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Comparison of Sedation Levels of Intramuscular Ketamine Premedication with Oral Ketamine Premedication in Pediatric Patients Using Bispectral Index

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Abstract:-

- ***Introduction***

In paediatric patient, preoperative anxiety tends to affect the appearance of delirium, sleep disorders and changes in postoperative behavior. Premedication drugs given without needles are more acceptable for children

- ***Objective***

This study aimed to determine the sedation level of oral ketamine premedication compared to intramuscular ketamine in paediatric patients using bispectral index.

- ***Method***

This study used a randomized controlled clinical trial method. The research was conducted in the Central Hospital of H. Adam Malik and Hospital network in the city of Medan in February 2019. The total sample obtained was 22 for the oral ketamine administration group and 22 samples for the intramuscular ketamine administration group.

- ***Results***

The results obtained showed that the level of sedation in intramuscular administration had a faster sedation effect than oral administration. Sedation levels on average were lower in intramuscular administration compared with oral which were observed at T1, T2, T3(p value 0,00). But the level of sedation tends to be the same starting from the observation time T4 to T6. The biggest change occurred in the IM group, which amounted to 36.50 compared to group O of 33.91(p value 0,01).

- ***Conclusions***

The administration of intramuscular ketamine had faster sedation effect than oral administration. But there was no difference in sediment levels between intramuscular and oral ketamine administration at 20 to 30 minutes.

Keywords:- *Ketamine, Peroral, Intramuscular, Bispectral Index.*

I. INTRODUCTION

In children, preoperative anxiety tends to cause delirium, sleep disorders and changes in postoperative behavior. To prevent surgery anxiety and separation from parents, adequate pharmacological intervention with pediatric sedation before the induction of anesthesia was found to be more effective than behavioral intervention (Kain *et al.* 2004).

The main goal of premedication is to reduce stress by maintaining hemodynamic parameters, facilitate the induction of anesthesia and induce amnesia. The child's age, weight, medication history, allergic status, and medical or surgical conditions are underlying factors that must be considered before giving premedication. In many cases, medicines given without needles are more preferable for children, families, and the medic team. Oral premedication does not increase the risk of aspiration pneumonia. (Riva *et al*, 1997).

Fasting before surgery has developed rapidly over the years and become an optimal guide for pediatric patients. This approach has been shown to significantly reduce stress associated with prolonged periods of fluid deficiency before anesthesia and surgery. For most patients, the presence of solid particles and/or fluid volumes greater than 0.8 ml/kg before induction of anesthesia, can cause symptomatic pulmonary aspiration of gastric contents in cases of regurgitation (Bouvet, 2011)

Child sedation in the ED is good for emergency therapy procedures that may be painful or that require a calm and cooperative child (such as wound closure, abscess drainage, Foreign body retrieval, lumbar puncture or fracture reduction) or to obtain diagnostic information (for example through medical imaging) is important aspects of medical practice (Mason, 2012). Sedation and analgesia for painful procedures are certainly considered as the standard of care that must be offered to all children if possible (Krauss *et al*., 2015). Although there are several guidelines published (Godwin *et al*., 2014), there are many variations in local and international practice in terms of choice of sedation agents and sedation procedures (Schofield *et al.*, 2013). Most of the literature relates to the parenteral route in the administration of sedatives,

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especially intravenous (IV) or intramuscular (IM) because of their ability to titrate doses and the reliability of the effects of the drug when administered through this route (Mason, 2012).

Underlying the use of ketamine, apart from pharmacodynamics is its safety profile. Ketamine is a drug that has been studied to more than 10,000 patients in more than 105 studies. The relative safety of ketamine compared with other agents is in its almost universal use stated in the literature in all indications, all patient groups, all administrative routes and in a variety of settings from the operating room to the emergency room, battlefield, prehospital environment, in developing and advanced countries (Svenson & Abernathy, 2007; Polomano *et al*., 2013; Bisanzo, *et al.*, 2012). The aspects of clinical effects that contribute to its safety are maintenance of airway protective reflexes even in deep sedation; maintenance of spontaneous ventilation with minimal, very rare or clinically insignificant hypoventilation; very rare apnea; low levels of hypopnoea and rare hypoxia; persistence or slight increase in heart index and increase in blood pressure but minimal changes to systemic vascular resistance due to direct smooth muscle relaxation; maintenance cerebral perfusion pressure during induction of anesthesia or deep sedation. Furthermore, ketamine is famous for its wide therapeutic range (Mion & Villevieille, 2013; White *et al*., 1982).

In general, severe and life-threatening side effects from the use of ketamine for pediatric sedation are very rare (Howes, 2004). Ketamine is fat soluble with low protein binding which results in a distribution volume of 2.3 L/kg at stable conditions. Bioavailability through intravenous, intramuscular, intranasal, rectal and oral pathways is 100%, 93%, 50%, 25%, and 20%, respectively. Peak plasma levels occur in 1 minute via IV route and within 5 minutes via the IM route. Ketamine is metabolized into active and inactive metabolites. The most studied and dominant active metabolite is norketamine which first appears in the blood 2-3 minutes after IV ketamine administration and reaches a peak in 30 minutes. (Mion & Villevieille, 2013). The rate of elimination of ketamine is high (similar to liver blood flow) by eliminating half-life of 2-3 hours, norketamine lasts more than 5 hours after administration of ketamine and its pharmacological effects, especially analgesia, contributes to the sustained effect of ketamine during the elimination phase with analgesia significantly superior to anesthesia (White *et al*, 1982). Until now, especially in Indonesia, there are no guidelines in choosing the route of administration of ketamine for sedation in children. Based on this background, we are interested in researching this issue.

II. RESEARCH METHODS

A. Research design

The design of this study was a randomized controlled clinical trial to determine differences in the level of sedation of intramuscular ketamine premedication to oral ketamine premedication in pediatric patients who will undergo anesthesia using Bispectral index.

B. Place

This study was conducted in H. Adam Malik Central Hospital Medan.

C. Time

The study was conducted on February 4-28, 2019.

D. Population

The study population was all pediatric patients who will undergo Central anesthesia in H. Adam Malik Central Hospital Medan.

E. Sample

The study sample was patients who met the inclusion and exclusion criteria. After being calculated statistically, all samples were divided into 2 groups:

- Group A received intramuscular ketamine 5 mg/kgBW premedication
- Group B received 15 mg/kg of oral ketamine premedication which was added to placebo syrup to 5 cc

- *Inclusion Criteria*
  - 1 - 12 years old
  - Patients with physical status ASA 1 and 2
  - Weight according to BMI
- *Exclusion Criteria*
  - The patient's parents refused to take part in the study
  - Patients with contraindications to the medications studied
  - Patients with neurology and/or psychiatry
- *Drop Out Criteria*
  - Heart and lung emergencies occur

F. Sample size

The estimation of sample size in this study was calculated based on the following formula:

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

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
X_1-X_2 = clinical judgement

From the calculations with the formula above, the sample size obtained was: n1 = n2 = 20 people, plus 10%for possible dropout, so it was 22 people. So the total number of samples from the two groups was 44 people.

G. Informed Consent

After obtaining approval from the Ethics Committee (Appendix 8), the parents or guardians of the patients received an explanation of the procedure to be undertaken and stated in writing their willingness on the informed consent sheet.

H. Procedure

➢ *Patient and Drug Preparation*

- After being approved by the Health Research Ethics Committee of the North Sumatera University Medical Faculty (Appendix 8) and the Health Research Ethics Committee at Haji Adam malik Central Hospital (Appendix 9) and obtaining informed consent, all samples were included in the inclusion and exclusion criteria.
- During the preoperative examination visit, the patient's parents were explained about the planned action for general anesthesia and the research procedure which includes examining the effects of sedation up to 24 hours after surgery.
- Samples were randomly divided into 2 groups, group A received intramuscular ketamine 5 mg/kg and group B received oral ketamine 15 mg/kg, then randomized by trained volunteers.
- Randomization was done by block, each sequence consisted of 4 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 is prepared by volunteers who did the randomization (researchers did not know the composition of the drugs given).
- The drug dose of group A, ketamine of 5 mg/kgBW, was injected intramuscularly 30 minutes before surgery.
- The drug dose of group B, ketamine of 15 mg/kgBW, was added into placebo syrup to 5 ml 30 minutes before surgery.

➢ *Implementation of the Study*

- After the patient arrived in 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, oxygen saturation) and a bispectral index monitor were installed.
- Both groups were prepared for general anesthesia.
- After giving ketamine, the time was recorded as T0, and sedation levels were assessed using bispectral index. This assessment was carried out directly by researchers who were not involved in administering drugs to these patients.
- Both groups of patients were given 0.01mg/KgB SA injection and 0.01mg/kgBB midazolam intravenously.
- The patients were then observed in the premedication room and transferred to the operating room 30 minutes after the administration of ketamine.
- The observation of sedation levels and the need for additional sedative drugs was carried out directly by researchers at minutes 0 (T0), 5 (T1), 10 (T2), 15 (T3), 20 (T4), 25 (T5), and 30 (T6) after the administration of ketamine.
- The results of observational data in both groups were compared statistically
- 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.

I. Data Management and Analysis Plans

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. RESULTS AND DISCUSSION

A. Characteristics of the sample

This research was conducted for 1 month, in February 2019 at Haji Adam Malik Hospital in Medan. This study aims to determine the differences in the level of sedation of intramuscular ketamine premedication to oral ketamine premedication in pediatric patients who will undergo anesthesia using Bispectral index.

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Characteristics	Treatment				total		P value
	IM		O				
	n	%	n	%	n	%	
Sex							
Male	12	54.5%	10	45.5%	22	50.0%	0.763*
Female	10	45.5%	12	54.5%	22	50.0%	
Age (mean±SD)	4.73±3.47		5.55±3.53				0.365**
Diagnosis							
Angiofibroma	1	4.5%	0	0.0%	1	2.3%	
ASD	3	13.6%	2	9.1%	5	11.4%	
Atresia	4	18.2%	6	27.3%	10	22.7%	
epilepsy	1	4.5%	0	0.0%	1	2.3%	
Hirschprung post pull through	7	31.8%	8	36.4%	15	34.1%	0.564*
Ovarian Cyst	1	4.5%	0	0.0%	1	2.3%	
Meningocele	2	9.1%	0	0.0%	2	4.5%	
PDA	3	13.6%	3	13.6%	6	13.6%	
Patellar Tendon Rupture	0	0.0%	1	4.5%	1	2.3%	
Skin defect cruris	0	0.0%	1	4.5%	1	2.3%	
Intra-Abdomen Tumor	0	0.0%	1	4.5%	1	2.3%	
ASA							
1	15	68.2%	16	72.7%	31	70.5%	1.000*
2	7	31.8%	6	27.3%	13	29.5%	
Total	22	100.0%	22	100.0%	44	100.0%	

Table 1:- Characteristics of the sample
* Chi Square test
** Mann Whitney test

The samples obtained in this study amounted to 44 samples that were in accordance with the inclusion and exclusion criteria, with 22 sample group were given the treatment of intramuscular ketamine and 22 sample group treated with ketamine orally. The sample characteristics of the sampe are shown in Table 1 below.

Table 1 shows the distribution of characteristics of respondents based on the treatment group. Sex, male in IM group were 12 respondents (54.5%) and in O group were 10 respondents (45.5%) while female in IM group were 10 respondents (45.5%) and in O group were 12 respondents (54.5 %). From the results of the statistical test, p value (0.763)> 0.05, which means that there is no difference in the proportion of sex between the IM group and O group. Age, the mean age in the IM group was 4.73 years old while in the O group was 5.55 years old. From the results of the statistical test, the p value (0.365)> 0.05 means that there is no difference in the mean age between the IM group and O group.

ASA, score 1 in IM group were 15 respondents (68.2%) and in O group were 16 respondents (72.7%) while score 2 in IM group werec7 respondents (31.8%) and in O group were 6 respondents (27.3%). From the results of the statistical test, the p value (1,000)> 0.05 means that there is no difference in the proportion of ASA scores between the IM group and O group.

B. Description of sedation level in the use of intramuscular ketamine

The distribution of sedation level in the use of intramuscular ketamine is shown in Table 2

sedation level	Time for intramuscular ketamine administration						
	T0	T1	T2	T3	T4	T5	T6
81-100	22	19	0	0	0	0	0
61-80	0	3	22	22	9	3	3
41-60	0	0	0	0	13	19	19
21-40	0	0	0	0	0	0	0
0-20	0	0	0	0	0	0	0

Table 2:- Sedation level in the use of intramuscular ketamine

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Table 2 shows that the level of sedation in intramuscular ketamine administration began to reduce the level at 10 minutes observation time (T1) and almost all samples experienced a decrease in sedation in BIS 61-80 in 10-15 minutes. The level of sedation in oral ketamine administration has the same level of sedation at 25 minutes (T5) and 30 minutes (T6).

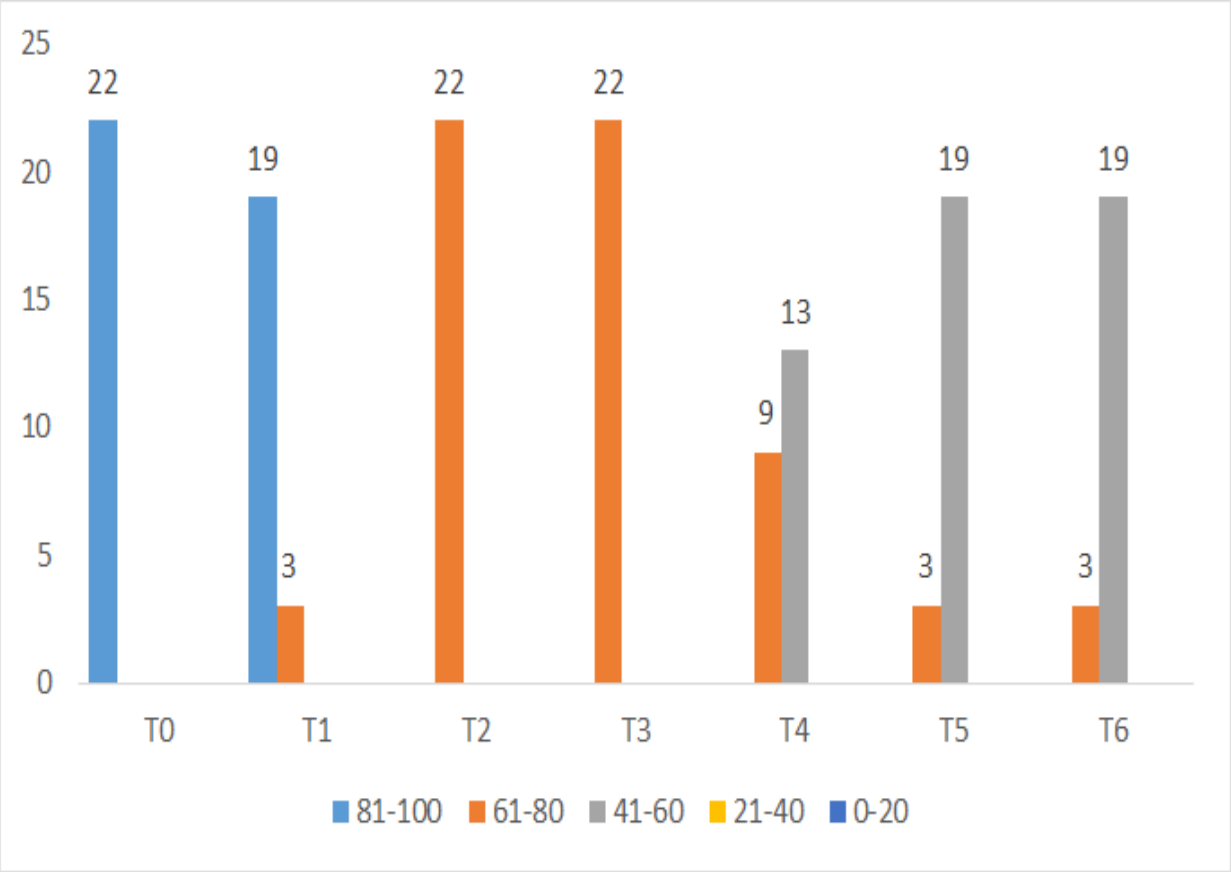

Fig 1:- Level of sedation in intramuscular ketamine administration

C. Description of sedation level in oral ketamine use

The description of the sedation level distribution in oral ketamine use is shown in Table 3

Sedation level	**Time for oral ketamine administration**						
	T0	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
81-100	22	22	10	1	0	0	0
61-80	0	0	12	21	18	6	6
41-60	0	0	0	0	4	16	16
21-40	0	0	0	0	0	0	0
0-20	0	0	0	0	0	0	0

Table 3:- The description of the sedation level in oral ketamine use

Table 3 shows that the level of sedation in the administration of oral ketamine began to decrease the level at 10 minutes observation time (T2) and the sedation level experienced a significant decrease after 15 minutes observation time (T3). The level of sedation in oral ketamine administration has the same level of sedation at 25 minutes (T5) and 30 minutes (T6).

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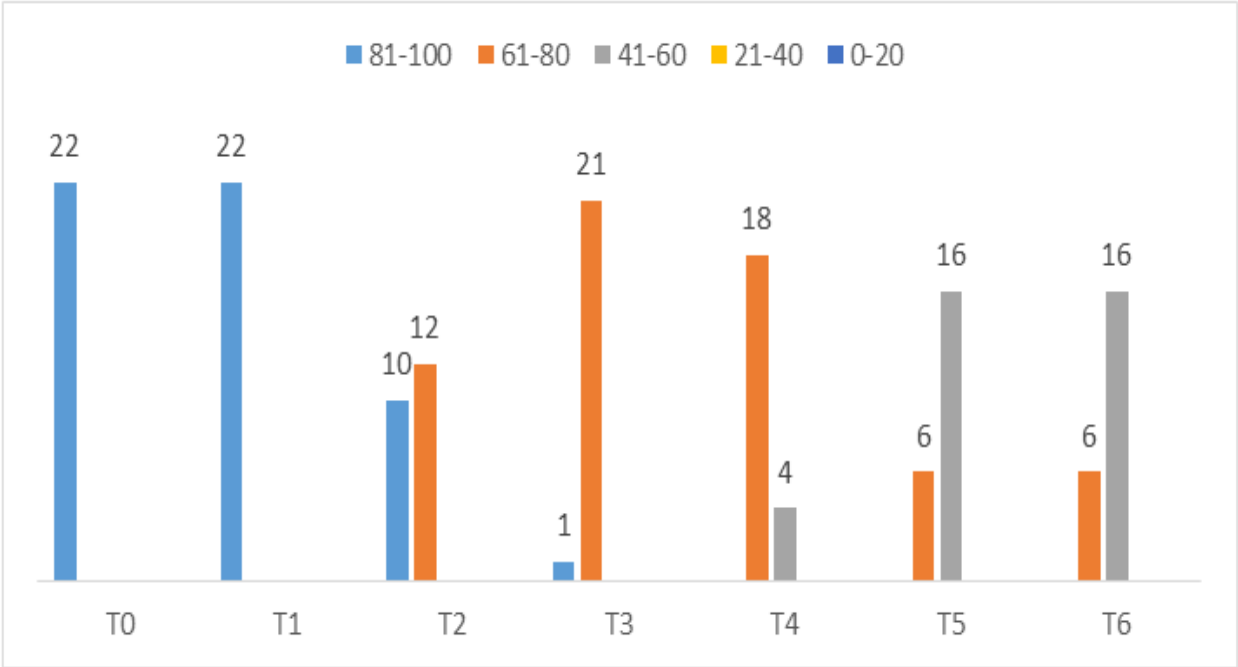

Fig 2:- Sedation level for oral ketamine administration

Based on Figure 2 it can be concluded that the sedation level has decreased in 10 minutes to the first 25 minutes. The number of samples experiencing sedation levels in BIS 81-100 decreased from 22 samples in T2 minutes to 1 sample at T3 minutes. While the sedation level 61-80 was reduced from 21 samples at T3 minutes to 6 samples at T5 minutes.

D. Comparison of the sedation level of intramuscular ketamine premedication to oral ketamine premedication in pediatric patients using the bispectral index.

The comparison of the sedation level of intramuscular ketamine premedication to oral ketamine premedication in pediatric patients using the bispectral index was shown in Table 4

Group		**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**Difference**	**P value**
IM	Mean	94.09	83.77	72.73	66.91	57.59	57.59	57.59	36.50	0.000*
	SD	2.81	3.50	1.83	1.72	2.56	2.56	2.56	2.26	
O	Mean	93.23	88.18	81.64	74.23	59.32	59.32	59.32	33.91	0.000*
	SD	2.84	2.04	4.54	3.66	1.59	1.59	1.59	2.45	
P value		0.317**	0.000***	0.000***	0.000***	0.001***	0.011**	0.011**	0.011**	

Tabel 4:- The comparison of the sedation level of intramuscular ketamine premedication to oral ketamine premedication in pediatric patients using the bispectral index.

* Friedman test

** t Independent test

*** Mann Whitney test

Table 4 shows the score of changes that occur in each observation. In the IM group, the initial observations obtained a mean of 94.09 and the final observations obtained a mean of 57.79, the results of the statistical test obtained p value (0.000) <0.05 which means that there are mean differences from initial observations to final observations with a continuous decline in the mean value. Whereas in O group, the initial observations obtained a mean of 93.23 and in the final observation obtained a mean of 59.32, the results of the statistical test obtained p value (0.000) <0.05, which means that there are mean differences from initial observations to final observations with a continuous decline in the mean value. From these results, the biggest change occurred in the IM group, which amounted to 36.50 compared to O group with 33.91.

This study also looked at a comparison of sedation levels in oral ketamine and intramuscular ketamine presented with a graph (Figure 3).

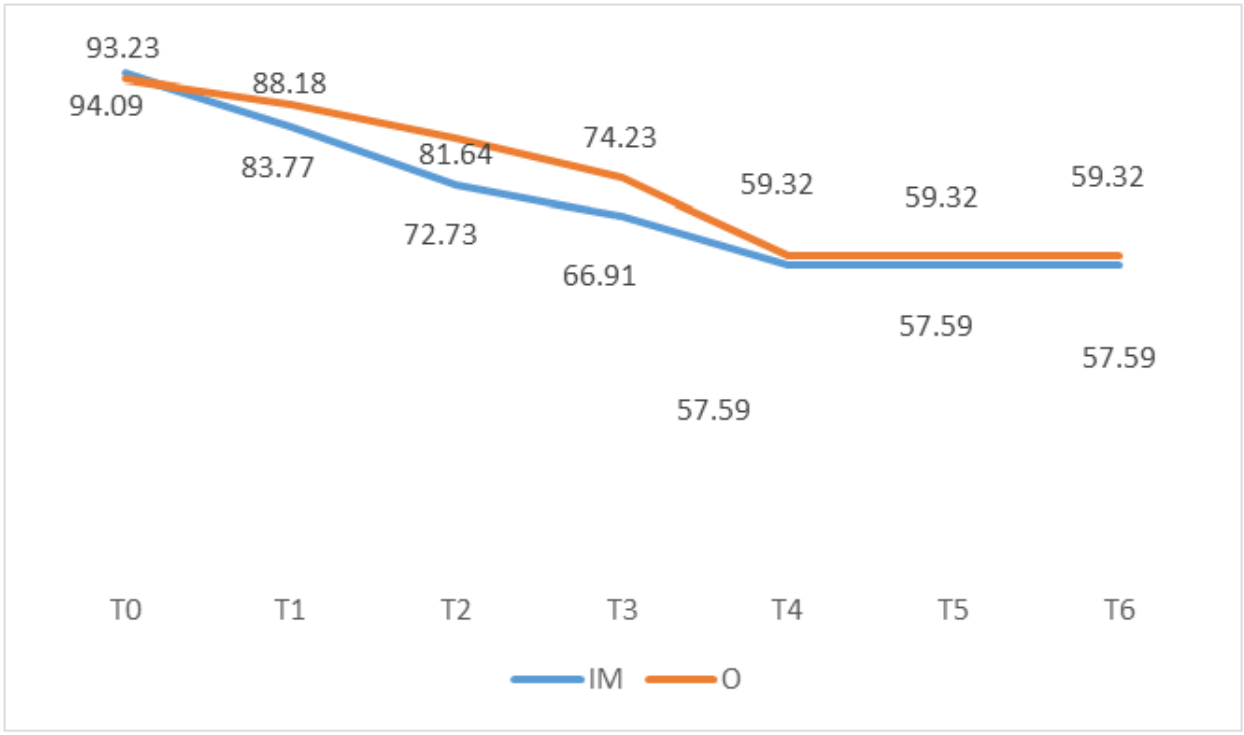

Fig 3:- Comparison of sedation levels in oral ketamine and intramuscular ketamine

Figure 3 shows that sedation levels in intramuscular administration have a faster sedation effect than oral administration. Sedation levels on average were lower in intramuscular administration compared with oral which were observed at T1, T2, T3. But the level of sedation tends to be the same starting from the observation time T4 to T6.

IV. DISCUSSION

This study was conducted to determine the level of sedation of intramuscular ketamine premedication compared to oral ketamine premedication in pediatric patients using the Bispectral Index. Pediatric anesthesia always presents a big challenge because it relates to the most psychologically vulnerable age groups. Although anesthesia during surgery prevents children from remembering the actual surgical events, the children often experience stress during the preparation for surgery. The use of effective sedatives significantly minimizes emotional trauma associated with perioperative anxiety and sequelae. Provision of premedication drugs aims to reduce stress response by maintaining hemodynamic parameters, facilitate the induction of anesthesia and induce amnesia. In many cases, medicines given without needles are more preferable for children, families and the medic team.

Apart from the above objectives, giving premedication to children is also useful to separate children from their parents. Ideal premedication should include the ease of administration, faster sedation effects, and minimal side effects. In the study conducted, it was found that oral administration of ketamine was preferred by children because of the sweet taste and less painful. This is in accordance with other studies conducted in which children prefer the painless administration of drugs.

The samples obtained in this study amounted to 44 samples that were in accordance with the inclusion and exclusion criteria, with 22 sample group were given the treatment of intramuscular ketamine and 22 sample group treated with ketamine orally. The sample characteristics of the sampe are shown in Table 1.

Based on Table 2, it shows that the level of sedation in intramuscular ketamine administration began to reduce the level at the time of observation of 5 minutes (T1) and almost all samples experienced a decrease in sedation in BIS 61-80 in 10-15 minutes. In a study conducted by Mehdi *et al*., In children who were given Ketamin intramuscular premedication 4mg/Kg, 86.7% of patients experienced sedation in 5 minutes while in 10 minutes, all patients who were the object of the study were completely sedated. In a study by Hannalah & Patel in 1989 also showed that the administration of ketamine at a dose of 2mg/Kg showed changes in child behavior, they became calmer in 3 minutes.

Table 3 shows that the level of sedation in the administration of oral ketamine began to decrease the level at 10 minutes observation time (T2) and the sedation level experienced a significant decrease after 15 minutes observation time (T3). A study conducted by Funket, *et al*. in 2000 also showed a decrease in the degree of consciousness in children under premedication of oral ketamine began in 12 minutes. This is also in accordance with studies conducted by Geetanjali *et, al* (2003) and studies by Altiparmak et, al (2016) which showed that in most children given oral ketamine, sedation began to be

obtained in 15 to 20 minutes. In the study conducted by geetanjali also mentioned that the sedation score at 30 minutes and the score of anxiety on separation from parents was also satisfactory.

The study conducted by Turhanoglu, *et. al*. in 2003 regarding the administration of various doses of ketamine administered orally as premedication showed that administration at the lowest dose (4mg/KgBW) did not provide the expected sedation effect in which a dose of 8mg/KgBW results in faster and more satisfying sedation thereby reducing anxiety or undesirable response in the induction of anesthesia. This study also shows that there is no long-term sedation effect in conscious recovery postoperative in the recovery room.

JA Kulkarni, et.al, showed that oral ketamine is an effective pre-medication in pediatric patients. This study found that ketamine was well received by all children. All patients experience calm separation from parents. Recent research has shown that administering a small amount of fluid before taking general anesthesia (5-15ml) to children does not affect the risk of aspiration of gastric contents.

Turhanoglu *et, al*. in his research also said that the administration of flavored mixtures in ketamine drugs greatly influenced the tendency of children in accepting oral premedication. In addition, sweet taste also minimizes the risk of nausea or vomiting in children shortly after the administration of ketamine. In this study, the use of cherry syrup mixed with ketamine according to a dose of up to 5ml is very preferred and there are no complaints about the taste caused.

In this study, we obtained the result that intramuscular or oral administration of ketamine has the same level of sedation at 25 minutes (T5) and 30 minutes (T6). Figure 3 shows that sedation levels in intramuscular administration have a faster sedation effect than oral administration. Sedation levels on average were lower in intramuscular administration compared with oral administration which was observed at T1, T2, T3. But the level of sedation tends to be the same starting from the observation time T4 to T6.

V. CONCLUSIONS

- There is a significant difference in the start of the sedation in intramuscular ketamine premedication compared to oral ketamine premedication based on BIS values.
- In the premedication of intramuscular ketamine the patient was found to be sedated starting in 10 minutes while the premedication of oral ketamine, the sedation worked starting in 15 minutes.
- There is no difference in the level of sedation between administration of intramuscular ketamine and oral ketamine in 20 minutes onwards.

SUGGESTIONS

- Further research needs to be done about the comparison of side effects caused after surgery on the administration of ketamine premedication through both intramuscular and oral.
- In terms of reducing trauma in pediatric patients before surgery, giving premedication through a non-painful pathway in this case can be done considering the same effectiveness in terms of achieving sedation levels even though they have a longer onset.

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