function, and concomitant use of drugs that inhibit the liver enzyme cytochrome P4503A4 (CYP3A4) such as azole antifungals, human immunodeficiency virus protease inhibitors, Diltiazem, and Phenytoin [15].

BIS is used as a guide to determine the intraoperative depth of anesthesia. Inadequate anesthetic depth may trigger laryngospasm and loss of airway patency. It was found that the incidence of intraoperative awareness was lower in patients who received Midazolam premedication before induction of general anesthesia than in those who did not receive it [16]. The BIS value in each individual may vary as this value may overlap with multiple levels of anesthesia [17]. Published research examining the impact of BIS monitoring on sedation with a combination of Midazolam and Propofol during endoscopic retrograde cholangiopancreatography (ERCP). The study found that while BIS monitoring did not improve oxygenation or reduce cardiopulmonary complications, it did result in faster recovery times for patients [18]. In addition, the use of BIS monitoring can help maintain cardiopulmonary stability thereby improving patient safety.

Two facts may explain the difference between digestive and respiratory endoscopy. Cardiovascular side effects, such as hypotension and arrhythmias are usually not seen during gastrointestinal endoscopy but are more frequently seen under respiratory endoscopy [19].

Effects of Midazolam Use on Vital Signs of Gastro Intestinal Endoscopy Patients

This study shows that there is a decrease in TDS before and after the sedation procedure is performed. In addition, the average

value of TDS also decreased between groups M0, M1, and M2. The TDS value at T4 of the M2 group also showed the lowest value among the other groups. A study conducted by Ulusoy et al. in 2016 conducted on 40 endoscopic retrograde cholangiopancreatography (ERCP) patients using Midazolam 0.015 mg/kgBW as premedication showed that there was a decrease in the MAP T4 value [13]. A double-blind placebo- controlled randomized trial (RCT) study conducted by MUI in 2005 on 130 patients who were going to perform upper gastroendoscopy using 7.5 mg of oral Midazolam as premedication showed that there was no significant difference in systolic blood pressure between the placebo group and the intervention group (p=0.37). This study showed that the TDS value of 0.06 mg/kgBW T4 Midazolam administration was lower than the other groups. The results of this study are also linear with the study conducted by Mui et al. also showed a decrease in MAP in the Midazolam group (131.1 mmHg) compared to the placebo group (134.1 mmHg) [20].

In addition, these results are also linear with a study conducted by Sebghatollahi et al. in 2017 showing that there was a decrease in TDS in the group given 7.5 mg of Midazolam given intravenously in 136 patients who will undergo endoscopy [21]. Clinical Trial study conducted by Wawrzyniak et al. in 2014 involving 40 sinus surgery endoscopy patients who had been given Midazolam 0.01 mg / kgBW orally showed that there was a decrease in TDS after anesthesia induction was performed [22].

This study showed that there was a decrease in TDD before and after the sedation procedure was performed. In addition, the average TDD value also decreased between groups M0, M1, and M2. The TDD value at T4 of the M2 group also showed the lowest value among the other groups. The results of this study are also supported by a Clinical Trial study conducted by Wawrzyniak et al. in 2014 involving 40 sinus surgery endoscopy patients who had been given Midazolam 0.01 mg/kgBB orally showed that there was a decrease in TDD after anesthesia induction was performed [22].

This study showed that MAP had a decrease in TDS values before and after the sedation procedure was performed. In addition, the mean value of MAP also decreased between the M0, M1, and M2 groups. In addition, this study shows that there is a decrease in blood pressure which is more found in the M2 group. The MAP value at T4 of the M2 group also showed the lowest value among the other groups. Midazolam can reduce MAP by 10 mmHg with minimal blood pressure fluctuations during the procedure [23]. An RCT study conducted by Pushkarna et al. in 2019 involving 60 patients who performed ERCP procedures also showed that there was a decrease in MAP in the group given Midazolam 0.05 mg/kgBW intravenously at the 5th, 10th, and 20th minutes which was not clinically significant [24]. A study conducted by Cho et al. in 2011 involving 44 endoscopic submucosal dissection patients in Korea showed that the average systolic blood pressure of participants before the intervention was 131±22 mmHg. However, during the duration of surgery, 6 patients experienced a decrease in blood pressure of more than 20 mmHg (27.3%) [25]. In addition, a Clinical Trial study conducted by Wawrzyniak et al. in 2014 involving 40 sinus surgery endoscopy patients who had been given Midazolam 0.01 mg / kgBW orally showed that there was a decrease in MAP after anesthesia induction was carried out [22].

This study shows that there is a decrease in HR values before and after the sedation procedure is performed. The HR value at T4 of the M2 group also showed the lowest value among the other groups. In addition, the average HR value also decreased between groups M0, M1, and M2. A study conducted by Sebghatollahi et al. in 2017 showed that there was a decrease in HR in the group given 7.5 mg of Midazolam given intravenously to 136 patients who would undergo endoscopy, where the heart rate was higher at 5 minutes after starting the procedure ($P < 0.001$) [21]. The results of this study are also linear with a study conducted by Cho et al. in 2011 involving 44 patients with endoscopic submucosal dissection in Korea showing that the average HR changed from 72±14/min before the intervention and to 100±13/min [25]. In addition, a Clinical Trial study conducted by Wawrzyniak et al. in 2014 involving 40 sinus surgery endoscopy patients who had been given Midazolam 0.01 mg/kgBW orally showed that there was a decrease in HR after induction of anesthesia was carried out [22].

Midazolam lowers peripheral vascular resistance, thereby reducing high blood pressure. Therefore, in this study, blood pressure decreased as a result of Midazolam premedication [26]. MAP decreased significantly as the dose of Midazolam increased [27]. Midazolam has different effects on the cardiovascular system including decreased myocardial contractility, systemic vascular resistance, and venodilation, all of which result in decreased arterial blood pressure. This decrease in systemic vascular resistance and venodilation leads to a decrease in cardiac filling pressure, which further reduces cardiac output. In response, the baroreceptor reflex arch is activated which causes the heart rate to increase proportionally to compensate for the decrease in cardiac output [28].

Midazolam induces parasympathetic dominance at very high doses but sympathetic dominance at low doses [26]. By decreasing the activity of autonomic centers in the brainstem, Midazolam reduces the release of catecholamines (such as norepinephrine), leading to decreased vascular tone and heart rate. Decreased sympathetic tone leads to peripheral vasodilation, lowering systemic vascular resistance and consequently reducing blood pressure. In addition, decreased sympathetic output, combined with decreased parasympathetic activity may result in decreased heart rate. The anxiolytic effect of Midazolam also reduces stress-induced increases in heart rate and blood pressure, indirectly contributing to the overall cardiovascular effect. However, clinical settings and patient conditions may affect these results [29], [30].

Effect of Midazolam Use on Complications of Gastro Intestinal Endoscopy Patients

This study showed that the administration of Midazolam premedication at doses of 0.03 and 0.06 mg/kgBWwas not found to have significant changes regarding complications of its use, such as hemodynamic or respiratory disorders. A study conducted by Ulusoy et al, in 2016 which aims to determine the effectiveness of Midazolam and tramadol as premedication conducted on 40 endoscopic retrograde cholangiopancreatography (ERCP) patients using Midazolam 0.015 mg/kgBB as premedication showed that there were no cardiovascular complications and others [13]. Different results were shown by an RCT study conducted by Pushkarna et al. in 2019 which aimed to compare the effectiveness of Midazolam and Dexmedetomidine involving 60 patients who performed ERCP procedures which showed that premedication using Midazolam showed significantly more side effects compared to Dexmedetomidine, such as choking, agitation, and post-op vomiting nausea. However, this study showed concordant results that there were no cardiovascular adverse effects due to the use of Midazolam as premedication [24], [31].

Midazolam is a class of Benzodiazepine used as premedication to reduce patient anxiety before endoscopic procedures are performed. Risk of side effects and complications, such as respiratory depression, muscle weakness, sedation, and loss of coordination may occur [32]. However, the use of Midazolam can also cause cardiovascular complications, such as hypotension and airway obstruction. The Society of Anesthesia and Sleep Medicine states that obstructive sleep apnea can occur after sedation with Propofol and this risk will increase with Midazolam, so its use should always be well considered [33]. Evaluation of tissue perfusion is the most important component of cardiovascular assessment. Hypotension experienced during sedation is usually caused by vasovagal episodes or the use of sedative and anesthetic agents that suppress sympathetic outflow to the cardiovascular system. Benzodiazepines, such as Midazolam and diazepam, have a mild vasodilator effect and usually produce a slight decrease in arterial blood pressure, even in normal sedative doses. Combined use of Benzodiazepines and opioids can significantly lower blood pressure. In addition, complications of Midazolam in patients include paradoxical reactions characterized by aggressiveness, agitation, talkativeness, disorientation, and tachycardia. This reaction often occurs with Benzodiazepine [34].

Effects of Midazolam Use on Cortisol Levels

This study showed that there was no significant difference in pre-treatment and post-treatment cortisol levels (p=0.394; p 0.962). This indicates that, prior to treatment, all samples had similar baseline cortisol levels. In addition, the comparison between pre-procedure and post-procedure cortisol levels also showed no significant difference (p=0.382). In line with the results of this study, a study conducted by Giordano et al, in 2023 showed that the premedication of Midazolam 0.02 mg/kgBW given intravenously to 70 participants showed that there was no significant difference in pre-procedure and post-procedure cortisol levels of stomatology surgery [35]. However, it was found that there was an increase in cortisol levels in the placebo group from pre-procedure (119.9 ± 56.7) and post-procedure (182.8 ± 140.5) conditions. Cortisol levels in the M2 group also increased between pre-procedure (75.5±37.5) and post-procedure (81.6±25.6). However, cortisol levels in the M1 group decreased from pre-procedure (85.7±32.7) and post-procedure (85.3±29.4) conditions. Research on pre-procedure and post-procedure cortisol levels of gastrointestinal endoscopy with Midazolam as premedication is still quite limited.

Preoperative anxiety delays postoperative recovery of gastrointestinal function. Negative emotions such as anxiety and depression lead to activation of the Hypothalamus-pituitary-adrenal (HPA) axis and increased stress response in humans, which in turn leads to increased cortisol and adrenaline levels and triggers natural killer cell activity [23]. Cortisol is a glucocorticoid hormone secreted by the adrenal cortex. Its main function is to regulate lipid, protein, carbohydrate, and water metabolism acts to maintain vascular reactivity and regulate blood cell count. It has also been demonstrated that changes in cortisol levels can directly affect nervous system sensitivity, and inflammatory responses. Increased adrenocortical cortisol secretion can occur following any type of stress, whether physiologic or psychogenic [36]. In addition, the cortisol diurnal cycle may also affect cortisol levels when measured during surgery. Surgical cortisol levels during later periods (e.g. evening) have been reported to result in an earlier return to normal levels compared to earlier periods (e.g. morning). Elevated cortisol levels in response to severe stress, such as endoscopy. Will increase the rate at which protein breakdown exceeds protein synthesis, resulting in net catabolism of muscle protein to provide substrate for gluconeogenesis. Further substrate for gluconeogenesis is provided through the breakdown of fat [37]. During acute stress, ACTH levels initially increase in a large spike pattern followed by an increase in cortisol. With the prolongation of the stress response, ACTH will return to basal levels. This means that the increase in cortisol levels lags behind ACTH by about 5~20 minutes. Its peak value in the blood is reached within 10~30 minutes after stress [38].

Benzodiazepines, of which Midazolam is one of the main drugs in premedication, also have other beneficial effects in the perioperative period. They can reduce oxygen and energy consumption and affect levels of stress hormones such as cortisol [32]. Although Midazolam is considered a tranquilizer, in some patients, it may cause restlessness and agitation [39]. The role of Midazolam premedication as an agitation measure is still a matter of debate. Intravenous administration of Midazolam before the end of surgery has been shown to reduce agitation when patients appear [40]. Midazolam is commonly used as a premedication to reduce anxiety and stress before medical procedures, including gastrointestinal endoscopy. Its anxiolytic and sedative properties help relieve the psychological stress response that can increase cortisol levels. Studies have shown that administering Midazolam before surgery can significantly lower cortisol levels compared to the control group, demonstrating its effectiveness in reducing the body's stress response [36]. Compared to Lorazepam and Diazepam,

Midazolam has the best anti-anxiolytic effect. Diazepam often causes pain during injection and venous thrombosis in addition, the anti-anxiety effect is also prolonged because its active metabolites have a long plasma half-life [23].

The administration of midazolam premedication in this study was carried out shortly before induction in the operating room, which should be done in the operating room, causing the possibility of onsite from midazolam as a premedication drug not working optimally. This has the potential to affect cortisol levels at the end of the procedure.

4. CONCLUSION

This study examined the relationship between the administered dosage of Midazolam as premedication and cortisol levels in patients undergoing gastrointestinal endoscopy. The findings indicate that there is no significant relationship between the two variables. For better clinical practice, based on the research findings and analysis, the researchers recommend conducting further prospective studies comparing Midazolam premedication dosage with other sedative drugs in longer-duration surgeries concerning cortisol levels. Additionally, the use of the TIVA TCI (Target Control Infusion) technique is suggested to standardize TIVA techniques.

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