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Comparison of the Effectiveness of Intramuscular 0.5 Mg Neostigmine and Intramuscular 1 Mg Neostigmine for Bladder Emptying after Spinal Anesthesia

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Abstract:-

- ***Background***

Neostigmine causes accumulation of acetylcholine around the cholinergic nerve endings. Bladder contractions depend heavily on stimulation of muscarinic receptors induced by acetylcholine in the bladder detrusor muscle.

- ***Purpose***

This study aims to compare the effectiveness of intramuscular 0.5 mg neostigmine and 1 mg neostigmine in accelerating bladder emptying after spinal anesthesia

- ***Method***

The study was a double-blind randomized clinical trial. The study was conducted at the Haji Adam Malik General Central Hospital (RSUP HAM) Medan and Putri Hijau Hospital Grade II Medan from December 2018 to February 2019. The total sample obtained was 37 samples of treatment group A (IM 0.5 mg neostigmine) and 37 samples of treatment group B (IM 1 mg neostigmine).

- ***Results***

The results were the means of urine volume at the initial observation until the final observation. In the treatment group with 0.5 mg Neostigmine, the initial (T0) observation of urine volume was 133.51 cc and in the final treatment (T5) observation was 63.51 cc, the results of the statistic test, p values (0.000) < 0.05, which means there is a change in the mean of urine volume from initial observation to final observation. The distribution of emptying velocity in the treatment group with 0.5 mg Neostigmine and 1 mg neostigmine obtained p-value (0.000) < 0.05 which means there is a difference in the proportion of urinary velocity between the treatment group of 0.5 mg Neostigmine with 1 mg Neostigmine group.

- ***Conclusion***

The 1 mg neostigmine has a faster onset of action compared with 0.5 mg neostigmine.

Keywords:- *Neostigmine, Urinary Velocity, Urine Volume*

I. INTRODUCTION

Spinal anesthesia began to widespread and be popularly used around the 1940s. The working principle of spinal anesthesia is to place local anesthetic agents into the subarachnoid space around the nerve bundles that come out of the spinal cord, causing no delivery of impulses to either the central nerve or peripheral nerves. Impulses that cannot be delivered occur in the autonomic, motor and sensory nervous system (Khadke *et al*., 2015).

Post-surgical urinary retention is a problem that often occurs after anesthesia and surgery with an incidence ranging from 5% to 70% in all surgical procedures. Post-surgical urinary retention is defined as the inability to empty the bladder voluntarily after anesthesia and surgery. Many factors contribute to the incidence of post-surgical urinary retention, namely the type of anesthesia and analgesia, male, comorbidity, imbalance in the administration of fluids during Durante surgery and drugs such as beta-blockers and anticholinergic agents (Kort, Bemelmans, Vons dan Schotanus, 2017).

Voiding ability is a complex process and involves many afferent and efferent neural pathways, reflexes and central and peripheral neurotransmitters. The urine capacity in the adult bladder is 400-600 ml. When the bladder volume reaches 150 ml, the first desire to micturate will appear, whereas when the volume reaches 300 ml, the full feeling will arise due to activation of the pressure receptors on the bladder wall (Dahab *et al*., 2011).

Previous studies have shown that spinal anesthesia with lidocaine and bupivacaine can cause a significant disruption of bladder function, such as loss of desire to micturate after spinal anesthesia. In addition, neuraxial anesthesia causes detrusor muscle disorders. In a meta-analysis by Baldini et al., It was reported that the effect of anesthesia on the incidence of post-surgical urinary retention under general anesthesia was lower than spinal anesthesia. Spinal anesthesia such as bupivacaine and tetracaine can slow the return of postoperative bladder function, causing distention of the bladder that exceeds its

normal capacity (Tjokorda, 2018 ; Baldini, 2009 ; Niazi dan Taha, 2014).

Pharmacologically, post-surgical urinary retention and anesthesia can be managed with cholinergic agents, anticholinesterases, alpha, sedative, and prostaglandin receptor blockers. Neostigmine is an acetylcholinesterase inhibitor or anticholinesterase agent that hydrolyzes the acetylcholine neurotransmitters at the nervous system synapse and neuromuscular junction. Neostigmine causes the accumulation of acetylcholine around the cholinergic nerve endings. Bladder contractions depend heavily on stimulation of muscarinic receptors induced by acetylcholine in the bladder detrusor muscle. Neostigmine can increase intravesical pressure, causing detrusor hyperactive contractions.

In the study of Tjokorda, who compared the effect of bladder emptying using 0.5 mg neostigmine with the control group of 0.9% NaCl. The results showed that neostigmine proved effective in inducing bladder emptying. Tjokorda in his study said the time needed to empty the bladder after the neostigmine injection was statistically significant and faster than the control group ($p < 0.05$) with an average time of 40 minutes. Until now, there have been no studies comparing the effectiveness of neostigmine doses in accelerating bladder emptying (Tjokorda, 2018).

Therefore, based on the background and reference of the above studies, the authors were interested in conducting a study comparing the effectiveness of intramuscular 0.5 mg neostigmine and 1 mg neostigmine in accelerating bladder emptying after spinal anesthesia.

II. RESEARCH METHODS

A. Research Design

This study is a double-blind randomized clinical trial to assess the comparison of the effectiveness of intramuscular 0.5 mg and 1 mg neostigmine to accelerate bladder emptying (Notoadmojo, 2010).

B. Place and Time of Research

This research was conducted in the operating room and postoperative observation room in the Haji Adam Malik General Central Hospital (RSUP HAM) Medan and Putri Hijau Hospital Grade II Medan. This research started from December 2018 until the number of research subjects was fulfilled.

C. Research Population and Samples

The study population was all patients who underwent surgery with elective and scheduled spinal anesthesia in Haji Adam Malik General Central Hospital (RSUP HAM) Medan and Putri Hijau Hospital Grade II Medan. The research subjects were all patients who underwent surgery under spinal anesthesia and fulfilled the inclusion and exclusion criteria. The research subjects were divided into 2 groups, they were the IM 0.5 mg neostigmine group and the IM 1 mg neostigmine group.

➢ *Inclusion Criteria*

- Willing to take part in the study by signing an informed consent.
- 18-50 years old.
- Having an ideal body weight according to BMI.
- Physical status based on the American Society of Anesthesiologists (ASA) I-II.
- Undergoing surgery in the lower abdominal area (except surgery in the pelvis, urology, anorectal and hernia).

➢ *Exclusion Criteria*

- The research subject withdraws from the study.
- The research subject has a history of local anesthetic allergies
- The research subject is allergic to neostigmine
- There is a local infection at the site of injection of spinal anesthesia
- Has a history of abnormalities of the genitourinary, neurological and cardiovascular tracts.
- Impaired kidney function

➢ *Drop Out Criteria*

- Duration of surgery > 2 hours
- Bleeding during surgery exceeds > 15% of the estimated blood volume.
- Changes in anesthesia techniques from spinal anesthesia to general anesthesia.

D. Sample size

The sample size used in this study was determined using an independent continuous data formula for experimental designs (Wahyuni, 2007) :

$$n1 = n2 = \sigma^2 \frac{(Z1 - \frac{\alpha}{2} + Z1 - \beta)^2}{(\mu 0 - \mu a)^2}$$

- α used is 0.05 with 80% power
- $Z1 - \frac{\alpha}{2} = 1{,}96$ and $Z1 - \beta = 0{,}842$
- σ^2, μ0, and μa obtained from previous research:

σ = 8,1
μ0 = 6,07
μa = 4,68

Based on the above formula, the number of research subjects in each group was 32 people, so the total research subjects in the two groups were 72 people.

E. Procedure

After obtaining approval from the Ethics Committee of the Medical Faculty of North Sumatra University, research samples were taken at the Haji Adam Malik General Central Hospital (RSUP HAM) Medan and Putri Hijau Hospital Grade II Medan. Before conducting the study, each patient who would undergo elective surgery using spinal anesthesia was given an explanation of the purpose, advantages, disadvantages, and procedures of the study to, then, subsequently sign an agreement willing to

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participate in the study. All research subjects who met the inclusion and exclusion criteria underwent an elective surgery preparation process. Disguised randomization was carried out by trained volunteers. One day before the scheduled surgery, the researcher records the complete identity of the patient and conducts a history and physical examination. The research subjects were fasting for 8 hours pre-operation, infusion access was installed and given ringer lactate maintenance fluid of 40 cc/kg/24 hours and premedication of 0.5 mg alprazolam tablets at night. Research subjects were still permitted to drink around 200 ml for up to 2 hours before the anesthetic induction process.

All research subjects were asked to micturate first before being transferred to the operating room. At the operating room, the researchers re-examined the identity, diagnosis, anesthesia action plan and infusion access for the research subject (infusion was installed with 18G abocath, threeway and infusion flow smoothly). Furthermore, the research subjects were installed standard monitoring devices such as electrocardiography, blood pressure and oximetry monitors, and the research subjects were given oxygen through the nasal cannula by 2 liters/minute. In the lateral position, the subarachnoid cavity is punctured with the Quincke type G27 needle at L3/L4 or L4/L5 using the median or paramedian approach until a backflow of cerebrospinal fluid is encountered. After cerebrospinal fluid is released, hyperbaric 0.5% bupivacaine is inserted. Block height was assessed based on skin dermatomes using the pinprick test. During the surgery, the researchers confirmed the hemodynamic status of the research subjects was stable and recorded the amount of bleeding. The research subjects were randomly divided into 2 groups, the 0.5 mg neostigmine group and 1 mg neostigmine group, according to previous randomization. After the surgery was complete, the patient was transferred to the postoperative observation room. Before the neostigmine injection, the researcher performed an ultrasound of the bladder to assess urine volume in the bladder. Then, the patient is given a 0.5 mg or 1 mg neostigmine injection randomly. Neostigmine injection is given when Bromage scores (motor block assessment) was 1 and sensory block height reached S2 dermatome.

Bladder ultrasonography was performed every 10 minutes until spontaneous micturition occurred T0 (when the drug is inserted), T1 (10 minutes after T0), T2 (20 minutes after T0), T3 (30 minutes after T0), T4 (40 minutes after T0), T5 (50 minutes after T0), T6 (60 minutes after T0). In the event of urinary retention, after spinal anesthesia (inability to micturate with a bladder volume > 600 ml detected using ultrasonography), the research subject must be catheterized. Measurement of urine volume in the bladder was measured using the formula prolate ellipsoid method.

$$Urine\ volume = length\ x\ width\ x\ height\ x\ 0{,}52$$

The researchers recorded data on the hemodynamic status of the study subjects before and after surgery, duration of surgery, dose of spinal anesthesia, height of sensory block, duration of surgery, amount of fluid during surgery, bladder volume before neostigmine injection, time of first micturition after neostigmine injection, first post-injection spinal anesthesia, urine volume, post-micturition residual volume and number of patients who need to be catheterized. All data collected were tabulated and analyzed statistically.

F. Informed Consent dan Ethical Clearance

All research participants included in this study were given an explanation of the objectives, benefits, advantages and disadvantages, and examination procedures of the study conducted. Participation as the research subjects was voluntary. For research permission, approval was obtained from research subjects and the Ethics Committee of the Faculty of Medicine, University of North Sumatra

III. RESULTS

- *Sample Characteristics*

The study was conducted for 2 months, January-February 2019 at the Haji Adam Malik Hospital Medan and the University of North Sumatra Hospital. This study aims to compare the effectiveness of intramuscular 0.5 mg neostigmine and 1 mg neostigmine in accelerating bladder emptying after spinal anesthesia.

The samples obtained in this study were 74 samples that were in accordance with the inclusion and exclusion criteria, with 37 samples of the treatment group A (IM 0.5 mg neostigmine) and 37 samples in the treatment group B (IM 1 mg neostigmine). The sample characteristics are shown in Table 1.

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Characteristics			Group		Total	P Value
			0.5 mg Neostigmin	1 mg Neostigmin		
Age	21-40 years old	n	10	3	13	0.000
		%	27.0%	8.1%	17.6%	
	41-60 years old	n	27	34	61	
		%	73.0%	91.9%	82.4%	
ASA	1	n	5	5	10	0.000
		%	13.5%	13.5%	13.5%	
	2	n	32	32	64	
		%	86.5%	86.5%	86.5%	
Sex	Male	n	31	28	59	0.000
		%	83.8%	75.7%	79.7%	
	Female	n	6	9	15	
		%	16.2%	24.3%	20.3%	
Total		n	37	37	74	
		%	100.0%	100.0%	100.0%	

Table 1:- Sample Characteristics

Table 1 shows the distribution of sample characteristics based on the treatment group. Sex, males in the 0.5 mg neostigmine group were 31 samples (83.8%) and in the 1 mg neostigmine group were 59 samples (79.7%) while the females in the 0.5 mg neostigmine group were 6 samples (16.2%) and in the 1 mg neostigmine group were 15 samples (20.3%). The most dominant age in the 0.5 mg neostigmine group and 1 mg neostigmine was around 41-60 years with each percentage of 73.0% and 91.9%. The sample in this study was mostly ASA 2 with 86.5% both in the treatment group of 0.5 mg neostigmine or 1 mg neostigmine.

Characteristics		Group	
		0.5 mg Neostigmin	1 mg Neostigmin
MAP	Mean	95.3	93.8
	SD	9.2	9.6
	Nilai p	0.00	0.01
HR	Mean	77.4	81.2
	SD	9.4	9.4
	Nilai p	0.00	0.00
Temperature	Mean	36.7	36.7
	SD	0.17	0.35
	Nilai p	0.00	0.002

Table 2:- Hemodynamic Characteristics

Based on table 2, it was found that MAP in patients with 0.5 mg neostigmine was higher at 95.3±9.2 mmHg compared to MAP patients given the 1 mg neostigmine. However, 1 mg neostigmine patients' HR was higher than the 0.5 mg neostigmine patients' HR. For temperatures, both groups had the same mean value of 36.7 ^{0}C.

- *Comparison of Urine Volume in Group A (0.5 mg neostigmine) and Group B (1 mg Neostigmine)*

The comparison of urine volume in group A (0.5 mg neostigmine) and group B (1 mg neostigmine) is shown in table 3

Group		T0	T1	T2	T3	T4	T5	P value
0.5 mg Neostigmin	Mean	133.51	179.19	226.22	201.59	116.49	63.51	0.000**
	SD	19.61	18.62	18.16	21.81	23.95	24.41	
1 mg Neostigmin	Mean	131.89	108.11	74.32	52.16	50.59	50.08	0.000**
	SD	18.83	18.68	15.91	20.57	23.76	25.36	
Nilai p		0.703*	0.809*	0.008*	0.005*	0.001*	0.000*	

Table 3:- The comparison of urine volume in group A (0.5 mg neostigmine) and group B (1 mg neostigmine)
(* Mann Whitney Test, ** Friedman Test)

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Table 3 shows the mean of urine volume in the initial observation until the final observation. In the treatment group with 0.5 mg Neostigmine, the mean of urine volume in the initial observation (T0) was 133.51 cc and in the final treatment (T5) was 63.51 cc, the results of the statistic test obtained p values (0.000) < 0.05 which means there was a change in the man of volume urine from initial observation to final observation. In the treatment group with 1 mg Neostigmine, the mean of urine volume in the initial observation (T0) was 131.89 cc and in the final treatment (T5) was 50.08 cc, the statistical test results obtained p-value (0.000) < 0.05 which means there was a change in mean of urine volume from initial observation to final observation. The comparison of differences or changes that occurred between two groups obtained a value of p > 0.05 in T0 and T1 which means there was no difference in the mean changes of urine volume between 0.5 mg Neostigmine with 1 mg neostigmine, but at observation T2, T3, T4, the p-value > 0.005 which means there was a difference in mean changes of urine volume between 0.5 mg Neostigmine with 1 mg neostigmine. This is because the bladder emptying effect has begun to occur on T2 observations in the treatment of 1 mg neostigmine.

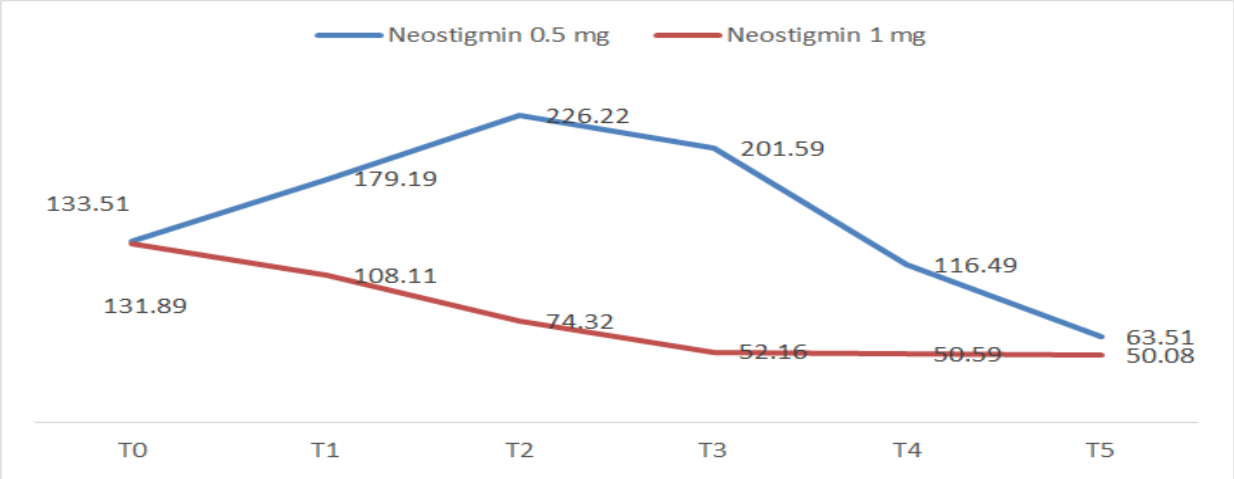


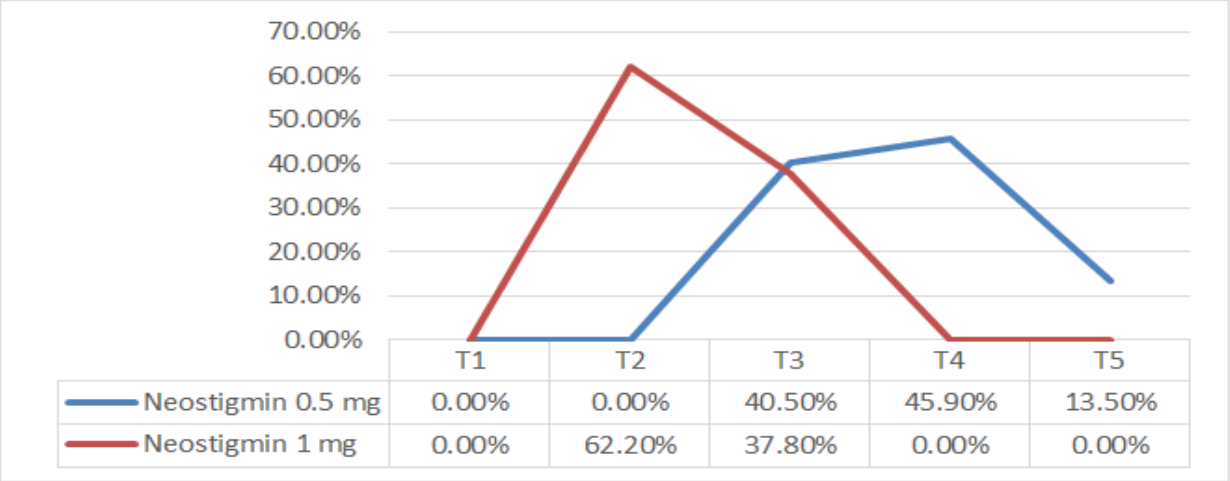
Fig 1:- Comparison of 0.5 neostigmine and 1 mg neostigmine urine volume in T1 to T5 observations

Comparison of urinary velocity in group A (0.5 mg neostigmine) and group B (1 mg neostigmine). The comparison of urinary velocity in group A (0.5 mg neostigmine) and group B (1 mg neostigmine) is shown in Table 4

Urinary velocity		Group		Total	P value
		0.5 mg Neostigmin	1 mg Neostigmin		
T1	n	0	0	23	0.000
	%	0.0%	0.0%	31.1%	
T2	n	0	23	14	
	%	0.0%	62.2%	18.9%	
T3	n	15	14	15	
	%	40.5%	37.8%	20.3%	
T4	n	17	0	17	
	%	45.9%	0.0%	23.0%	
T5	n	5	0	5	
	%	13.5%	0.0%	6.8%	
Total	n	37	37	74	
	%	100.0%	100.0%	100.0%	

Table 4:- The comparison of urinary velocity in group A (0.5 mg neostigmine) and group B (1 mg neostigmine)

Table 4 shows that the urinary velocity distribution in the treatment group with 0.5 mg neostigmine and 1 mg neostigmine. In the treatment group with 0.5 mg neostigmine, the velocity with the highest proposition was obtained by observing T4 with 45.9% while the lowest proportion was in T5 observation with 13.5%. Whereas in the treatment group with 1 mg neostigmine, the velocity with the highest proposition was obtained in T1 observation of 62.2% while the lowest proportion was in T2 observation with 37.85%. The results obtained the p-value (0.000) < 0.05, which means that there was a difference in the proportion of urinary velocity between the treatment group of 0.5 mg Neostigmine and 1 mg Neostigmine.



	T1	T2	T3	T4	T5
Neostigmin 0.5 mg	0.00%	0.00%	40.50%	45.90%	13.50%
Neostigmin 1 mg	0.00%	62.20%	37.80%	0.00%	0.00%

Fig 2:- Comparison of the urinary velocity of 0.5 neostigmine and 1 mg neostigmine in T1 to T5 observations

Comparison of urine volume and urinary velocity in the administration of 0.5 mg neostigmine and 1 mg neostigmine

The comparison of urine volume and urinary velocity in the administration of 0.5 mg neostigmine and 1 mg neostigmine is shown in Figure 3

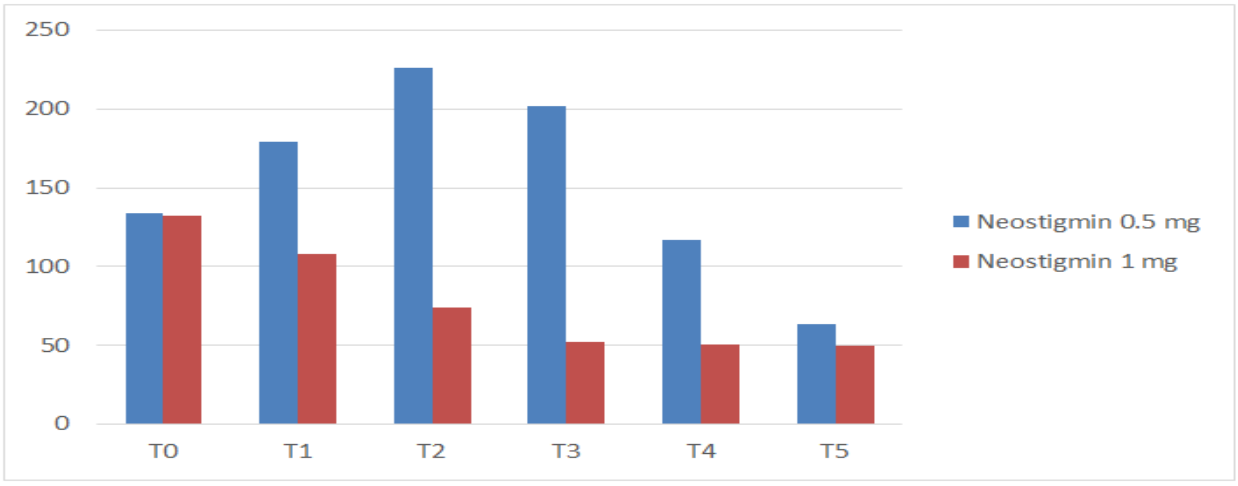


Fig 3:- Comparison of urine volume and urinary velocity in the administration of 0.5 mg neostigmine and 1 mg neostigmine

Based on Figure 3, in the 1 mg neostigmine group, the urine volume decreased starting at T1 and significantly decreased at T2, this occurred due to the onset of action of 1 mg neostigmine which had begun to occur in the first 10 minutes with a peak onset time of 20 minutes. While in 0.5 mg neostigmine, the urine volume decreased at the time of T3 observation and significantly decreased at the time of T4 observation, this occurred as the onset of 0.5 mg neostigmine began to occur in 30 minutes with peak onset time at 40 minutes. So it can be concluded that the 1 mg neostigmine group has a faster work onset compared to 0.5 mg neostigmine, with a statistically significant difference p-value (0,000) < 0.005 (Table 3).

IV. DISCUSSION

This study was conducted to compare the effectiveness of intramuscular 0.5 mg neostigmine and 1 mg neostigmine in accelerating bladder emptying after spinal anesthesia. Neostigmine can increase intravesical pressure, causing detrusor hyperactive contractions.

Based on Table 1 and Table 2, it was found that MAP in patients with 0.5 mg neostigmine was higher at 95.3±9.2 mmHg compared to MAP patients given the 1 mg neostigmine. However, 1 mg neostigmine patients' HR was higher than the 0.5 mg neostigmine patients' HR. For temperatures, both groups had the same mean value of 36.7 ^{0}C. This is in line with the theory that the cardiovascular effects of anticholinesterase drugs reflect the effects of acetylcholine accumulation on the heart which causes bradycardia, blood vessels that cause decreased vascular systemic resistance, and end nerve fibers end cholinergic postganglionic. Cardiac effects of anticholinesterase drugs can be attenuated with anticholinergic drugs that block muscarinic receptors but not cholinergic nicotinic receptors (Alwin C. Powers & David D' Alessio, 2011).

Based on table 3, there was no difference in the mean changes of urine volume between 0.5 mg Neostigmine with 1 mg neostigmine in T0 and T1, but at observation T2, T3, T4, the p-value > 0.005 which means there was a difference in mean changes of urine volume between 0.5 mg

Neostigmine with 1 mg neostigmine. This is because the bladder emptying effect has begun to occur on T2 observations in the treatment of 1 mg neostigmine. This is in accordance with the literature that neostigmine is an acetylcholinesterase inhibitor that causes accumulation of acetylcholine around the cholinergic nerve terminal. Acetylcholine will stimulate contractile muscarinic receptors in the bladder smooth muscle (detrusor) and cause bladder contractions. The long duration of acetylcholine in the receptor results in stronger smooth muscle contractions. (Hegde and Eglen, 1999; Nakahara *et al.*, 2003; Taylor, 2011) Bladder function is regulated by interactions between the somatic, parasympathetic and sympathetic nervous systems. The parasympathetic nervous system provides the main excitatory innervation of the detrusor muscle. Postsynaptic M2 and M3 muscarinic receptors are considered as the most important even though many receptor systems and mediators are responsible for detrusor contractions. In addition, in this study, 1 mg neostigmine has begun to cause bladder emptying effects on the T3 observation (30 minutes) so that bladder emptying has begun to differ significantly. This is consistent with the literature that stated that the onset of neostigmine action in parenteral administration is around 10-30 minutes. (Butterworth, Mackey and Wasnick, 2013; Lexicomp, 2019)

The results of this study are in accordance with the theory that neostigmine is a carbamate inhibitor of the acetylcholinesterase enzyme that hydrolyzes the neurotransmitter acetylcholine at the nervous system synapse and at the neuromuscular junction to end cholinergic signaling. Obstacles to the anticholinesterase enzyme trigger an increase in the concentration of acetylcholine at the synapse, causing longer cholinergic neurotransmissions (Liu, 2017 ; Dahyanti, Salam & Ahmad, 2011).

Table 4 shows that the treatment group with 0.5 mg neostigmine obtained the highest urinary velocity with proposition at T4 observation, whereas in the treatment group with 1 mg neostigmine, the highest urinary velocity was found in T1 observation. The results obtained the p-value (0.000) < 0.05, which means that there is a difference in the proportion of urinary velocity between the treatment group of 0.5 mg Neostigmine and 1 mg Neostigmine. This is consistent with a study conducted by Senapathi (2018) that neostigmine effectively accelerates bladder emptying after spinal anesthesia with p-value < 0.05. Time for the first micturition after IM injection and time for first micturition after spinal anesthesia was significantly faster in the neostigmine group. Postvoid residual volume was also significantly lower in the neostigmine group, which indicates that neostigmine increases muscle contraction after spinal anesthesia. However, the effectiveness of IM neostigmine to accelerate bladder emptying was not followed by a significant reduction in the incidence of postoperative urinary retention (POUR).

The same result was also conveyed by Mustafa (2018) in the experimental study that Neostigmine (10 μM) induced bladder contractions. Neostigmine is a reversible acetylcholinesterase inhibitor, inducing bladder contractions by stimulating muscarinic receptors. Neostigmine is used as a treatment of bladder disorders in a number of situations (Stallard and Prescott, 1988; Mokrý *et al.*, 2005). This study shows that acetylcholinesterase inhibitors add to the cholinergic innervation effect. Although in this study it was found that the effects of neostigmine were stronger in pregnancy. (Mustafa, 2019) Nakahara said that neostigmine increases the pressure of sedation in a concentration-dependent state. Thus AChe inhibition not only prevents the degradation of endogenous acetylcholine but also stimulates the release of endogenous acetylcholine from nerve endings (Nakahara et al., 2003). The same finding was also found by Somogyi and de Groat that neostigmine and physostigmine increase the amount of acetylcholine release by the cholinergic nerve. In addition to preventing the destruction of acetylcholine, it also turns out to facilitate activation of M1 receptors on cholinergic nerves. This action requires the initial release of acetylcholine (Somogyi and de Groat, 1992).

V. CONCLUSIONS

- In T0 and T1 observations, there is no difference in the mean changes of urine volume between 0.5 mg Neostigmine and 1 mg neostigmine, but in T2, T3, T4 observations there is a difference in mean changes of urine volume between 0.5 mg Neostigmine and 1 mg neostigmine. This is because the bladder emptying effect has begun to occur in T2 observation of 1 mg neostigmine treatment. Bladder emptying in 0.5 mg neostigmine treatment has occurred in T3.
- There is a difference in the proportion of urinary velocity between the treatment group of 0.5 mg Neostigmine and 1 mg neostigmine.
- The 1 mg neostigmine group has a faster onset of action compared to 0.5 mg neostigmine group.
- Suggestions
- This research is expected to be the initial basis for neostigmine research to accelerate bladder emptying in larger sample patients of spinal anesthesia.
- This research is expected to be an input for decision-makers at the Haji Adam Malik General Central Hospital in Medan to include the administration of neostigmine in spinal anesthesia patients as part of the operational standard of hospital services.

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