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The Effects of Ketamin-Midazolam and Ketamin-Propofol on Bispectral Index Score as Sedatives During Bone Marrow Puncture Procedure Among Pediatrics

Aldiar[1], Fredi Heru Irwanto[2*], Andi Miarta[2], Irfannuddin[3]

[1] Resident of Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Universitas Sriwijaya, Mohammad Hoesin Hospital, Palembang, Indonesia
[2] Consultant of Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Universitas Sriwijaya, Mohammad Hoesin Hospital, Palembang, Indonesia
[3] Department of Physiology, Faculty of Medicine Universitas Sriwijaya, Palembang, Indonesia

***Corresponding author:**
Fredi Heru Irwanto

Consultant of Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Universitas Sriwijaya, Mohammad Hoesin Hospital, Palembang, Indonesia

Email:

fhaeroo.dr@gmail.com

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ABSTRACT

Background: Bone Marrow Puncture (BMP) is an invasive procedure associated with pain and anxiety. The ketamine-midazolam and the ketamine-propofol is an effectivecombination with minimal side effects. This study of the study aims to compare the effect of the combination of ketamine-midazolam and ketamine-propofol on sedation depth based on BIS in pediatric leukemia patients undergoing BMP.

Methods: This study was a randomized controlled trial that was done single-blinded. The population was all pediatric patients diagnosed with leukemia who underwent BMP at RSMH and performed sedation. The research sample is the population that fulfill the inclusion and exclusion criteria. The sample size foreach group was 25, with 50 Subjects in total. Sampling was done by block randomization.

Results: This study found no differences in sex, age, and body weight between the two groups ([p=1.000], [p=0.845], and [p=0.147], respectively). In this study, there was no difference in mean MAP (p=0.592), oxygen saturation (p=0.164), heart rate (p=0.098), and respiratory rate(p=0.252) before intervention between the two groups. BIS value of the two groups had significant difference before and after the intervention where the two groups could reduce BIS to reach the optimal value of sedation <60 (p <0.05) There was no difference in BIS before intervention in the two groups (p=0.385). In this study, it was found that hypersalivation occurred more frequently in the ketamine-midazolam combination group.

Conclusion: The combination of ketamine-midazolam and ketamine-propofol was equally good for sedation as indicated by a decrease in the mean BIS in patients undergoing BMP.

Keywords: Bone-Marrow Puncture, Bispectral-Index Score, Ketamine, Midazolam, Propofol

Introduction

Bone Marrow Puncture (BMP) is an invasive procedure commonly performed on children and has been associated with pain and anxiety. During these procedures, children often experience great fear and anxiety, this is traumatic for both the patient and the parents.[1,2] Optimal pain and distress management techniques for children requiring repeated procedures vary widely including sedation, anesthesia. general, and psychological therapies such as distraction techniques, hypnotherapy, and relaxation. [3] Poor sedation management can lead to long-term psychological harm.[4]

Procedural sedation is an important strategy in BMP by giving sedatives or analgesics to intentionally suppress level of consciousness. The use of procedural sedation is appropriate to reduce pain and anxiety during interventional or diagnostic procedures, including emergencies, for all age groups.[5,6]

The ideal procedural sedation drug should have sedative, analgesic, and amnestic properties as well as a rapid onset and short duration of action to allow safe and rapid recovery, be painless when administered, cause no significant side effects, and can maintain cardiopulmonary homeostasis. [7,8] Objectively assessing the depth of sedation can use the Bispectral Index Score (BIS) tool which providesthe best prediction of the level of consciousness. BIS is a noninvasive electroencephalographic method that shows changes in the electrical activity of the brain, which can monitor the patient's hypnotic state during sedation and anesthesia.[9,10]

The combination of ketamine-midazolam and the ketamine-propofol is an effective sedation combination with minimal side effects. Research comparing the combination of ketamine-midazolam and ketamine-propofol to the depth of sedation based on the Bispectral Index Score to the author's knowledge has never been done. Therefore, it is necessary to research the comparison of the combined effect of ketamine-midazolam and ketamine-propofol combination on sedation depth based on the Bispectral Index Score (BIS) in leukemia patients undergoing BMP.

Material and method

This research is a single-blind randomized controlled trial done at the Chemotherapy room at Dr. Mohammad Hoesin Central Hospital Palembang conducted after approval from the Ethics Committee of Medical Faculty of Sriwijaya University.

The study target population was all pediatric patients age 3-18 years old with a diagnosis of leukemia who will undergo BMP at Dr. Mohammad Hoesin Palembang on July-December 2020. The

sample size of each group was 23. Taking into account the 10% dropout criteria, the sample size for each group is 25, so the total sample is 50 people. Sampling was done by block randomization. Block randomization is carried out by trained volunteers, hereinafter referred to as the first volunteer. The treatment group was divided into two groups, namely group A and group B. The number of sequence combinations was 4. With closed eyes, drop the pen on the random table. Take a two-digit number, the number the pen points to is the initial number to determine the sequence. Then choose the number down from the first number until you get the number of sequences that match the sample size. Then the sequence obtained is arranged sequentially according to the envelope number. Then the second volunteerwho has been trained on research procedures will take an envelope to inform what interventions will be carried out on the research subject.

Patients with a history of allergy to ketamine, midazolam, or propofol, Patients with airway obstruction disorders, Patients with increased ocular pressure and intracranial pressure, and patients that refuse sedation were excluded from the study. Patients will be dropped out of the study if an allergic reaction occurred during sedation or the patient is apneic or dies during the procedure.

Patients who fulfiil the inclusion and exclusion criteria were informed and signed an informed consent 24 hours before the procedure. In the BMP room, an electrocardiogram (EKG), BIS, blood pressure, and SpO2 are monitored. SA 0.01 mg/kg was given as premedication to prevent bradycardia and hypersalivation. Patients were positioned in pronation or lateral decubitus position. Patients were then given oxygen via nasal cannula 2-4 L / min. Patients were randomly divided into two groups using the closed envelope method.

1. The patients in group 1 were initially given 0.05 mg / kg (iv) midazolam and then 2 minutes later, 0.5 mg / kg ketamine (iv).
2. Patients in group 2 were initially given 0.25 mg / kg (iv) propofol and 2 minutes later were given 0.5 mg / kg ketamine (iv).

The sedation rate was measured using the BIS score during the procedure. Mean arterial blood pressure (MAP), HR, SpO2, respiratory rate (RR), RSS, and drug dose were the parameters recorded. This parameter is recorded at the following times: (T0); at the beginning when the drug was given, (T1); 2 minutes after sedation was given, (T2); 5 minutes, (T3); 10 minutes, (T4), 15 minutes, (T5); 20 minutes, (T6); 25 minutes, (T7); 30 minutes, measured every 5 minutes until the patient is fully conscious. The

examination was carried out by 2 residents from the anesthesiology department as volunteers who had received an explanation of the research and direction on how the examination would be carried out and its interpretation. The results of the examination are recorded on the observation sheet. Observations were also carried out on side effects such as complaints of nausea, vomiting, hallucinations, bradycardia, bradypnea, hypotension, hypersalivation in the subject, starting from (T0) to completion of sedation, andevaluated for 24 hours post sedation. If the patient is hypotensive (blood pressure drops 20-30% basal blood pressure) the patient is given 250-500 ml of crystalloid or 100-250 ml of colloid. If the patient has bradycardia, given Sulfas Atropine 0.01 mg/kg BW - 0.02 mg/kg or epinephrine (0.5 ml of 2.25% solution with 3 ml of NS) If the patient is oxygen desaturated, the patient is given 100% oxygen via Non -ReBreathing Mask (NRM) and if desaturation is not corrected and the patient's apnea condition is subjected to intubation with Endotracheal Tube (ETT). Subjects who experience complaints of nausea or vomiting are given ondansetron therapy 4 mg (0.1 mg/kb in children). Subjects who are hypothermic aretreated with air warmers, to increase their body temperature to normal.

Data on the basic characteristics of research subjects were analyzed by univariate analysis to explain the population. Descriptive analysis in the form of numerical data is presented in graphical and narrative tables in the form of mean ± standard deviation or median (minimum-maximum) if not normallydistributed. Comparing the mean difference between the 2 groups was carried out by using the Independent T-test statistical test if the data were normally distributed and the Mann-Whitney if the data were not normally distributed. Categorical variables will be displayed as a percentage (number). Categorical data were analyzed using the Chi-Square Test. All statistical analyzes used SPSS version 22.

Results

The general characteristics of the samples are shown in table 1 with statistical analysis, it was found that there was no gender difference between the ketamine + midazolam and ketamine + propofol groups ($p = 1.000$), there was no difference in the mean age between the ketamine + midazolam and ketamine + propofol groups ($p = 0.845$) and there was no difference in mean weight. between the ketamine + midazolam and ketamine + propofol groups ($p = 0.147$). Patients in the ketamine + propofol group woke up faster than the midazolam ketamine group ($p = 0.000$) but there was no difference between the onset of sedation between the two groups ($p = 0.199$) (table 1)

Table 1. General characteristics of research subjects (n = 50).

Variable	Ketamin - Midazolam Group (n= 25)	Ketamin - Propofol Group (n = 25)	P-Value
Sex, n (%)			
Boys	18 (72.0)	19 (76.0)	1.000[a]
Girls	7 (28.0)	6 (24.0)	
Age (years)			
Mean ± SD	7.72 ± 3.75	7.60 ± 41.6	0.845[b]
Median (Min-Max)	7 (3-14)	8 (1-15)	
Body Weight (kg)			
Mean ± SD	19.12 ± 8.83	15.92 ± 8.69	0.147[b]
Median (Min-Max)	17 (8-40)	14 (4-40)	
Sedation onset			
Mean ± SD	1.37 ± 0.494	1.56 ± 0.506	0.199[b]
Median (Min-Max)	1 (1-2)	2 (1-2)	
Time to wake			
Mean ± SD	9.83 ± 0.38	8.64 ± 1.07	0.000[b]
Median (Min-Max)	10 (9-10)	9 (7-10)	
[a]Uji Chi *Square.* p = 0.05			
[b]*Mann Whitney Test.* p = 0.05			

Hemodynamic characteristics before intervention

In this study, the results showed that there was no difference in mean arterial pressure (MAP) before intervention (p = 0.592), oxygen saturation before intervention (p = 0.164), heart rate before intervention (p = 0.098) and respiratory rate before intervention (p = 0.252) between the ketamine + midazolam and ketamine + propofol groups (table 2).

Table 2. Hemodynamic characteristics of research subjects (n = 50).

Variable	Ketamin + Midazolam Group (n= 25)	Ketamin + Propofol Group (n = 25)	P Value
Sex, n (%)			
Boys	18 (72.0)	19 (76.0)	1.000[a]
Girls	7 (28.0)	6 (24.0)	
Age (years)			
Mean ± SD	7.72 ± 3.75	7.60 ± 41.6	0.845[b]
Median (Min-Max)	7 (3-14)	8 (1-15)	
Body Weight (kg)			

Mean ± SD	19.12 ± 8.83	15.92 ± 8.69	0.147[b]
Median (Min-Max)	17 (8-40)	14 (4-40)	
Sedation onset			
Mean ± SD	1.37 ± 0.494	1.56 ± 0.506	0.199[b]
Median (Min-Max)	1 (1-2)	2 (1-2)	
Time to wake			
Mean ± SD	9.83 ± 0.38	8.64 ± 1.07	0.000[b]
Median (Min-Max)	10 (9-10)	9 (7-10)	

[a]Uji Chi *Square*, p = 0.05
[b]*Mann Whitney Test*, p = 0.05

Bispectral index score (BIS) before intervention

In this study, the results showed that there was no difference in the Mean Bispectral Index Score (BIS) between both groups (p = 0.385) (table 3).

Table 3. Bispectral index score (BIS) for research subjects (n = 50).

Variable	Ketamin + Midazolam Group (n= 25)	Ketamin + Propofol Group (n = 25)	P-Value
BIS			
Mean ± SD	96.20 ± 1.472	95.84 ± 1.405	0.385
Median (Min-Max)	96 (93-98)	96 (93-98)	

Effectiveness of ketamine-midazolam and ketamine-propofol

Bispectral index score (BIS)

In the two groups of sedation combinations, the p-value was 0.000, so it can be concluded that there was a difference in mean BIS in each time group, BIS before intervention was greater than after intervention, this means that the two combinations could significantly reduce BIS. In Table 4 it can be seen that the ketamine-propofol group has a greater BIS value at 7 minutes after the intervention than the ketamine-midazolam group, this indicates that the ketamine + propofol group can raise awareness faster than the ketamine + midazolam group.

Table 4. Effectiveness of ketamine-midazolam and ketamine-propofol on BIS

Time	BIS (Mean ± SD)	*p-value*
Ketamin + Midazolam Group		
Before intervention	96.25 ± 1.48	0.000
1 minutes after intervention	62.33 ± 13.88	
2 minutes after intervention	52.50 ± 9.59	
3 minutes after intervention	53.66 ± 10.44	
4 minutes after intervention	53.70 ± 12.64	
5 minutes after intervention	55.79 ± 14.08	
6 minutes after intervention	64.00 ± 11.32	
7 minutes after intervention	71.54 ± 9.09	
8 minutes after intervention	80.08 ± 6.37	
9 minutes after intervention	86.62 ± 3.07	
10 minutes after intervention	91.04 ± 1.08	
Ketamin + Propofol Group		
Before intervention	95.84 ± 1.405	0.000
1 minutes after intervention	66.80 ± 13.88	
2 minutes after intervention	54.32 ± 12.48	
3 minutes after intervention	56.52 ± 12.76	
4 minutes after intervention	57.64 ± 14.87	
5 minutes after intervention	59.80 ± 16.96	
6 minutes after intervention	69.40 ± 12.60	
7 minutes after intervention	77.80 ± 9.54	
8 minutes after intervention	85.28 ± 7.11	
9 minutes after intervention	90.00 ± 2.98	
10 minutes after intervention	91.92 ± 1.49	

Mean arterial pressure (MAP)

In both groups of sedation. the p-value was <0.005 (0.008 and 0.000) so it can be concluded that there is a difference in Mean MAP in each time group, MAP before intervention is greater than after the intervention, this means that the two sedation combinations can significantly reduce MAP (Table 5).

Table 5. Effectiveness of ketamine-midazolam and ketamine-propofol on MAP

Time	BIS (Mean ± SD)	*p-value*
Ketamin - Midazolam Group		
Before intervention	68.28 ± 8.942	0.008
2 minutes after intervention	65.60 ± 9.287	
5 minutes after intervention	65.32 ± 9.335	
10 minutes after intervention	64.92 ± 7.604	
15 minutes after intervention	64.68 ± 6.427	

20 minutes after intervention	65.08 ± 7.153	
Ketamin + Propofol Group		
Before intervention	66.92 ± 8.129	0.000
2 minutes after intervention	63.64 ± 7.879	
5 minutes after intervention	63.96 ± 7.673	
10 minutes after intervention	63.48 ± 6.084	
15 minutes after intervention	63.84 ± 5.991	
20 minutes after intervention	64.60 ± 6.813	

Oxygen saturation (SpO2)

In the Ketamine - Propofol Group, there is a significant difference in oxygen saturation and oxygen saturation increases at 5 minutes to 20 minutes after the intervention, which means that the combination can significantly increase oxygen saturation. There was no significant difference in the ketamine + midazolam combination group (table 6)

Table 6. Effectiveness of ketamine-midazolam and ketamine-propofol on oxygen saturation

Time	BIS (Mean ± SD)	*p-value*
Ketamin - Midazolam Group		
Before intervention	99.04 ± 0.351	0.063
2 minutes after intervention	98.88 ± 1.092	
5 minutes after intervention	99.20 ± 0.764	
10 minutes after intervention	99.24 ± 0.764	
15 minutes after intervention	99.36 ± 0.489	
20 minutes after intervention	99.36 ± 0.569	
Ketamin + Propofol Group		
Before intervention	98.60 ± 1.155	0.001
2 minutes after intervention	97.80 ± 1.414	
5 minutes after intervention	98.80 ± 1.291	
10 minutes after intervention	98.92 ± 0.759	
15 minutes after intervention	99.40 ± 0.577	
20 minutes after intervention	99.12 ± 0.600	

Heart rate (HR)

In both groups, the combination of sedation obtained p-value was <0.005 (0.000 and 0.007), it can be concluded that there is a significant difference in mean heart rate in each time group and the two sedation combinations can significantly reduce heart rate (table 7).

Table 7. Effectiveness of ketamine-midazolam and ketamine-propofol on heart rate

Time	Heart Rate (Mean ± SD)	*p-value*
Ketamin - Midazolam Group		
Before intervention	96.52 ± 13.29	0.000
2 minutes after intervention	101.3 ± 10.92	
5 minutes after intervention	99.92 ± 9.798	
10 minutes after intervention	98.92 ± 10.47	
15 minutes after intervention	97.04 ± 11.53	
20 minutes after intervention	96.76 ± 12.07	
Ketamin + Propofol Group		
Before intervention	102.64 ± 12.32	0.007
2 minutes after intervention	102.92 ± 13.39	
5 minutes after intervention	102.64 ± 11.73	
10 minutes after intervention	101.64 ± 11.99	
15 minutes after intervention	100.76 ± 13.46	
20 minutes after intervention	100.40 ± 13.64	

Respiratory rate (RR)

Both groups of sedation combination obtained p-value <0.005 (0.009 and 0.000) so it can be concluded that there is a significant difference in Mean respiratory rate in each time group, the respiratory rate 20 minutes after the intervention is lower than before intervention, this means that the two sedation combinations can reduce respiratory rate significantly (Table 8).

Table 8. Effectiveness of ketamine-midazolam and ketamine-propofol on respiratory rate

Time	**Heart Rate (Mean ± SD)**	***p-value***
Ketamin - Midazolam Group		
Before intervention	20.76 ± 1.451	0.009
2 minutes after intervention	21.28 ± 1.400	
5 minutes after intervention	20.64 ± 1.497	
10 minutes after intervention	19.96 ± 1.369	
15 minutes after intervention	20.52 ± 1.194	
20 minutes after intervention	20.36 ± 1.114	
Ketamin + Propofol Group		
Before intervention	21.12 ± 1.424	0.000
2 minutes after intervention	19.12 ± 1.739	
5 minutes after intervention	19.52 ± 1.735	
10 minutes after intervention	19.20 ± 2.236	
15 minutes after intervention	19.52 ± 2.163	
20 minutes after intervention	20.12 ± 1.787	

Comparison of effectiveness between ketamine-midazolam and ketamine-propofol

Bispectral index score (BIS)

In this study, the results showed that there was no difference in Mean Bispectral Index Score (BIS), 2 minutes after intervention (p = 0.255), 5 minutes after intervention (p = 0.868), 10 minutes after intervention (p = 0.777), 15 minutes after intervention (p = 0.643) and 20 minutes after intervention (p = 0.800) between Ketamine + Midazolam Group and ketamine + propofol (Table 9).

Table 9. Bispectral index score (BIS) of research subjects per time (n = 50).

Bispectral index score **(BIS)**	**Ketamin + Midazolam Group (n= 25)**	**Ketamin + Propofol Group (n = 25)**	**P-Value**
2 minutes After intervention			
Mean ± SD	61.96 ± 13.72	67.36 ± 13.58	0.255
Median (Min-Max)	53 (48-82)	77 (50-82)	
5 minutes After intervention			
Mean ± SD	52.12 ± 9.58	54.60 ± 12.29	0.868
Median (Min-Max)	50 (43-73)	50 (40-73)	
10 minutes After intervention			
Mean ± SD	53.64 ± 10.23	56.32 ± 12.86	0.777
Median (Min-Max)	53 (42-75)	53 (38-75)	
15 minutes after intervention			
Mean ± SD	53.80 ± 12.38	57.16 ± 15.12	0.643
Median (Min-Max)	56 (40-79)	56 (40-79)	
20 minutes After intervention			
Mean ± SD	55.72 ± 13.79	59.24 ± 17.39	0.800
Median (Min-Max)	54 (42-86)	54 (40-86)	

Mean Arterial Pressure

The results showed that there was no difference in mean arterial pressure (MAP) 2 minutes after intervention (p = 0.520), 5 minutes after intervention (p = 0.576), 10 minutes after intervention (p = 0.675), 15 minutes after intervention (p = 0.589) and 20 minutes after intervention (p = 0.533) between Ketamine + Midazolam Group and ketamine + propofol (table 10)

Table 10. Mean arterial pressure of research subjects per time (n = 50).

Mean Arterial Pressure	Ketamin + Midazolam Group (n= 25)	Ketamin + Propofol Group (n = 25)	P-Value
2 minutes After intervention			
Mean ± SD	65.60 ± 9.287	63.64 ± 7.879	0.520[a]
Median (Min-Max)	64 (50-80)	63 (50-79)	
5 minutes After intervention			
Mean ± SD	65.32 ± 9.335	63.96 ± 7.673	0.576[b]
Median (Min-Max)	64 (50-80)	63 (51-77)	
10 minutes After intervention			
Mean ± SD	64.92 ± 7.604	63.48 ± 6.084	0.675[a]
Median (Min-Max)	65 (51-75)	63 (53-75)	
15 minutes After intervention			
Mean ± SD	64.68 ± 6.427	63.84 ± 5.991	0.589[a]
Median (Min-Max)	62 (52-73)	62 (54-76)	
20 minutes After intervention			
Mean ± SD	65.08 ± 7.153	64.60 ± 6.813	0.533[a]
Median (Min-Max)	64 (52-75)	63 (55-78)	

Oxygen saturation

In this study, the results showed that there was no difference in mean oxygen saturation (SpO2) 5 minutes after intervention (p = 0.242), 10 minutes after intervention (p = 0.134), 15 minutes after intervention (p = 0.702) and 20 minutes after intervention (p. = 0.158) between Ketamine + Midazolam Group and ketamine + propofol. However, there was a difference in mean oxygen saturation (SpO2) 2 minutes after intervention (p = 0.009) between Ketamine + Midazolam Group and ketamine + propofol (table 11).

Table 11. Research Subjects Oxygen Saturation Per Time (n = 50).

Pulse oximetry	Ketamin + Midazolam group (n= 25)	Ketamin + Propofol group (n = 25)	P-Value
2 minutes after intervention			
Mean ± SD	98.88 ± 1.092	97.80 ± 1.414	0.009
Median (Min-Max)	99 (96-100)	98 (96-100)	
5 minutes after intervention			
Mean ± SD	99.20 ± 0.764	98.80 ± 1.291	0.242

Median (Min-Max)	99 (97-100)	99 (94-100)	
10 minutes after intervention			
Mean ± SD	99.24 ± 0.764	98.92 ± 0.759	0.134
Median (Min-Max)	99 (98-100)	99 (98-100)	
15 minutes after intervention			
Mean ± SD	99.36 ± 0.489	99.40 ± 0.577	0.702
Median (Min-Max)	99 (99-100)	99 (98-100)	
20 minutes after intervention			
Mean ± SD	99.36 ± 0.569	99.12 ± 0.600	0.158
Median (Min-Max)	99 (98-100)	99 (98-100)	

Heart rate

There was no difference in Mean heart rate (HR) 2 minutes after intervention (p = 0.498). 5 minutes after intervention (p = 0.129), 10 minutes after intervention (p = 0.397), 15 minutes after intervention (p. = 0.143) and 20 minutes after intervention (p = 0.189) between Ketamine + Midazolam Group and ketamine + propofol (Table 12).

Tabel 12. Heart rate of research subjects per time (n = 50).

Heart Rate	Ketamin + Midazolam Group (n= 25)	Ketamin + Propofol Group (n = 25)	P-Value
2 minutes after intervention			
Mean ± SD	101.28 ± 10.92	102.92 ± 13.39	0.498[a]
Median (Min-Max)	96 (86-120)	106 (68-120)	
5 minutes after intervention			
Mean ± SD	99.92 ± 9.798	102.64 ± 11.73	0.129[a]
Median (Min-Max)	94 (88-118)	104 (72-118)	
10 minutes after intervention			
Mean ± SD	98.92 ± 10.468	101.64 ± 11.99	0.397[b]
Median (Min-Max)	94 (82-119)	107 (72-119)	
15 minutes after intervention			
Mean ± SD	97.04 ± 11.53	100.76 ± 13.46	0.143[a]
Median (Min-Max)	95 (80-122)	104 (68-122)	
20 minutes after intervention			
Mean ± SD	96.76 ± 12.07	100.4 ± 13.64	0.189[a]
Median (Min-Max)	96 (80-120)	104 (65-120)	

Table 13. Respiratory rate of research subjects per time (n = 50).

Respiratory rate	Ketamin + Midazolam group (n= 25)	Ketamin + Propofol group (n = 25)	P-Value
2 minutes after intervention			
Mean ± SD	21.28 ± 1.400	19.12 ± 1.739	0.000
Median (Min-Max)	22 (18-24)	20 (16-22)	
5 minutes after intervention			
Mean ± SD	20.64 ± 1.497	19.52 ± 1.735	0.000
Median (Min-Max)	20 (18-22)	20 (16-22)	
10 minutes after intervention			
Mean ± SD	19.96 ± 1.369	19.20 ± 2.236	0.327
Median (Min-Max)	20 (18-22)	20 (14-22)	
15 minutes after intervention			
Mean ± SD	20.52 ± 1.194	19.52 ± 2.163	0.086
Median (Min-Max)	20 (18-22)	20 (14-22)	
20 minutes after intervention			
Mean ± SD	20.36 ± 1.114	20.12 ± 1.787	1.000
Median (Min-Max)	20 (18-22)	20 (16-22)	

Tabel 14. Comparison of side effects and complications between ketamine-midazolam and ketamine-propofol

Variable	Group		P-value
	Ketamin-Midazolam	Ketamin-Propofol	
Nausea, n (%)	0 (0)	0 (0)	1.000
Hypersalivation, n (%)	7 (28)	1 (4)	0.049
Hypotension, n (%)	0 (0)	1 (4)	1.000
Bradypnea, n (%)	0 (0)	1 (4)	1.000
Bradiycardi, n (%)	0 (0)	0 (0)	1.000
Desaturation, , n (%)	0 (0)	0 (0)	1.000
Hypothermia, , n (%)	0 (0)	0 (0)	1.000
Halucination, n (%)	0 (0)	0 (0)	1.000

Respiratory rate

Results showed that there was no difference in Mean respiratory rate (RR) 10 minutes after

intervention (p = 0.327), 15 minutes after intervention (p = 0.086) and 20 minutes after intervention (p = 1.000) between the Ketamine + Midazolam Group and ketamine. + propofol. However, there was a difference in Mean respiratory rate (RR) of 2 minutes (p = 0.000) and 5 minutes after intervention (p = 0.242) between the Ketamine + Midazolam Group and ketamine + propofol. There was a significant difference in respiratory rate between Ketamine + Midazolam Group and ketamine + propofol at the second and fifth minutes.

Comparison of side effects and complications between ketamine-midazolam and ketamine-propofol

In this study there were only differences in the side effects of hypersalivation between the two treatment groups, hypersalivation was found to be significantly more in the ketamine + midazolam combination group.

Discussion

In this study, the mean age of leukemia patients in both groups was approximately 7 years with a range of 1 to 15 years. These results are in line with research conducted by Belen et al in 2012 which reported that the average age of pediatric leukemia patients in the four treatment groups ranged from 6.52 to 7.98 years with a range of 0 to 18 years.[11] Another study conducted by Hashemi et al., In 2003 reported that the average age of pediatric leukemia patients was 6.8 ± 3.1 and 6.1 ± 2.9 years.[12] Whereas in a study conducted by Fernandez et al., In 2019 the mean age of childhood leukemia patients was 8 years with a range of 5 months to 18 years.[13]

From the statistical analysis, it was found that there was no difference in mean arterial pressure, oxygen saturation, heart rate, and respiratory rate between the two treatment groups. There were also no differences in age, sex and body weight between the two treatment groups, and can be concluded that changes in hemodynamics and brain function as a result of the treatment were not influenced by the confounding factors above.

Patients in the ketamine + propofol group woke up faster than the ketamine midazolam group (p = 0.000), this is in line with the research of Shah et al., In 2010, the results showed that when compared to ketamine alone, the combination of ketamine and propofol in faster recovery, less vomiting, higher satisfaction scores, but similar efficacy and airway complications.[14] Faster wake-up time was also reinforced by the fast initial distribution half-life of propofol which ranges from 2 to 8 minutes so that

patients with the ketamine and propofol combination wake up faster than the midazolam ketamine group.[15]

In this study, the mean BIS in both groups was 96.2 and 95.84, which means that patients in a condition where before intervention is given, according to the theory which states that patients who are awake, the typical BIS score is 90 to 100.[16,17]

The ketamine-midazolam group achieved BIS 40 at 4 minutes (1 subject) while the ketamine-propofol group at 2 minutes (4 subjects) and BIS in the ketamine propofol group rose faster than the ketamine-midazolam group. The initial distribution half-life of propofol is 2 to 8 minutes whereas, in IV administration, midazolam is rapidly distributed, with a half-life of 6 to 15 minutes.[15] This suggests that ketamine propofol has a faster onset of sedation so that surgical procedures can be performed more quickly.

The BIS value in the ketamine + propofol group began to rise 10 minutes faster than the ketamine + midazolam group, but there was no difference in the effect of the combination of ketamine + midazolam and ketamine + propofol on sedation depth in BMP patients. In line with this study, the study by Dal et al showed that there was no difference in the effect of ketamine + midazolam and ketamine + propofol on sedation, the amount of drug use, oxygen saturation, RR, RSS value, patient satisfaction, and medical personnel. Both therapy groups had the same effect on sedation depth.[18]

This study also showed that after administration of ketamine + midazolam, the results were a decrease in MAP 2 minutes after intervention and decreased after 15 minutes, then increased again after 20 minutes of intervention with the highest reduction was 50 mmHg. The combination of ketamine + propofol and the combination of ketamine + propofol serves to provide a better analgesic and sedation effect without developing myocardial, respiratory depression and demonstrating hemodynamic stability.[18,19] The hemodynamic effect of midazolam is dose-related, but the effect of the drug on plasma shows that there is a change in arterial blood pressure.[20] The results of MAP monitoring in these patientsshowed no significant difference, which means that the combination of ketamine propofol and ketamine midazolam was equally good. So that the effect of increasing blood pressure from ketamine can be improved by doing a combination of midazolam and propofol.

There was a significant difference in oxygen saturation levels in the ketamine-propofol group before and after the intervention. This decrease in oxygen saturation levels was found to reach 94% in one subject in the ketamine-propofol group at the second minute, this decrease does not include a desaturation

condition and does not require special treatment because in the next minute the patient immediately experienced an increase in saturation to 100%.

Ketamine + Propofol Group oxygen saturation was slightly lower than ketamine + midazolam. This proves that the side effects of respiratory depression that often occur due to midazolam can be eliminated in combination with ketamine. Respiratory depression, transient cognitive impairment, and pain at the injection site are some of the side effects of propofol.[21] Research by Shah et al in 2010 found that the ketamine propofol combination had a better sedation effect than given alone but even though propofol was given together with ketamine, the ketamine-propofol combination still had airway complications in the form of decreased saturation and decreased respiratory rate. Propofol itsel f theoretically causes a potent respiratory depressive effect compared to other sedation drugs, in combination with ketamine alone is expected to reduce this effect, but this study found a decrease in saturation and respiratory rate in the propofol ketamine group.

Ketamine increases arterial blood pressure, heart rate, and cardiac output. After induction of anesthesia with benzodiazepines, there are severeal things to maintained such as heart rate, ventricular filling pressure, and cardiac output.[15] Pharmacodynamics of propofol has the effect of lowering the heart rate so that the administration of propofol can reduce the side effects of increasing the heart rate of ketamine drugs.[22] In line with this, this study found no difference. means that the heart rate between the two groups and both groups can maintain the heart rate in the normal range.

The decrease in respiratory rate did not cause bradypnea conditions, the decrease in respiratory rate reached the lowest rate, namely 14 times per minute at 10 and 15 minutes in the propofol group. This is following the pharmacological aspects of propofol which have a potential respiratory depression effect.

There was a significant difference in respiratory rate between Ketamine + Midazolam Group and the ketamine - propofol group at the second and fifth minutes. The Respiratory rate of Ketamine + Propofol Group is slightly lower than that of ketamine - midazolam group. These results differ from those of Drummod et al., Who reported the effect of the ketamine-midazolam combination on the activity of airway muscle and found that 10 out of 12 patients who was given midazolam had airway obstruction and respiratory depression.[23] Sedation drugs alone could theoretically cause respiratory depressive effects. which is potent compared to other sedation drugs, the combination with ketamine is used to improve the effects of respiratory depression so that it can be seen only in the second and fifth minutes there is a significant difference and improves in the next minute. There was no difference between the two groups

showing that the ketamine-midazolam and ketamine-propofol groups were equally good as a combination sedation agent to reduce the effects of airway depression.

Hypersalivation more significantly in the ketamine + midazolam combination group. Ketamine has the potential for hypersalivation side effects, this can be reduced by the use of midazolam or propofol.[24-26] In this study, combination of ketamine + propofol was able to suppress these side effects, but the side effects could not be reduced by the combination with midazolam. This is in line with the study of Gelenet al. Who had hypersalivation in the combination of ketamine-midazolam in high children, namely 16.9% during sedation and 24.5% after sedation.[27] Another study by Karapinar et al also found that the incidence of hypersalivation was the top five effects, side administration of the ketamine-midazolam combination in sedation in children.[28] Administration of single midazolam can cause hypersalivation so that it can exacerbate the condition of ketamine hypersalivation, and it can be concluded that midazolam is not effective for reducing the risk of hypersalivation and it is suggested that proper pre-medication should be needed.

Conclusion

There was no difference in sedation depth according to the Bispectral Index Score (BIS) between the combination of ketamine-midazolam and ketamine-propofol as sedation for patients undergoing BMP, but there was a difference in oxygen saturation at the 2nd minute after the intervention and there was a difference in the Mean respiratory rate between the ketamine-midazolam and ketamine-propofol group in the second and fifth minutes after the intervention. Significant differences occurred in the side effects of hypersalivation, hypersalivation was found more in the ketamine-midazolam combination group.

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