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Sedation Levels Comparison in Intravenous 0.05, 0.08 and 0.1 Mg/KgBW Midazolam Premedication in General Anesthesia Using Bispectral Index

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Abstract:-

- ***Background***

Midazolam is water-soluble. When administered intravenously to adults at a dose of 1-2 mg, it is effective for premedication, sedation during regional anesthesia and short procedures.

- ***Research Purpose***

To know the sedation levels comparison in 0.05 mg/kgBW, 0.08 mg/kgBW and 0.1 mg/kgBW midazolam premedication.

- ***Method***

Randomized and Double-blind randomized controlled trial. This study was conducted at Haji Adam Malik General Central Hospital in Medan in February 2019. The study population was all patients who underwent anesthesia in RSUP. H. Adam Malik. In the study conducted on 66 samples divided into 3 groups, group A received intravenous midazolam 0.05 mg/kgBW and group B received intravenous midazolam 0.08 mg/kgBW and group C received intravenous midazolam 0.1 mg/kgBW. Kolmogorov - Smirnov test was used for numerical data normality test, while for categorical data, the chi-square test was used.

- ***Results***

Based on this study, the drug type A obtained mean value of 95 at T0 and at T7 observation it obtained a mean value of 75.05 which means a decrease of 19.95. The result of statistical tests was p value (0.000) < 0.05. In drug type B, the mean value of the T0 observation was 95.77 and the T7 observation was 53.59, which meant a decrease of 42.18. The result of statistical tests was p value (0.000) < 0.05. Whereas in drug type C, the mean value at T0 observation was 96.09 and in observation of T7 it was 51.00, it means that it was a decrease of 45.09. The result of statistical tests was p value (0.000) < 0.05.

- ***Conclusions***

A dose of 0.05 mg/KgBW midazolam provides a better sedation effect and can maintain the depth of sedation with a BIS value between 60-80 compared to a dose of 0.08 mg/KgBW and 0.1 mg/KgBW which cause the depth of sedation to enter the level of general anesthesia with a value of BIS <60.

Keywords:- *Midazolam, Sedation Effect, Bispectral Index (BIS)*

I. INTRODUCTION

In performing anesthesiology services for patients who will undergo surgery or diagnostic actions, there are several steps that must be taken like pre-anesthesia evaluation, pre-anesthesia preparation, anesthesia (induction, maintenance and recovery) and post-anesthesia. Premedication is part of pre-anesthesia preparation which aims to prepare patients both physically and mentally for anesthetic procedures (Lee *et al*, 2014).

Surgery Anxiety is a common emotional phenomenon but also leads to perioperative physiological and psychological changes. The main goal of pre-treatment is to eliminate anxiety. An ideal paramedic must have a route of non-invasive administration, fast and reliable onset, rapid elimination, consistent and predictable results, and good patient recipience. At the same time, the procedure must also be free of side effects such as hemodynamic instability, respiratory problems, and delayed recovery (Bansal *et al*, 2015).

The main purpose of premedication is to free the patient from anxiety, fear, pain, muscle tension, and reduce sympathetic nerve activity by providing psychological sedation to protect the basal physiological state against mental stress. There are several classes of drugs used for the purposes of premedication, including sedatives, anticholinergic narcotics, antihistamines, antacids, and H2 antagonists. Included in the sedative group are barbiturates, benzodiazepines, and butyrophenones. Midazolam belongs to the benzodiazepine group which is water soluble (Katzung, 2011).

At this time sedation is the end result of the evolutionary process in changing consciousness, possibly starting with the discovery of the ether's analgesic properties. A medical student from Rochester, New York, William Clarke, used the ether during tooth extraction in

January 1842. Many believe that this procedure may have been the first successful use of ether. The technique of sedation using ether was further developed by Crawford Long during excision of neck tumors (Morgan, 2012).

The benzodiazepines commonly used as premedication are midazolam, lorazepam, and diazepam. Midazolam is a water-soluble group. When administered intravenously to adults at a dose of 1-2 mg, it is effective for premedication, sedation during regional anesthesia and short procedures. In children, they can be given at a dose of 0.05 mg/kg body weight 30 minutes before the induction of anesthesia to produce good sedation and anxiolytic effects without producing a longer recovery of consciousness. Higher doses (0.1 - 0.3 mg/kg body weight) can be used for the induction of anesthesia. Midazolam has a shorter work start, higher retrograde amnesia rate, and lower sedation compared to diazepam. The benzodiazepine antagonists that can be used are flumazenil, but the effects of respiratory depression that have occurred cannot be reversed. (Katzung, 2011)

At Haji Adam Malik General Central Hospital in Medan, the frequency of general anesthesia performed was 62% from January 2018 to November 2018. Whereas midazolam was almost used in every surgery with multiple doses of midazolam anesthesia (SIRS RSUP HAM, 2018). For this reason, the authors were interested in conducting research on the use of midazolam with several doses as a premedication for surgery.

II. RESEARCH METHODS

A. Research Design

The design of this study used randomized and Double-blind randomized controlled clinical trials to determine differences in sedation levels of various doses of midazolam premedication in patients who will undergo general anesthesia using bispectral index.

B. Place And Time

This study was conducted at Haji Adam Malik General Central Hospital in Medan in February 2019.

C. Population

The study population was all patients who underwent general anesthesia in Haji Adam Malik General Central Hospital. The study sample was patients who met the inclusion and exclusion criteria. After being calculated statistically, all samples were divided into 3 groups, they are:

- Group A received intravenous midazolam premedication 0,05 mg/kgBW
- Group B received intravenous midazolam premedication 0,08 mg/kgBW
- Group C received intravenous midazolam premedication 0,1 mg/kgBW

D. Research Criteria

The inclusion criteria were patients aged 19 - 60 years old with the physical status of ASA 1 and 2. The exclusion criteria in this study were patients who refused to take part in the study, patients with contraindications to the drugs studied, patients with neurological and psychiatric disorders and use of alprazolam/diazepam routinely. For drop out test: there were life-threatening heart, lung and brain emergencies after midazolam administration and an allergic reaction (anaphylactic shock) after midazolam administration.

E. Sample Size

$$n1 = n2 = n3 = 2\left[\frac{(Z\alpha + Z\beta)S}{(X1 - X2)}\right]$$

n = sample size
Z_α = 1.96 (standard deviation of α 0.05)
Z_β = 0.84 (standard deviation of β 0.02)
S = standard intersection, taken from a library of 1.9^{73}
X_1-X_2 = clinical judgement

From the calculations with the above formula, the sample size obtained is: n1 = n2 = n3 = 20 people so that the total 3 groups are 60 samples, plus 10% if there is a dropout, therefore it is 66 people.

F. Informed Consent

After obtaining approval from the Ethics Committee, patients get an explanation of the procedures and state in writing their willingness on the informed consent sheet.

G. Procedures

After being approved by the Medical Research Ethics Committee of the Medical Faculty, North Sumatera University, Haji Adam Malik General Central Hospital, Medan, the researchers obtained the informed consent. The sample was a population that had met the inclusion and exclusion criteria. During the preoperative examination visit, the patients received explanation about the planned activities for general anesthesia and the research procedure includes examining the effects of sedation before surgery. The samples were randomly divided into 3 groups, Group A received intravenous midazolam premedication 0.05 mg/kgBW, Group B received intravenous midazolam premedication 0.08 mg/kgBW, Group C received intravenous midazolam premedication 0.1 mg/kgBW, then block randomization was performed by trained volunteers. Randomization is done by block, each sequence consists of 6 subjects, with a number of possible combinations of 11 sequences. Then the pen was dropped on a random number. The number indicated by the pen was the initial number to determine the appropriate sequence. Then 11 pairs of numbers below were selected from the first pair of numbers so that the number of sequences was obtained according to the number of samples. Then the sequences obtained were arranged according to the envelope number. The drug was prepared by volunteers who did the randomization (researchers did not know the composition of the drugs given). The group A was given midazolam 0.05 mg/kgBW and was diluted with normal saline to a volume of 10 ml

and injected intravenously 30 minutes before surgery. The group B was given midazolam 0.08 mg/kgBW and was diluted with normal saline to a volume of 10 ml and injected intravenously 30 minutes before surgery. The group B was given midazolam 0.1 mg/kgBW and was diluted with normal saline to a volume of 10 ml and injected intravenously 30 minutes before surgery.

The implementation of the study was carried out after the patient arrived at the waiting room for the operating room, the patient was re-examined for identity, diagnosis, plan of action for anesthesia, access to infusion before signing in. Then the patient was taken to the premedication room before a standard monitor (ECG, blood pressure, heart rate, breath frequency, and oxygen saturation) and a bispectral index monitor were installed. The three groups were prepared for general anesthesia. After midazolam administration, time is recorded as T0, and sedation levels are assessed using the bispectral index. This assessment is carried out directly by researchers who are not involved in administering drugs to these patients. The patient was then observed in the premedication room and transferred to the operating room 30 minutes after midazolam administration. Assessment of sedation levels and drug side effects was carried out directly by researchers at the 0th minute (T0), 1st minute (T1), 5th minute (T2), 10th minute (T3), 15th minute (T4), 20th minute (T5), 25th minute (T6), and 30th minute (T7) after midazolam administration. The results of observational data in the three groups were compared statistically on T1, T2, T4 and T7. The study was stopped if the research subjects refused to participate further and there was a life-threatening emergency in airway, heart, lung, or brain.

H. Data Analysis

After the required data had been collected, then completeness of the data was checked again before the tabulation and processing. Then the data was coded to facilitate tabulation. The data were tabulated into the master table using statistical processing software. Numerical data is displayed in the mean + SD (standard deviation), while categorical data is displayed in numbers (percentages). Demographic data: Kolmogorov-Smirnov test was used for Numerical data normality test. The research hypothesis was tested using the Spearman correlation test. The 95% confidence interval with a p value<0.05 was considered significant.

III. RESEARCH RESULT

A. Demographic Characteristics of Research Correspondents

This research was conducted in February - March 2019 at the Surgical Installation of Haji Adam Malik General Central Hospital in Medan. This research was conducted using the Double Blind Randomized Control Trial method. This study had 66 samples who would undergo General Anaesthesia. The samples were assessed for the level of depth of sedation using the Bispectral Index device which was given at the time of premedication before the patient underwent general anaesthesia. Sedation level is assessed at the 0th minute (T0), 1st minute (T1), 5th minute (T2), 10th minute (T3), 15th minute (T4), 20th minute (T5), 25th minute (T6), and 30th minute (T7) after midazolam administration.

Characteristics		The drug						Total		*P value*
		A		B		C				
		n	%	n	%	n	%	n	%	
Sex	Male	8	36.4%	8	36.4%	10	45.5%	26	39.4%	0,214
	Female	14	63.6%	14	63.6%	12	54.5%	40	60.6%	
Total		22	100.0%	22	100.0%	22	100.0%	66	100.0%	

Table 1:- Demographic Characteristics of Research Correspondents by Sex

Based on table 1. in this study, the 66 samples were divided into 3 treatment groups, and in group A, 8 (36.4%) samples were male and 14 (63.6%) samples were female. In group B there were 8 (36.4%) samples of males and 14 (63.6%) samples of females. In group C there were 10 (39.4%) samples of males and 12 (54.5%) samples of females. From the results of statistical tests, normal distribution in table 1 was found (p> 0.05).

Characteristics		The drug						Total		P value
		A		B		C				
		n	%	n	%	n	%	n	%	
Age	19 – 32	3	13.6%	4	18.2%	1	0.4%	8	12.1%	0.348
	33 - 46	7	31.8%	6	27.2%	8	36.4%	21	31.8%	
	47 – 60	12	54.6%	12	54.6%	13	59.2%	37	56.1%	
Total		22	100.0%	22	100.0%	22	100.0%	66	100.0%	

Table 2:- Demographic Characteristics of Research Correspondents by Age

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Based on table 2. group A had 3 (13.6%) samples aged 19-32 years old, 7 (31.8%) samples aged 33-46 years old and 12 (54.6%) samples aged 47-60. While group B had 4 (18.2%) samples aged 19-32 years old, 6 (27.2%) samples aged 33-46 years old and 12 (54.6%) samples aged 47-60 years old. Group C had 1 (0.4%) sample in the age group of 19 - 32 years old, 8 (36.4%) samples aged 33-46 years old and 13 (59.2%) samples aged 47-60 years old. From the results of statistical tests, normal distribution in table 2 was found (p> 0.05).

Characteristics		The drug						Total		P Value
		A		B		C				
		n	%	n	%	n	%	n	%	
ASA PS	1	2	9.1%	4	18.2%	9	40.9%	15	22.7%	0,089
	2	20	90.9%	18	81.8%	13	59.1%	51	77.3%	
Total		22	100.0%	22	100.0%	22	100.0%	66	100.0%	

Table 3:- Demographic Characteristics of Research Correspondents Based on ASA PS

Based on table.3. group A had 2 (9.1%) samples with ASA PS 1 and 20 (90.9%) samples with ASA PS 2. While group B had 4 (18.2%) samples with ASA PS 1 and 18 (81.8%) samples with ASA PS 2. Group C had 9 (40.9%) samples with ASA PS 1, 13 (59.1%) samples with ASA PS 2. From the results of statistical tests, normal distribution in table 3 was found (p> 0.05)

B. Research Test Results

The drug		BIS								P value
		T0	T1	T2	T3	T4	T5	T6	T7	
A	Mean	95.00	92.86	66.32	63.59	66.50	64.95	75.36	75.05	0.000*
	SD	1.72	1.21	1.67	1.94	1.63	2.48	2.13	2.26	
B	Mean	95.77	95.77	66.59	64.73	64.18	55.50	53.82	53.59	0.000*
	SD	1.15	0.61	1.71	2.33	2.32	2.77	1.53	1.74	
C	Mean	96.09	95.95	66.64	64.09	57.50	53.91	53.41	51.00	0.000*
	SD	0.97	0.84	1.71	2.07	1.85	2.04	1.59	2.56	
P value		0.023*	0.000*	0.768*	0.268*	0.000*	0.000*	0.000*	0.000*	

Table 4:- Mean Value of BIS in the administration of Midazolam

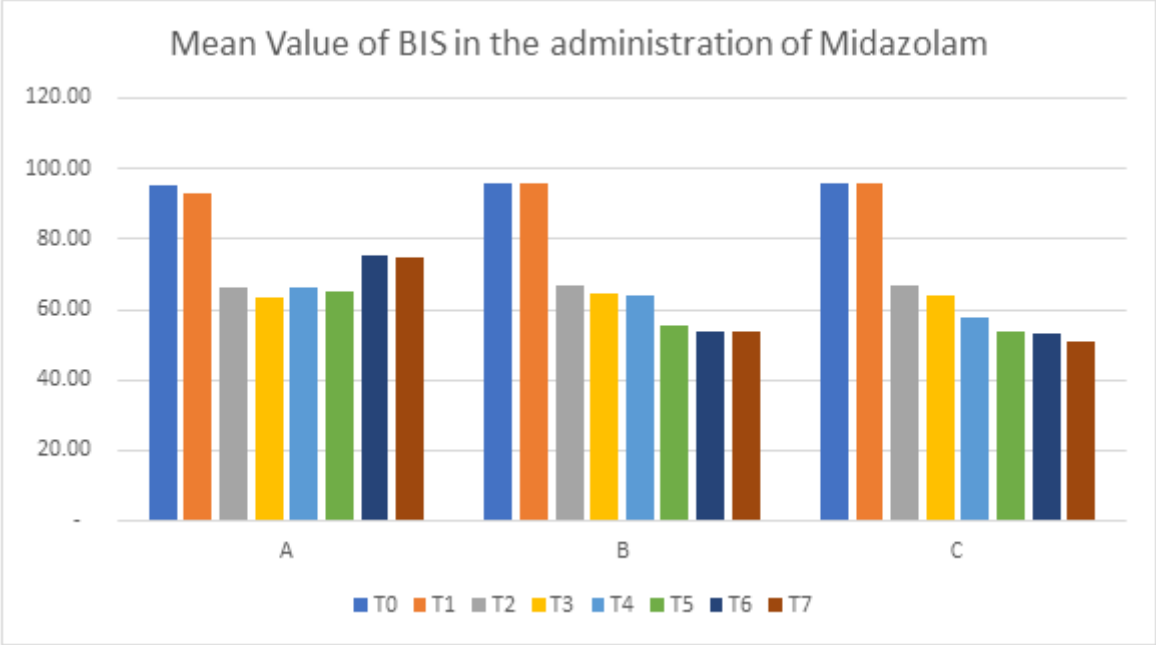

Fig 1:- Mean Value of BIS in the administration of Midazolam

Table 4 shows changes in BIS mean per observation based on the type of intervention. In drug A, the mean value of T0 was 95, and in the T7 observation, it was 75.05 which means a decrease of 19.95. The results of statistical tests obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug A from the initial observation to the final observation. In drug B, the mean value of the T0 observation was 95.77 and the T7 observation was 53.59, which means a decrease of 42.18. The results of the statistical test obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug B from the initial observation to the final observation. Whereas in drug C, the mean value at T0 observation was 96.09 and in observation of T7 it is obtained the mean of 51.00 which means a decrease of 45.09. The results of the statistical test obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug C from the initial observation to the final observation.

Based on the comparison of differences from T0 - T7 observations based on the types of treatment, p value (0.000) <0.05, which means that there is a difference in mean differences between interventions with one another, where the greatest change occurs in the use of drug type C (45.09) and the smallest change occurs in use of drug type A (19.95).

Based on the comparison of differences from T0 - T7 observations based on the types of treatment, p value (0.873) > 0.05 which means there is no difference in the mean between one intervention to another, but the type of intervention with the greatest change occurs in the use of drug type B (0.05) while the use of drug type C occurs an increase of 0.05.

IV. DISCUSSION

A. Demographic Characteristics of Research Samples

The study was carried out at the Haji Adam Malik General Central Hospital in Medan from February to March 2019 and was participated by 66 samples according to the inclusion and exclusion criteria. From the characteristics of the study based on sex (Table 1) it was found that group A had the most samples with females with 14 (63.6%) samples and 8 (36.4%) samples with males. In group B, the most samples were females with 14 (63.6%) samples and 8 (36.4%) samples were males. Whereas in group C, the most samples were females with 12 (54.5%) samples and 10 (45.5%) samples were males. Based on sex characteristics, the results of the test are relatively homogeneous (p> 0.05).

From the correspondent demographic characteristics based on age group, in group A, most participants came from 47-60 years old patients with a sample size of 12 (54.6%) and followed by 33-46 years old patients with 7 (31.8%) samples and the least were 19-32 years old patients with 3 (13.6%) samples. In group B, most participants came from 47-60 years old patients with a sample size of 12 (54.6%) and followed by 33-46 years old patients with 6 (27.2%) samples and the least were 19-32 years old patients with 4 (18.2%) samples. Whereas in group C, most participants came from 47-60 years old patients with a sample size of 13 (59.2%) and followed by 33-46 years old patients with 8 (36.4%) samples and the least were 19-32 years old patients with 1 (0.4%) sample. Based on the characteristics of the age group, the results of the test are relatively homogeneous (p> 0.05).

Based on the demographic characteristics of the ASA PS division, in group A, most participants were ASA 2 with 20 (90.9%) samples and followed by ASA 1 with 2 (9.1%) samples. In group B, most participants were ASA 2 with 18 (81.8%) samples and followed by ASA 1 with 4 (18.2%) samples. Whereas in Group C, most participants were ASA 2 with 13 (59.1%) and followed by ASA 1 with 9 (40.9%) samples. Based on the characteristics of ASA PS the results of the test were relatively homogeneous (p> 0.05).

B. Research Test Results

Table 4 shows the change in BIS mean at each observation after the intervention was given. In drug A, the mean value of T0 was 95, and in the T7 observation, it was 75.05 which means a decrease of 19.95. The results of statistical tests obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug A from the initial observation to the final observation. In drug B, the mean value of the T0 observation was 95.77 and the T7 observation was 53.59, which means a decrease of 42.18. The results of the statistical test obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug B from the initial observation to the final observation. Whereas in drug C, the mean value at T0 observation was 96.09 and in observation of T7 it is obtained the mean of 51.00 which means a decrease of 45.09. The results of the statistical test obtained p value (0.000) <0.05, which means that there is a BIS mean change in the treatment group using drug C from the initial observation to the final observation. Based on the comparison of differences from T0 - T7 observations based on the types of treatment, p value (0.000) <0.05, which means that there is a difference in mean differences between interventions with one another, where the greatest change occurs in the use of drug type C (45.09) and the smallest change occurs in use of drug type A (19.95).

Midazolam, like other benzodiazepines, results in a decrease in CMRO2 and analogous cerebral blood flow to barbiturates and propofol. Midazolam causes dose changes in regional cerebral blood flow in the brain region that is associated with normal functioning of the body, attention, and memory. Midazolam acts as a positive allosteric modulator on the gamma-aminobutyric acid (GABA) -A receptor. GABA-A receptors are selective ion channels (Griffin et al, 2013). This is in line with the study done by Kim et al which said that a dose of 0.08 can suppress the center of consciousness which indicated by a decrease in cerebral function that can be seen in the EEG (BIS) image(Kim et al, 2014).

V. CONCLUSIONS

- The use of 0.05 mg/KgBW midazolam can provide sedation effects that can reach sedation levels up to the BIS target > 60 - < 80 until the end of the study.
- Giving 0.08 mg/KgBW and 0.1 mg/KgBW midazolam gives a sedation effect that can reach the level of general anesthesia with BIS value < 60 in the 25th minute and 30th minute.
- The use of 0.05 mg/KgBW midazolam shows better result in maintaining the depth of sedation compared to 0.08 mg/KgBW and 0.1 mg/KgBW midazolam which can cause the sample to fall into the stage of general anesthesia.

SUGGESTIONS

- In accordance with the results of this study, 0.05 mg/KgBW midazolam can be used as a choice of sedation dose compared to 0.08 mg/KgBW and 0.1 mg/KgBW midazolam.
- In the next study, it is expected to assess the effect of midazolam administration on the time of conscious recovery of patients under general anesthesia.
- In the next study, it is expected to assess the effects of midazolam administration for a longer time and the addition of opioids with a larger number of samples to reduce the bias in previous studies.

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