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Comparison of the Scale of Pain From Injection of Propofol Preceded by Lidocaine and Ketamine Injections in General Anesthesia

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Abstract

- ***Background :***

ketamine administered at a dose of 10 mg before the injection of propofol reduces pain from the injection of propofol. The optimal dose of lidocaine is assumed to prevent pain from the injection of propofol. The aim of this study was to assess the comparison of the scale of pain from injection of propofol preceded by lidocaine and ketamine injections in general anesthesia.

- ***Method :***

Experimental analytical research with a double-blind randomized control trial design using a sample of 50 elective surgical patients. Patients were divided into two groups, treatment group (n = 25) given lidocaine and control group (n = 32) given ketamine. Pain scores were asked every 5-second interval and the highest pain scale was recorded as the research data. If the patient says no, the pain scale is 0. The measuring instrument used in the study was VAS. The data were analyzed using SPSS.

- ***Results :***

In this study it was found that in the ketamine treatment group, 13 people (52%) did not feel pain, 8 people (32%) felt mild pain, 3 people (12%) felt moderate pain, and 1 person (4%) felt severe pain. In the lidocaine group, 19 people (76%) did not feel pain, 8 people (20%) felt mild pain, 1 person felt moderate pain (4%) and no one felt severe pain. Severe degree of pain was not occurred in the lidocaine group, whereas in the ketamine group, there were still samples that experienced a severe degree of pain after injection of propofol. Based on the difference test conducted in the Mann-Whiteny test it was found that there was no difference in the degree of pain from the injection of propofol whether preceded by an injection of lidocaine or ketamine.

- ***Conclusion :***

There was no difference in the degree of pain from injection of propofol preceded by lidocaine and ketamine injections.

Keywords:- *Ketamine, Lidocaine, Visual Analogue Scale (VAS).*

I. INTRODUCTION

General anesthesia is a pharmacologically triggered loss of consciousness that can be restored. This can be from the use of intravenous agents, inhalation agents or both. Currently, the process of induction using short-acting intravenous drugs such as Propofol and ketamine is more often used (Raymer, 2012).

Propofol is an intravenous anesthetic agent widely used in daily medical practice for induction and maintenance of general anesthesia (Furuya *et al*, 2001). Propofol has a fast onset, short duration of action, easy titration, known profile of side effects, comfort when losing the consciousness as the anesthetic procedures are performed, and rapid recovery compared to other drugs such as thiopental (Euasobhon *et al*, 2016, Jalota *et al*. 2011). However, injection of propofol can cause pain such as a burning sensation, or very sharp pain during injection (Madenoglu *et al*, 2003, Singh *et al*, 2014). The incidence of pain caused by the injection of propofol is estimated at 28-90%. Scott *et al.* Reported the incidence of pain caused by propofol based on pain severity varying between 25-74% with severe pain of 32-52%. King *et al*. Reported the incidence of pain caused by propofol around 73%, Ho *et al* 91.7%, Yokota *et al* 87%, and Madenoglu *et al* 66.7% (Madenoglu *et al*, 2003).

Picard and Tramer examined the effect of lidocaine on pain caused by injecting propofol with a meta-analysis design study of 56 studies (Madenoglu *et al*, 2003). They found that administration of intravenous lidocaine at a dose of 0.5 mg/kg with a tourniquet 10-30 seconds before the injection of propofol was the best prevention of pain. However, the incidence of pain caused by the injection of propofol was still high, it was around 40% (Ozkocak *et al*, 2005). The efficacy of lidocaine is known to not only contribute to the effects of local anesthetics but other mechanisms may also be involved. Propofol is dissolved in the outer aqueous layer of lipid emulsions. In a study conducted by Doenicke *et al*., It appears that less propofol is in the aqueous phase, less pain is felt during the injection of the drug. Lidocaine mixed with propofol also appears to dissolve in the outer layer. The longer lidocaine remains there, the more likely it is to move into the emulsion and makes it less effective at inhibiting pain caused by injection of propofol (Kaabachi *et al*, 2007).

In a study conducted by Kaabachi *et al*., They found that the incidence of injection pain due to propofol induction in the group given ketamine was twice as large as in the group given lidocaine with children as the samples. They suspected that this is as a result of a local mechanism by which ketamine may activate NMDA receptors in the vascular endothelium. The physical properties of ketamine such as pH (acid) may not affect the concentration of free aqueous propofol which is responsible for the onset of pain. Simultaneous injection and relatively low doses do not provide sufficient time for the central analgesia from ketamine to work before a nociceptive stimulus from the injection of propofol occurs. The short time of endothelium contact with ketamine does not promote local work to NMDA receptors. These three mechanisms that might cause a lack of efficacy in mixing ketamine with propofol in reducing the incidence and intensity of pain caused by the injection of propofol according to a study conducted by Kaabachi *et al*. (Kaabachi *et al*, 2007).

The pain caused by the injection of propofol and the variation of the results of previous studies related to methods to reduce pain incidence and intensity due to injection of propofol made researchers interested in examining the scale of pain from a single injection of propofol, where the lidocaine and low-dose ketamine were injected before the injection propofol. Kaabachi *et al*. have conducted a study of pain caused by injecting propofol in pediatric patients. This is what makes the researchers wanted to conduct the study on adult patients.

II. METHODOLOGY

➢ *Research Design*

This study was an experimental analytic study with a double-blind study design randomized control trial. The research subjects were divided into two groups randomly ie the first group received lidocaine and the second group received low dose ketamine. This study aimed to assess the comparison of the scale of pain from injection of propofol which was preceded by lidocaine and ketamine injections in general anesthesia

➢ *Place and Time of Research*

The study was conducted at the Central Surgery Installation of Haji Adam Malik Hospital in Medan. After obtaining approval from the Health Research Ethics Commission of the Faculty of Medicine, University of North Sumatra - Haji Adam Malik Hospital Medan (ethical clearance). The study was conducted in January - February 2019.

➢ *Research Population and Samples*

The population in this study were all patients who underwent elective surgery at the Central Surgery Installation of Haji Adam Malik Hospital in Medan during January 2019. The study samples were a portion of the population that met the inclusion and exclusion criteria.

➢ *Inclusion Criteria*

Patients scheduled to undergo elective surgery at the Central Surgery Installation of Haji Adam Malik Hospital Medan in January 2019; The physical status of patients based on the ASA (American Society of Anesthesiologists) I-II; Patients scheduled to undergo surgery with general anesthesia; Aged 18 - 64 years old; The patients do not receive analgesia within 24 hours before surgery; and the samples willing to take part in the research and sign an informed consent.

➢ *Exclusion Criteria*

History of allergy to lidocaine or ketamine based on anamnesis and clinical samples. Patients with severe neurological or psychiatric disorders based on history and physical examination. Patients undergoing emergency surgical procedures (example: samples with acute abdomen). Pregnant patients based on anamnesis and obstetric physical examination. Patients who use long-term analgesia therapy. Patients with thrombophlebitis based on clinical examination, Patients with bad dorsal venous veins based on physical examination. Patients who withdraw from the study.

➢ *Research Procedures*

- The study started after obtaining ethical clearance. Research samples that met the inclusion and exclusion criteria were randomly selected and signed an informed consent agreement to participate in the study.
- The treatment was given in the operating room. Before administering the treatment, the patients were explained about the scale of pain to be assessed. The pain scale was measured by the VRS (Verbal Rating Scale) with levels 0-3. A score of 0 means no pain, a score of 1 means mild pain, a score of 2 means moderate pain, and a score of 3 means severe pain related to groaning, hand pulling, or movements.
- After routine monitoring in the operating room, an 18 G catheter was inserted into the vein on the dorsum of the hand and a three-way was installed directly to connect with a venous catheter. Normal 5mL/kg/hour infusion started.
- Patients were then divided randomly into 2 (two) groups. Randomization was done using envelopes to assign group number (I, II).
- A tourniquet was applied to the upper arm to allow a longer time the drug was assessed in the blood vessels.
- After the three-way tap was closed, the group I were given a lidocaine injection with a dose of 1 mg/kgBW and to group II a ketamine injection was administered at a dose of 0.1 mg/kg in 15 seconds.
- The closing time of the tourniquet for 30 seconds and the time for the injection of the drug were assessed, then the tourniquet was opened.
- Then propofol was injected in 2 groups at a dose of 2 mg/kg for 30 seconds and then a three-way tap was opened to normal saline
- The patients were asked whether there was pain felt in the hand or arm. If they said yes, then the pain score

was asked every 5-second interval and the highest pain scale was recorded as the research data. If the patients said no, the pain scale was 0.

- After the patients were unconscious, fentanyl was administered at a dose of 2 mcg/kgBW and Rocuronium at a dose of 0.6 mg/kgBW then the patients were intubated and the anesthesia was maintained.
- The data on patient characteristics and pain scale were recorded for statistical analysis.

➢ *Processing and Analysis of Data*

The data were presented in the form of mean ± standard deviation. Statistical analysis of patient characteristics data was performed by Mann-Whiteny and Wilcoxon test to see differences in pain scores in each group and Mann-Whitney test to see differences in scores between the two groups. Pain intensity was analyzed by the Mann-Whitney test with a value of $p < 0.05$ stated statistically significant.

III. RESEARCH RESULTS

➢ *Sample Characteristics*

This research was conducted for 2 months, January-February 2019 at the Central Surgery Installation. This study aimed to assess the comparison of the scale of pain from injection of propofol preceded by lidocaine and ketamine injections in general anesthesia. In other words, to assess the comparison of the pain scale between injecting lidocaine with propofol, and injecting low-dose ketamine with propofol.

The samples obtained in this study amounted to 50 samples that were in accordance with the inclusion and exclusion criteria. Sample characteristics are shown in Table 1.

Characteristic	Treatment				P value
	Ketamine		Lidocaine		
	n	%	n	%	
Sex					
Male	13	52	6	24	0,043
Female	12	48	19	76	
Age					
20-39 y.o	16	64	13	52	0,437
40-59 y.o	9	36	12	48	
ASA					
1	13	52	12	48	0,779
2	12	48	13	52	
BMI					
Normal	21	84	14	56	0,315
Fat	4	16	10	40	
Obese	0	0	1	4	
Location of injection					
Dorsam Manus	23	92	22	88	0,641
Dorsum Pedis	2	8	3	12	
Total	25	100	25	100	

*Mann-Whitney Test

Table 1:- Sample Characteristics

Based on table 4.1, it can be seen that the samples were homogeneous in both groups seen from age, ASA, BMI and location of injection, tested with a value of $p>0.05$. As for sex, the samples were not homogeneous for both groups with a value of $p<0.05$. It was expected that the age, ASA, BMI and location of injection variables did not affect the VAS value in the injection with propofol.

The sex description in the lidocaine and ketamine groups is shown in Figure 1.

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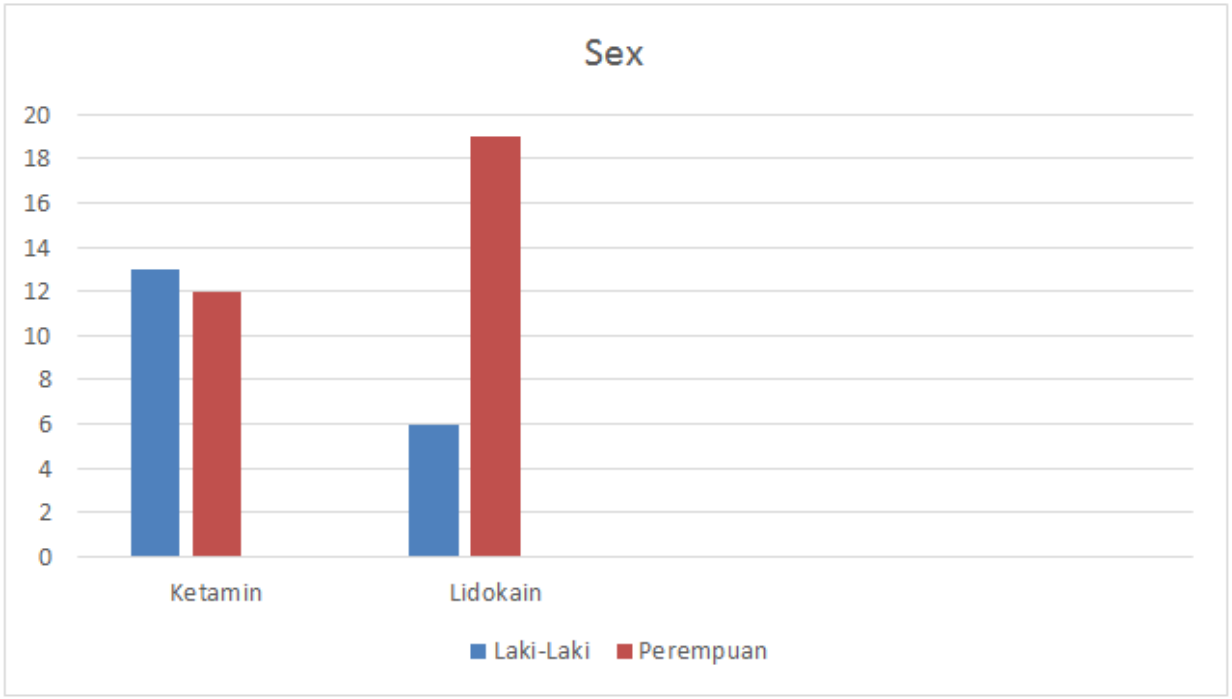

Fig 1:- Sex Description of the Samples

Based on Figure 1, it was found that male sex in the ketamine group were 13 samples (52%) and in the lidocaine group were 6 samples (24%) while female sex in the ketamine group were 12 samples (48%) and in the lidocaine group were 19 samples (76%). It can be seen that in this study the most dominant sex was female, with the highest female sex samples found in the lidocaine group.

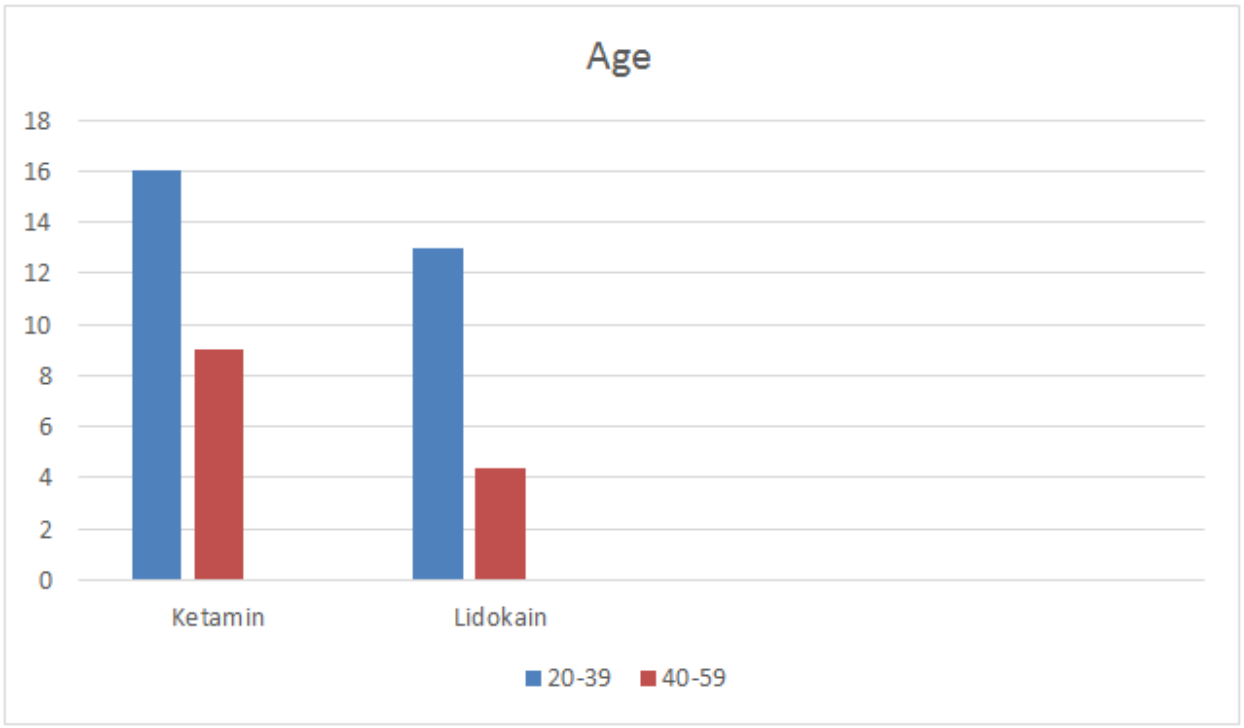

Fig 2:- Age Description of the Samples

Based on Figure 2, it was found that there were 16 samples (64%) in the age of 20-39 years old category in the ketamine group and 13 samples (52%) in the lidocaine group. There were 9 samples (36%) of 40-59 years old in the ketamine group and 12 samples (48%) in the lidocaine group. It can be seen that the older samples were most commonly found in the ketamine group.

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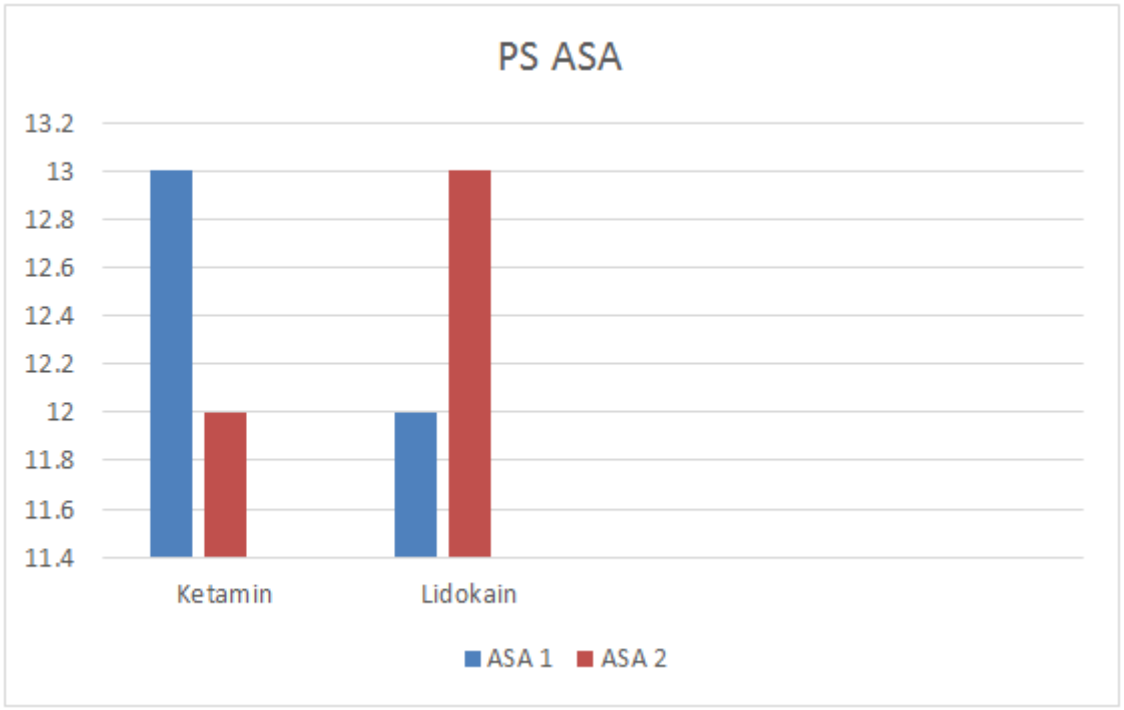

Fig 3:- ASA Grouping

Based on Figure 3, it was found that patients in this study were mostly in ASA 1, in the ketamine group there were 13 samples (52%) and in the lidocaine group there were 12 samples (48%) while the ASA 2 in the ketamine group were 12 samples (48%) and in lidocaine group were 13 samples (52%). It can be seen that there were equal numbers of samples in terms of ASA.

- *Body Mass Index*

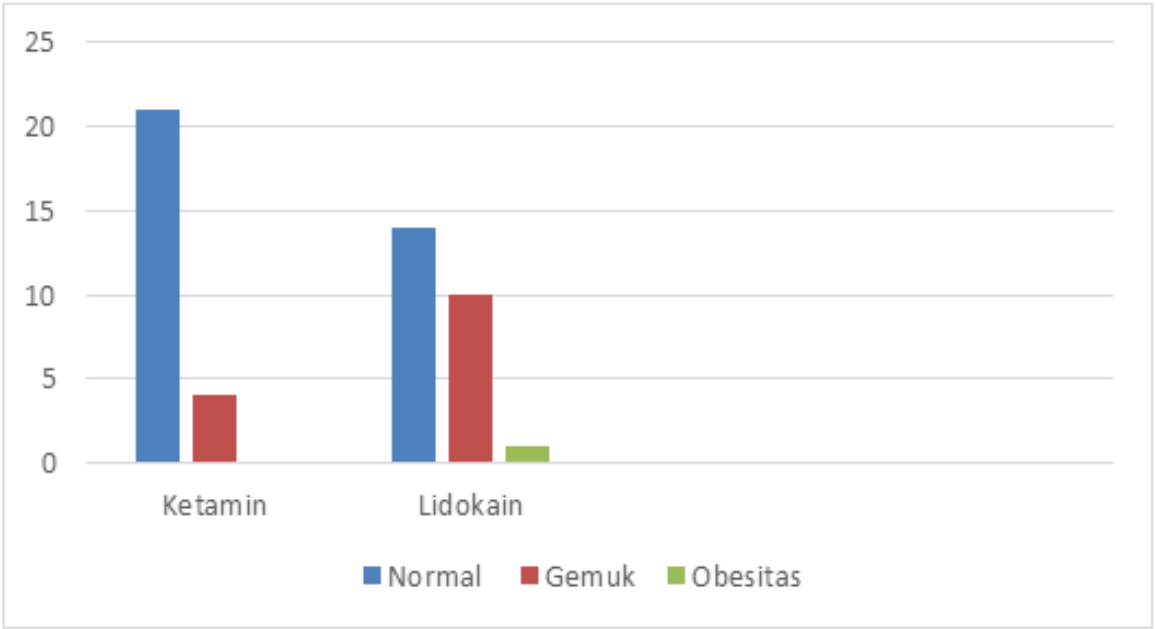

Fig 4:- BMI Description of Patients

Based on Figure 4, it was found that the patients in this study were mostly at normal BMI, in the ketamine group there were 21 samples (84%) and in the lidocaine group there were 14 samples (56%) while the BMI that was categorized as fat in the ketamine group were 4 samples (16%) and in the lidocaine group were 10 samples (40%). It can be seen that patients with fat BMI were most commonly found in the lidocaine group and almost all of the samples in this study had a normal BMI.

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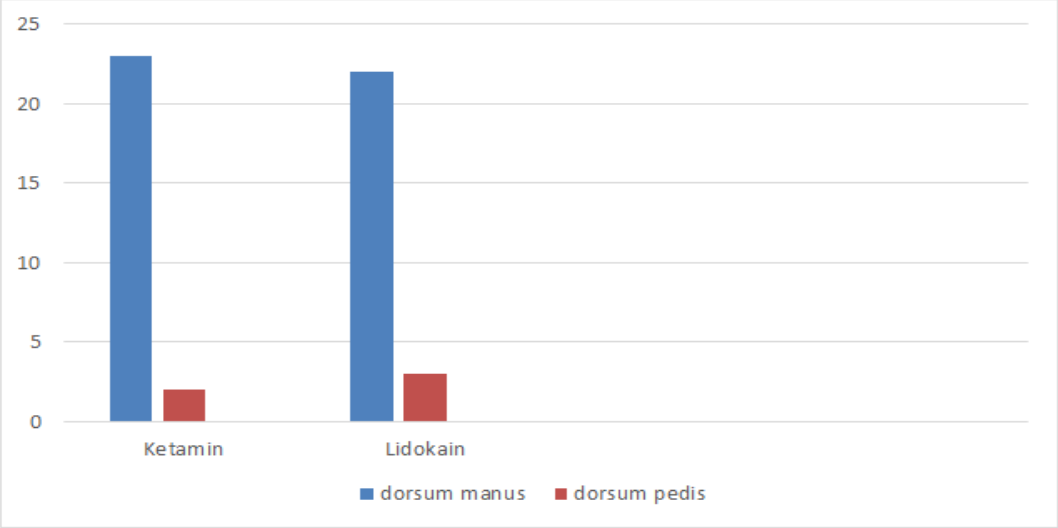

Fig 5:- Description of Location of Injection in the Samples

Based on Figure 5, it was found that the samples in this study mostly injected in dorsum manus with 23 people (92%) in the lidocaine and 22 people (88%) in the ketamine group.

Description of the degree of pain due to injection of propofol which is preceded by ketamine injection.

Description of the degree of pain due to injection of propofol which is preceded by ketamine injection is shown in table 2.

Group	No pain		Mild pain		Moderate pain		Severe pain		P value
	n	%	n	%	n	%	n	%	
Ketamine	13	52	8	32	3	12	1	4	0,012*

*Wilcoxon test

Table 2:- Description of the Degree of Pain Due to Injection of Propofol which is Preceded by Ketamine Injection.

Based on Table 2, it was found that in the ketamine treatment group, 13 people (52%) did not feel pain, 8 people (32%) felt mild pain, 3 people (12%) felt moderate pain and 1 person (4%) felt severe pain.

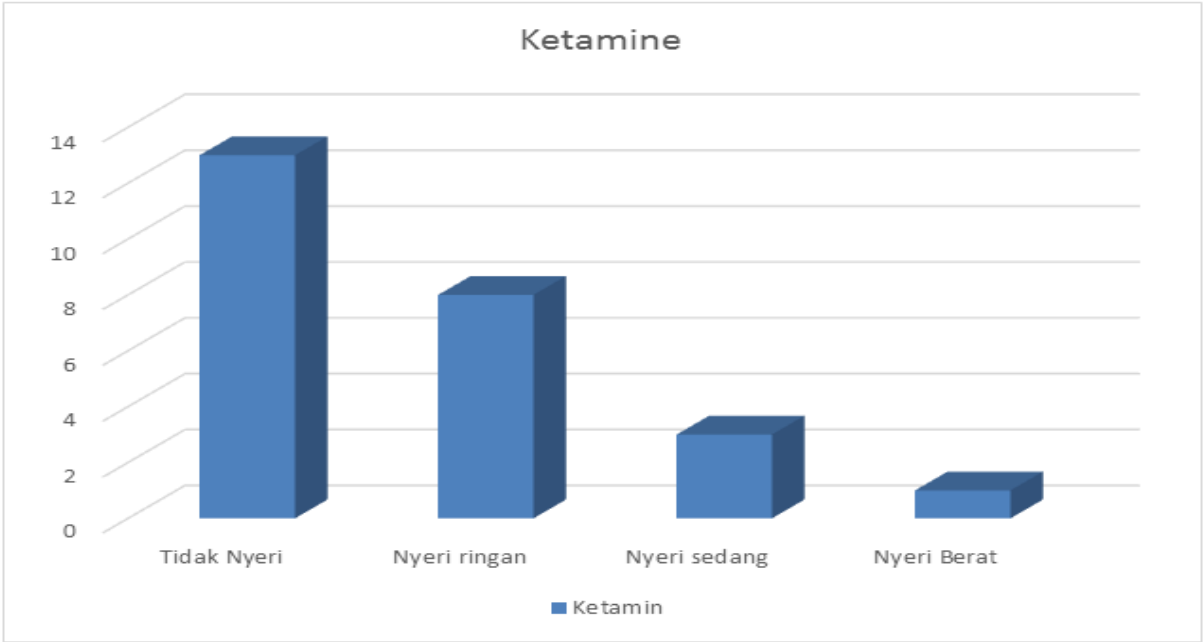

Fig 6:- Description of the Administration of Ketamine 0.1 mg/KgBw + Propofol 2 mg / KgBB for the Incidence of Pain.

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Description of the degree of pain due to injection of propofol which is preceded by lidocaine injection.

Description of the degree of pain due to injection of propofol which is preceded by lidocaine injection is shown in table 3

Group	No pain		Mild pain		Moderate pain		Severe pain		P value
	n	%	n	%	n	%	n	%	
Lidocaine	19	76	5	20	1	4	0	0	0,001*

*Wilcoxon test

Table 3:- Description of the Degree of Pain due to Injection of Propofol which is Preceded by Lidocaine Injection.

Based on Table 3, it was found that in the lidocaine treatment group, 19 people (76%) did not feel pain, 8 people (20%) felt mild pain, 1 person (4%) felt moderate pain and no one felt severe pain.

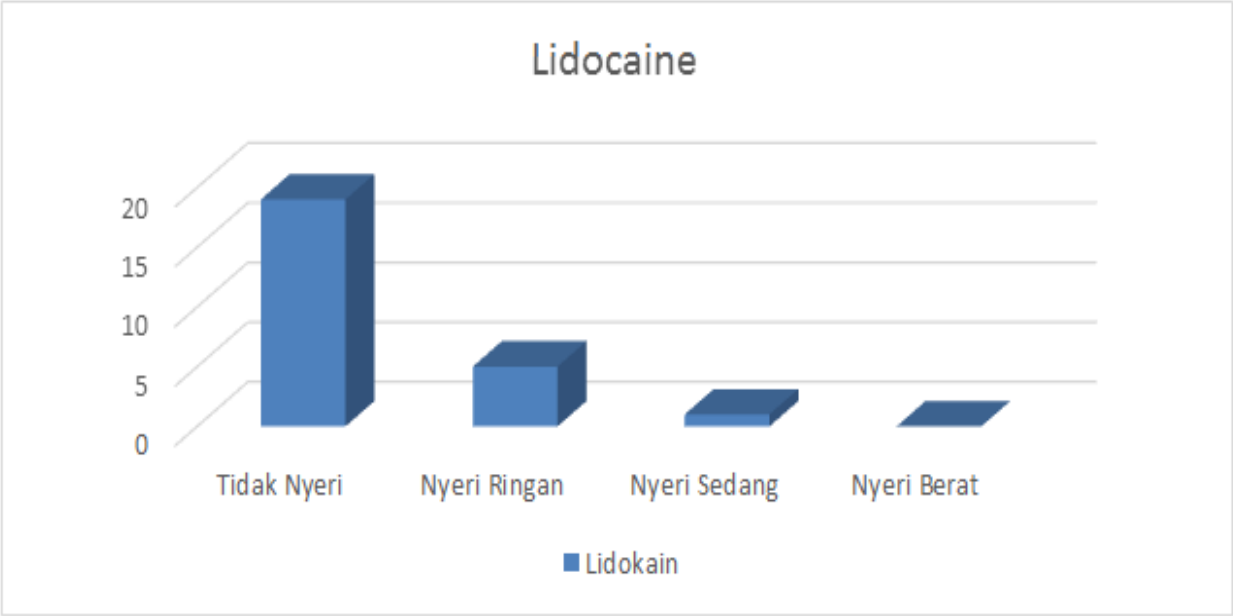

Fig 7

Comparison of the degree of pain due to injection of propofol which is preceded by lidocaine and ketamine injections

Comparison of the degree of pain due to injection of propofol which is preceded by lidocaine and ketamine injections is shown in Table 4

Pain		Group		Total	P value
		Ketamine	Lidocaine		
No pain	n	13	19	32	0.074
	%	52.0%	76.0%	64.0%	
Mild pain	n	8	5	13	
	%	32.0%	20.0%	26.0%	
Moderate pain	n	3	1	4	
	%	12.0%	4.0%	8.0%	
Severe pain	n	1	0	1	
	%	4.0%	0.0%	2.0%	
Total	n	25	25	50	
	%	100.0%	100.0%	100.0%	

Mann-Whitney test

Table 4:- Comparison of the Degree of Pain due to Injection of Propofol which is Preceded by Lidocaine and Ketamine Injections

Based on table 4, it was found that in the lidocaine group, there was not a severe degree of pain, whereas, in the ketamine group, there was one sample who felt severe pain after injection of propofol.

Based on the difference test conducted in the Mann-Whitney test it was found that there was no difference in the degree of pain from the injection of propofol preceded by of lidocaine and ketamine injections.

IV. DISCUSSION

This study was conducted to assess the comparison of the pain scale between injecting lidocaine with propofol, and injecting low-dose ketamine with propofol. Two common methods used to reduce the intensity and incidence of pain due to injection of propofol are, one, to administer lidocaine to the vein before the propofol, and two, by intravenous administration of ketamine which appears to have an effect in preventing pain due to injection of propofol in several studies (Kaabachi *et al*, 2007, Canbay *et al*, 2008).

Based on Tabel 2 it was found that in the ketamine treatment group, 13 people (52%) did not feel pain, 8 people (32%) felt mild pain, 3 people (12%) felt moderate pain and 1 person (4%) felt severe pain. The results of this study are in accordance with a study conducted by Tan *et al*., They found that administration of ketamine with a dose of 10 mg before injection of propofol reduced pain due to injection of propofol. Menigaux *et al*. Reported that ketamine at a dose of 0.15 mg/kg given after induction of anesthesia and before surgical incision could reduce the need for morphine in postoperative care (Furuya *et al*, 2001). A study conducted by Barbi *et al* found that premedication with ketamine 0.5 mg/kgBW was very effective in preventing pain due to infusion of propofol (Barbi *et al*, 2003). Zahedi *et al*. found that the administration of ketamine 100 µg/kgBW immediately before injection of propofol was a safe and effective method of preventing pain due to injection of propofol (Zahedi *et al*, 2009).

Based on Tabel 3, it was found that in the lidocaine treatment group, 19 people (76%) did not feel pain, 8 people (20%) felt mild pain, 1 person (4%) felt moderate pain and no one felt severe pain. Picard and Tramer examined the effect of lidocaine on pain caused by injecting propofol with a meta-analysis design study of 56 studies (Madenoglu *et al*, 2003). They found that administration of intravenous lidocaine at a dose of 0.5 mg/kg with a tourniquet 10-30 seconds before the injection of propofol was the best prevention of pain. However, the incidence of pain caused by the injection of propofol was still high, it was around 40% (Ozkocak *et al*, 2005).

Pain due to injection of propofol can occur at the time of induction and can cause a decrease in the quality of anesthesia services and increase patient morbidity (Lee, 2010). Data from research conducted by Lee showed the incidence of pain due to the injection of propofol can occur between 30-70% through several mechanisms. Propofol is an anesthetic agent that is currently available in the form of a liquid intravenous preparation with its solvents formulated in a lipid emulsion containing 10% soybeans, glycerol 3.25%, and phosphatide 1.2% (Miller, 2010). The mixture with propofol will make propofol works in two fractions, lipophilic and nonlipophilic fractions.

Bradykinin is a pain neurotransmitter that can stimulate venous nociceptors directly or through the formation of nitric oxide by activation of bradykinin. Nitric oxide that has been formed will cause venodilation and increase the permeability of venous pores to propofol or bradykinin that has been previously formed and increase the risk of pain on the injection of propofol.

The use of lidocaine to reduce pain in propofol has a different mechanism depending on how lidocaine is administered. The premedication of lidocaine as a local anesthetic has a way of working to inhibit pain through resistance at the stage of transmission of pain stimulation by closing the sodium canal from the nerve membrane, thereby blocking the movement of sodium cations into the cell. This will cause excitatory depolarization of pain that occurs in the peripheral veins will be disconnected and not channeled to the peripheral vein nerve fibers.

The use of tourniquet in this study aimed to inhibit the rate of blood flow in the vein so that it gives time for lidocaine to work on peripheral venous nerve fibers in the tunica media. The time of venous occlusion used in this study was 60 seconds according to the onset of lidocaine. The results of this study are consistent with several studies that have been done previously with the use of lidocaine treatment of tourniquet between 30-120 seconds showing good results compared to the mixture of lidocaine in reducing propofol injection pain. (Massad, 2006; Picard, 2000; Jalota, 2011).

The use of mixed lidocaine which mixes the lidocaine with propofol will cause a decrease in the pH of the mixture and cause a decrease in the fraction of nonlipophilic propofol, so the end result is associated with a decrease in bradykinin that causes pain and a decrease in nitric oxide which causes a decrease in peripheral vein permeability. This concept is supported by the results of Eriksson's study which showed a decrease in pH of propofol which was mixed with lidocaine. The pH of the mixture decreases to 6.1 from the initial pH of propofol ie 7.9-8.0.25 The above mechanism shows that the mixture of lidocaine works by inhibiting the pain transduction process.

The results of plasma bradykinin measurement after the injection of lidocaine mixture in the Nakane and Iwama's study showed bradykinin levels of 120 picograms/cc it was different to the control group with the injection of pure propofol which had 170 picograms/cc bradykinin levels (Nakane and Iwama, 1999). This shows that the administration of a mixture of lidocaine does not cause total elimination of bradykinin production, so bradykinin can still sensitize venous nociceptors and cause vasodilation and changes in permeability that allow the nonlipophilic free propofol fraction to stimulate nociceptors. Premixed methods also do not allow lidocaine to work optimally based on its onset (60-90 seconds) as local anesthesia to inhibit nerve transmission in the venous

media, because lidocaine that enters intravenously with propofol will immediately experience hemodilution and be carried along with venous blood flow.

The mixture of lidocaine in propofol is actually useful in reducing the degree of pain due to propofol injection, it can be seen in the study conducted by Koo. Koo reported that the administration of pure propofol had an incidence of pain of 87% with a degree of pain based on VRS criteria for the categories of no pain, mild pain, moderate and severe pain, respectively 13.2%, 42.9%, 36.3% and 6.6% (Koo *et al*., 2006). In his study, Zahedy also reported incidences of pain of 88% with pain levels of 12%, 34%, 40%, and 14% respectively (Zahedi, *et al.* 2009). The data illustrate that there was a decrease in the incidence and degree of pain due to injection of propofol in this study compared to data from the studies conducted by Koo and Zahedy. The difference in the mechanism of action of lidocaine in the two treatment groups is the underlying cause of the difference in the degree of pain from the injection of propofol. The mechanism of inhibition of lidocaine in the process of pain transmission by premedication of lidocaine accompanied by tourniquet treatment can be considered better in reducing the degree of pain due to injection of propofol compared to inhibition of the transduction process through the treatment of a mixture of lidocaine in propofol.

V. CONCLUSION

The hypothesis was rejected, which means there was no difference in the degree of pain from the injection of propofol which is preceded by lidocaine and ketamine injections

SUGGESTIONS

- This study is expected to be the starting point for comparative studies of pain scale between injecting lidocaine and propofol, and injecting low-dose ketamine with propofol with larger samples.
- This study is expected to be an input for decision makers at Haji Adam Malik Hospital in Medan to include ketamine and lidocaine as part of the operational standard of preoperative implementation services..

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