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Effectiveness of Bolus Administration to Continuous Intravenous Lidocaine on Pain Intensity after Mastectomy Surgery

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Abstract:-

- ***Introduction***

Administration of intravenous lidocaine as an adjunct to placebo in postoperative pain is highly recommended. Its use has been proven safe and effective in mastectomy surgery.

- ***Objective***

To determine the effectiveness of bolus administration of continuous intravenous lidocaine on pain intensity after mastectomy surgery at Haji Adam Malik General Hospital of Medan and North Sumatra University Hospital.

- ***Method***

This research is a randomized controlled and double-blind clinical trial. It was conducted for 2 months in November-December 2019. The total sample obtained was 42 patients. This sample was divided into 2 groups: group A (lidocaine) and group B (placebo). Data was collected using the VAS questionnaire at hours 0 (T0), 2 (T1), 4 (T2) and 6 (T3) after surgery ended.

- ***Results***

The results showed that the mean value of VAS-A in 72 patients was 4.14 ± 1.9. The mean MAP in the lidocaine group was 91.4 ± 6.8 mmHg while in the placebo group was slightly higher, which was 92.2 ± 5.2 mmHg (p = 0.541). The mean heart rate in the lidocaine group was 78.0 ± 6.06 times per minute while in the placebo group was slightly higher, which was 84.4 ± 7.3 times per minute (p = 0.003). In the lidocaine group, there was no correlation between MAP and postoperative VAS values (r = -0.106; p = 0.324) and a low negative correlation between heart rate and postoperative VAS values (r = -0.201; p = 0.524). VAS values in the lidocaine and placebo groups showed a significant difference in T0 observations (p = 0.039).

- ***Conclusion***

VAS values in the lidocaine group were lower than those in the placebo group at T0 observations, but not significantly different in T1, T2, and T3 observations.

Keywords:- *Postoperative Pain, Lidocaine, Hemodynamics.*

I. INTRODUCTION

Breast cancer is found throughout the world. In 2003, the incidence of breast cancer in the Netherlands was 91 per 100,000 population, in America 71.7 per 100,000 population, in Switzerland 70 per 100,000 population, in Australia 83.2 per 100,000 population, in Canada 84.7 per 100,000 population, and in 2002 in Indonesia 26 per 100,000 population and in Japan 16 per 100,000 population.

Intravenous lidocaine administration as an adjunct to placebo in postoperative pain is recommended. Its use has been proven safe and effective in the stomach, breast, spine, and, more recently, thoracic surgery. The lidocaine drug reduces opioid consumption, which can contribute to postoperative pulmonary complications (Tauzin-Fin et al., 2014; Dunn and Durieux, 2017). According to research conducted by Terkawi et al. (2015) in Virginia on 61 mastectomy patients, significant differences were obtained in postoperative pain mastectomy between groups given continuous lidocaine and those not given continuous lidocaine, with a significance value of p = 0.008. Research of Terkawi et. al. showed that there was a decrease in the pain incidence in patients who were given continuous lidocaine compared to patients who were not given continuous lidocaine (Terkawi et al., 2015).

Jay Thomas et al. in their study also mentioned that of 82 patients who had surgery given lidocaine for pain therapy, 82% of the patients evaluated reported that their pain was reduced after given lidocaine administration, 8% reported partial response, and 10% reported no benefits (Thomas et al., 2004).

Sharma (2009) in his research found that giving a single infusion of lidocaine provided pain relief and shorter pain duration in opioid-refractory patients with cancer pain. Sharma's research (2009) reported that in 50 cancer pain patients given lidocaine infusion there was a significant difference in decrease in the degree of pain compared with patients not given lidocaine, with a significance of p <0.0012. Side effects observed were tinnitus, perioral numbness, sedation, mild dizziness and headaches (Sharma et al., 2009). In many studies, analgesic effects have persisted after lidocaine infusion is stopped, which indicates prevention of central hypersensitivity, peripheral hypersensitivity, or both. Inhibition of NMDA receptors, polymorphonuclear leucocyte priming, or both can play a role in this effect. Perioperative lidocaine was also found to

have a preventive effect on postoperative pain up to 72 hours after abdominal surgery (Ramaswamy, Wilson and Colvin, 2013). Based on the above background, the author intended to find out how effective the administration of continuous intravenous lidocaine was to the intensity of pain after mastectomy surgery at Haji Adam Malik General Hospital, Medan and North Sumatra University Hospital.

II. METHODS

➢ *Research Design*

The design of this study used a randomized controlled and double-blind clinical trial to determine the effectiveness of bolus administration of continuous intravenous lidocaine on pain intensity after mastectomy surgery.

➢ *Research Place and Time*

This research was conducted in elective operating room of Haji Adam Malik General Hospital of Medan and North Sumatra University Hospital. The study began after ethical clearance and permission from the Haji Adam Malik General Hospital, North Sumatra University Hospital and the Faculty of Medicine of North Sumatra University were published until the sample size was met.

➢ *Research Population and Samples*

The research population included all subjects who were electively scheduled to undergo mastectomy surgery with general anesthesia techniques at the Haji Adam Malik General Hospital and North Sumatra University. The research sample was the population that fulfilled the inclusion and exclusion criteria. This sample was divided into 2 groups:

a. Group A, who received an injection of lidocaine with an initial bolus of 1.5 mg/kg dissolved with 0.9% NaCl to 5 ml followed with continuous lidocaine 2 mg/kg/hour using a 20 ml syringe pump.
b. Group B, who received 0.9% NaCl injection with an initial bolus of 5 ml, followed with by continuous 0.9% NaCl 20 ml using a syringe pump in accordance with the dose of lidocaine.

➢ *Inclusion and Exclusion Criteria*

Inclusion criteria in this study were patients aged 19-65, patients of ASA 1 and ASA 2 physical status, patients undergoing mastectomy, patients with BMI of 18.5-24.9 kg/m, patients with normal ECG, patients who agreed to participate in the study and sign the research informed consent. Exclusion criteria were patients who received opioid analgesics before surgery, patients who had a history of lidocaine allergy, patients with hepatic impairment with operations longer than 4 hours and patients with a history of heart disease or heart rhythm disorders. Drop out criteria included an emergency heart and lung and allergic reactions after the use of the drugs under study.

➢ *Procedure*

1. When the patient arrived in the surgical waiting room, she/he was rechecked for identity, diagnosis, anesthesia action plans, and access to infusion (make sure the infusion system has been installed with 18G abocath and equipped with three-way stopcock, and infusion flow is smooth).
2. The patient was then taken to the operating room, then a standard monitor was installed (ECG, blood pressure, heart rate, breathing frequency, oxygen saturation).
3. Both groups of patients were given 10 ml/kgBB of Ringer Lactate fluid preloading.
4. Both groups were prepared for general anesthesia. Give premedication with midazolam 0.05 mg/kg, fentanyl 2 mcg/kg, and wait for the 5-minute onset.
5. Patients received an injection of lidocaine with an initial bolus of 1.5 mg/kg dissolved with 0.9% NaCl to 5 ml, followed with continuous lidocaine 2 mg/kg/hour in Nacl 0.9% 20 ml given using a syringe pump in a 20 ml syringe at a speed of 20cc per hour. Group B was given 0.9% NaCl injection with an initial bolus of 5 ml. Followed by a continuous 0.9% NaCl 20 ml using a syringe pump according to the lidocaine dose with a speed of 20cc per hour.
6. Patients were induced with propofol 2 mg/kg, rocket muscle relaxant 1 mg/kg. After onset was reached for 1 minute, direct laryngoscopy was performed with a laryngoscope and the trachea was intubated with an appropriate endotracheal tube.
7. The surgery began. Maintenance of sedation used Isoflurane (1 percent volume) with an oxygen and N2O ratio equal to 2 to 2, maintenance of analgesia used fentanyl 0.5 - 1 mcg/KgBB every 30 minutes and maintenance of muscle relaxants used 0.2 mg/Kg rururonium every 30 minutes.
8. After surgery, after the patient fulfilled the extubation criteria, she/he was extubated (GCS 15). They must be fully conscious and time was recorded as T0, and the VAS was assessed using a VAS ruler. The patient was then asked while being showed the scale according to the pain perception perceived by the patient. This assessment was carried out directly by the author.
9. Assessment of dose equivalence and side effects of drugs with a target VAS value <4 was carried out directly by the author at 0-Hour (T0), 2 (T1), 4 (T2) and 6 (T3) after surgery ended.
10. T0 began after the patient was extubated and fully awake.
11. The results of observational data in the two groups were compared statistically.
12. The research was stopped if the study subjects refused to participate further, if the operation was prolonged so that additional general anesthesia was needed, an allergic reaction to lidocaine occurred, or life threatening emergency airway, heart, lung, and brain occurred.

➢ *Data Analysis*

After the required data was collected, it was checked again for its completeness before tabulation and processing. Then the data was given encoding to facilitate tabulation. Data was tabulated into the master table using SPSS software. Numerical data were displayed in mean values + SD (standard deviation), while categorical data were displayed in numbers (percentages). The normality test used the Shapiro-Wilk test. The difference test used the T-test if the data was normally distributed would use the Mann-Whitney test if the data was not normally distributed. A 95% confidence interval with a p value <0.05 was considered significant.

III. RESULTS

➢ *Sample Characteristics*

This research was carried out for 2 months, in November-December 2019 at Haji Adam Malik General Hospital of Medan and North Sumatra University Hospital. This study aimed to determine the effectiveness of bolus administration of continuous intravenous lidocaine on pain intensity after mastectomy surgery at Haji Adam Malik General Hospital of Medan and North Sumatra University Hospital. The samples obtained in this study amounted to 42 samples that fit the inclusion and exclusion criteria. Sample characteristics are shown in Table 1.

Variable	Lidocaine (n=21)	Placebo (n=21)	p
Age (Mean±SD)	45.76±11.12	44.43±10.70	0.201[b]
IMT (Mean±SD)	22.70±1.47	23.68±1.27	0.737[b]
Ethnicity (%)			
Javanese	9 (42.9)	6 (28.6)	0.865[a]
Batak	4 (19.0)	8 (38.1)	
Mandailing	0 (0)	3 (14.3)	
Nias	0 (0)	1 (4.8)	
Karo	3 (14.3)	2 (9.5)	
Malay	4 (19.0)	1 (4.8)	
Minang	1 (4.8)	0 (0)	
PS ASA (%)			
I	15 (71.4)	12 (57.1)	0.340[a]
II	6 (28.6)	9 (42.9)	
Surgery duration (Mean±SD)	213.33±14.08	215.24±11.00	0.390[a]
Total	21	21	

Table 1:- Sample characteristics
Notes: [a]Mann-Whitney Test; [b] Independent t-Test

Based on Table 1, from the distribution of sample characteristics in the study it was found that the mean age of patients in the lidocaine group was 45.76 ± 11.12 years and in the placebo group 44.43 ± 10.70 years. Most of the patients were of Batak ethnic group, with a percentage of 38.1%. Patients had an average body mass index (BMI) of 22.70 ± 1.27 kg/m² in the lidocaine group and 23.68 ± 1.47 kg/m¬2 in the placebo group, and both in the lidocaine group and placebo group, the majority belonged to ASA I.

➢ *Comparison of Hemodynamics in the Lidocaine and Placebo Groups*

Comparison of hemodynamics in the lidocaine and placebo groups is shown in Table 2.

Hemodynamics	Lidocaine (n=21) (Mean±SD)	Placebo (n=21) (Mean±SD)	p
Mean arterial pressure (MAP)	91.4 ± 6.8	92.2 ± 5.2	0.541
Heart rate	78.0 ± 6.0	84.4 ± 7.3	0.003

Table 2:- Comparison of hemodynamics in the lidocaine and placebo groups
Notes: p (comparison between the lidocaine and placebo groups), *α<0.05

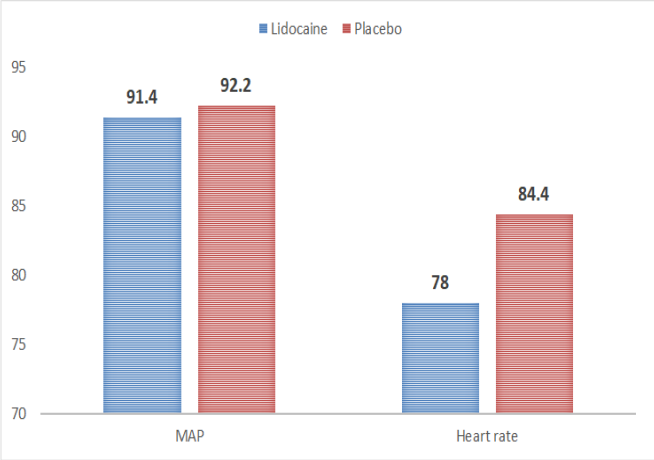

Fig 1:- Comparison of hemodynamics in the lidocaine and placebo groups

Based on Table 2 and Figure 1, it was found that the mean MAP in the lidocaine group was lower than the mean MAP in the placebo group. The mean MAP in the lidocaine group was 91.4 ± 6.8 mmHg while in the placebo group it was slightly higher, which was 92.2 ± 5.2 mmHg. Statistical tests using the Mann-Whiteny test at 95% CI and α = 0.05 resulted in a p value of 0.541 (p> 0.05) so that Ho was accepted, meaning that there was no significant difference between the mean MAP values in the lidocaine group and the placebo group.

Table 2 also shows the differences in mean heart rate in the lidocaine and placebo groups. The mean heart rate in the lidocaine group was lower than the mean heart rate in the placebo group. The mean heart rate in the lidocaine group was 78.0 ± 6.06 times per minute while in the placebo group it was slightly higher, which was 84.4 ± 7.3 times per minute. Statistical tests using the Mann-Whiteny test at 95% CI and α = 0.05 resulted a p value of 0.003 (p <0.05) so that Ho was rejected, meaning there was a significant difference between heart rates in the lidocaine group and the placebo group.

➢ *Correlation of Hemodynamics and VAS Values in the Lidocaine and Placebo Groups*

Correlation of hemodynamics and VAS values in the lidocaine and placebo groups is shown in Table 3.

Hemodynamics	Lidocaine (n=21)		Placebo (n=21)	
	r	p	r	p
MAP	-0.106	0.324	0.456	0.019
Heart rate	-0.201	0.524	0.203	0.03

Table 3:-Correlation of hemodynamics and VAS values in the lidocaine and placebo groups
Notes: Pearson correlation test

Table 3 shows a moderate positive correlation between MAP and postoperative VAS values and a low positive correlation between heart rate and postoperative VAS values in the placebo group. This means that the higher the MAP and heart rate, the higher the VAS value after the patient's surgery. While in the lidocaine group no correlation was found between MAP and postoperative VAS values and there was a low negative correlation between heart rate and postoperative VAS values, which means an increase in MAP and heart rate during intraoperative did not affect the VAS value of postoperative patients.

➢ *Comparison of VAS Values after Surgery in the Lidocaine and Placebo Groups*

Table 4 shows the comparison of VAS values after surgery in the lidocaine and placebo groups.

VAS	Lidocaine (n=21)	Placebo (n=21)	p^a
T0	4.33±1.7	5.48±1.7	0.039*
T1	2.81±2.0	3.52±1.5	0.102
T2	2.05±2.0	2.67±1.2	0.117
T3	2.05±2.0	2.67±1.2	0.117
p^b	0.001*	0.001*	

Table 4:- Comparison of VAS values after surgery in the lidocaine and placebo groups
Notes: p^a (comparison of VAS values in the lidocaine and placebo groups, Mann-Whitney test); p^b (comparison of VAS values at each observation time, Friedman test), T0 (After fully conscious), T1 (2 hours after surgery), T2 (4 hours after surgeryT3 (6 hours after surgery), *α<0.05.

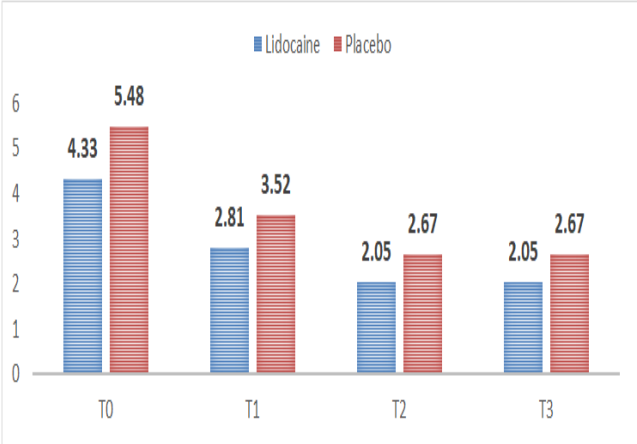

Fig 2:- Comparison of VAS in the lidocaine and placebo groups

Based on Table 4 and Figure 2, it was found that the VAS values in the lidocaine and placebo groups showed a significant difference in T0 observations (p = 0.039) and the T0 VAS values in the lidocaine group were lower than those in the placebo group, but in the T1, T2, and T3 observations there was no significant difference in VAS values.

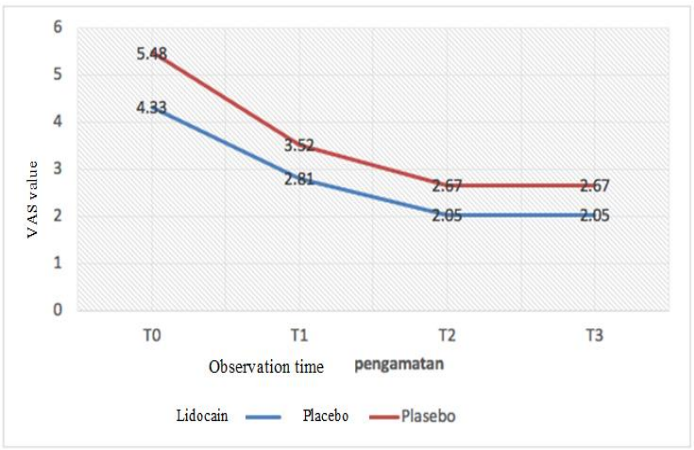

Fig 3:- Changes in VAS values on observations of T0, T1, T2, and T3 in the lidocaine and placebo groups

Based on Table 4 and Figure 3, both in the lidocaine and placebo groups, the VAS values at each time of observation T0, T1, T2 and T3 experienced statistically significant changes (p = 0.001). In the lidocaine group the T0 VAS value was lower than the T0 VAS value in the placebo group, although both groups continued to decline until T3 observation. The decrease in VAS in the lidocaine group only occurred in T0 observations compared with the placebo group. This was presumably because the lidocaine duration of action was around 60-120 minutes with a half-life of about 96 minutes, so the effect of lidocaine as an adjuvant analgesic was only effective within 2 hours after extubation.

IV. DISCUSSION

In this study observations were made on 42 patients who would undergo elective surgery. The study was conducted for 2 months at Haji Adam Malik General Hospital of Medan and North Sumatra University Hospital. This study aimed to determine the effectiveness of bolus administration of continuous intravenous lidocaine on pain intensity after mastectomy surgery. The samples obtained in this study were 42 samples. Based on Table 1, which shows the distribution of sample characteristics in the study, it was found that the mean age, ethnicity, ASA, BMI, and surgery duration of patients in the lidocaine and placebo groups were homogeneously distributed with p values> 0.05, which means that age, ethnicity, ASA, BMI, and surgery duration did not affect the value of VAS in patients. In addition, these results indicate that Bataknese patients have the most percentage. The average body mass index (BMI) was within normal limits and the majority of patients belonged to PS ASA I.

Based on Table 2, it was found that the mean MAP and heart rate values in the lidocaine group were more stable compared to the placebo group. This is in line with research conducted by Dogan (2016) on 60 patients who underwent laparoscopic cholecystectomy; it was reported that intraoperative lidocaine infusion was able to suppress the increased hemodynamic response. Konay et al (2019) also reported similar results in clinical studies using a sample of 48 patients; it was found that lidocaine was able to maintain more stable hemodynamics with an average MAP value of 85.1 mmHg. In general, lidocaine can suppress the automaticity of the heart muscle and reduce the duration of the refractory phase. The contractility and conduction of the heart muscle are also suppressed by local anesthetics at greater concentrations. Effects arise due to changes in the heart muscle cell membrane (sodium channel blockade) and inhibition of the autonomic nervous system (Morgan 2013, Stoelting 2006). The effect of lidocaine was able to increase plasma noradrenaline levels during surgery and cause an increase in adrenergic impulses. This was reported in a study with venous occlusion in the extremities that contribute to good cardiovascular tolerance to the surgical response, anesthetic agents and antiarrhythmic drugs (Edouard, 2016). Other evidence showing the effect of lidocaine on hemodynamics was also reported by Pinho (2017) who stated that the infusion of lidocaine was able to maintain stable hemodynamics through administration of lidocaine 1.5 mg/kg intravenous bolus and continuous lidocaine of 2 mg/kg/hour (Pinho, 2017). In another study, it was reported that lidocaine also had a blunting effect on hemodynamic responses in 30 patients with trauma to brain injury (Singh et. Al. 2018). Lidocaine works by inhibiting Na + canals thereby decreasing sodium and slowing the rate of membrane depolarization and the action potential does not occur (Morgan, 2018)

Based on Table 3, it appears that the higher the MAP and heart rate, the higher the patient's VAS value. This is consistent with research conducted by Soltani et al (2015) which stated that patients with increased hemodynamics showed higher pain intensity (Soltani et al. 2015). The correlation between hemodynamic response and pain stimulation was also demonstrated by Yucel et al (2015) using near-infrared spectroscopy (NIRS); pain stimulation can result in hemodynamic changes and persistence of changes in collateral signals in the primary somatosensory cortex (Yucel et al. 2016). However, the Midillin and Eser study (2015) reported that there was no relationship between increased hemodynamics and pain intensity in 100 patients undergoing cesarean section. Schonberger et. al. (2014) reported that there were no differences in hemodynamic status assessed with increasing degrees of pain as assessed by VAS (Schonberger et al., 2014). Pain can be described by changes in the autonomic nervous system (tachycardia, increased blood pressure, diaphoresis, rapid breathing) (Atchison and Vincent, 2012; Woolf et al., 2004). Surgical pain triggers a stress response, which is the neuron endocrine response that affects mortality and various morbidity of postoperative complications (Das, 2019)

Based on Table 4 and Figure 2, it was found that the VAS values in the lidocaine and placebo groups showed a significant difference in T0 observations (p = 0.039) and the VAS T0 values in the lidocaine group were lower than those in the placebo group, but in the T1, T2, and T3 there was a change in both groups, although the initial VAS (T0) in the lidocaine group was lower than in the placebo group (Figure 4.3). The results of this study are in line with Choi et al (2016) in 58 thyroidectomy patients given intravenous lidocaine; it was reported that intravenous lidocaine effectively reduced postoperative pain and improved the quality of patient recovery. The study reported significant differences between the groups given lidocaine and placebo from 2 hours post-surgery to 48 hours of observation (Choi et al. 2016). This is consistent with the literature that systemic lidocaine can weaken the nerve response to pain by reducing spike activity, amplitude, and conduction time in C-*unmyelinated* and A-δ *myelinated* fibers which are peripheral nerve fibers that mediate pain. The meta-analysis report by Weibel et al. (2018) showed that in 29 RCTs with a sample size of 1656 patients, the VAS value (1-4 hours) in the lidocaine group was 2.48 cm lower than in the placebo group. While on 24-hour observation in 33 RCT studies with 1847 samples, it was found that the VAS value of the lidocaine group was 0.48 cm lower than the placebo group. A good effect of lidocaine in suppressing VAS values was also reported at 48 hours of observation in 24 RCTs with a sample of 1404 patients, whereas in the lidocaine group the VAS value was 0.42 cm lower than in the placebo group (Weibel et al. 2018)

V. CONCLUSION

VAS values in the lidocaine and placebo groups showed significant differences in T0 observations (p = 0.039).

REFERENCES

[1]. Atchison, J. W. and Vincent, H. K. (2012) 'Obesity and low back pain: relationships and treatment', *Pain Management*, 2(1), pp. 79–86. doi: 10.2217/pmt.11.64.
[2]. Butterworth, J. F. *et al.* (2018) *Preoperative Assessment*. Morgan & Mikhail's Clinical Anesthesiology.
[3]. Choi, G. J. *et al.* (2016) 'Clinical Efficacy of Intravenous Lidocaine for Thyroidectomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial', *World Journal of Surgery*. Springer International Publishing, 40(12), pp. 2941–2947. doi: 10.1007/s00268-016-3619-6.
[4]. Édouard, A. *et al.* (1991) 'Effets de la lidocaïne sur la circulation artérielle et veineuse des membres chez l'homme', *Annales francaises d'anesthesie et de reanimation*, 10(6), pp. 529–534. doi: 10.1016/S0750-7658(05)80289-8.
[5]. Finucane, B. T. and Tsui, B. C.-H. (2017) *Complications of regional anesthesia : principles of safe practice in local and regional anesthesia*.
[6]. Flood, P., Rathmell, J. P. and Shafer, S. (2015) 'Neurologic System', in *Stoelting's Pharmacology & Physiology in Anesthetic Practice*. 5th edn. United States: Wolters Kluwer, pp. 98–160.
[7]. Katzung, B., Masters, S. and Trevor, A. (2009) *Basic and Clinical Pharmacology, 11th Edition*.
[8]. Lemmens, L. C. *et al.* (2006) 'The effect of national guidelines on the implementation of outpatient preoperative evaluation clinics in Dutch hospitals', *European Journal of Anaesthesiology*, 23(11), pp. 962–970. doi: 10.1017/S0265021506000895.
[9]. Midilli, T. S. and Eser, I. (2015) 'Effects of Reiki on Post-cesarean Delivery Pain, Anxiety, and Hemodynamic Parameters: A Randomized, Controlled Clinical Trial', *Pain Management Nursing*. American Society for Pain Management Nursing, 16(3), pp. 388–399. doi: 10.1016/j.pmn.2014.09.005.
[10]. Olawin, A. M. and M Das, J. (2019) *Spinal Anesthesia*, *StatPearls*. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537299/ (Accessed: 22 November 2019).
[11]. Powlovich, L. G., Nemergut, E. C. and Collins, S. R. (2018) 'Barash's Clinical Anesthesia, 8th ed', *Anesthesia & Analgesia*, 127(3), p. e41. doi: 10.1213/ANE.0000000000003548.
[12]. Rawal, N. *et al.* (2008) *Postoperative Pain Management - Good Clinical Practice*. European Society of Regional Anesthesia.
[13]. Rohlman, D. S. *et al.* (1994) 'A double-blind trial of bupropion versus desipramine for bipolar depression', *Journal of Clinical Psychiatry*, 55(9), pp. 391–393. doi: 10.1002/hup.
[14]. Schonberger, R. B. *et al.* (2014) 'Preoperative depression symptom severity and its impact on adherence to preoperative beta-blocker therapy.', *Journal of cardiothoracic and vascular anesthesia*. NIH Public Access, 28(6), pp. 1467–73. doi: 10.1053/j.jvca.2014.05.006.
[15]. Sesack, S. R. *et al.* (1998) 'Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter', *Journal of Neuroscience*, 18(7), pp. 2697–2708. doi: 10.1523/jneurosci.18-07-02697.1998.
[16]. Singh, S. *et al.* (2018) 'Comparison of effect of dexmedetomidine and lidocaine on intracranial and systemic hemodynamic response to chest physiotherapy and tracheal suctioning in patients with severe traumatic brain injury', *Journal of Anesthesia*. Springer Japan, 32(4), pp. 518–523. doi: 10.1007/s00540-018-2505-9.
[17]. Soltani, G., Molkizadeh, A. and Amini, S. (2015) 'Effect of intravenous acetaminophen (Paracetamol) on hemodynamic parameters following endotracheal tube intubation and postoperative pain in caesarian section surgeries', *Anesthesiology and Pain Medicine*, 5(6). doi: 10.5812/aapm.30062.
[18]. Soteriades, E. S. *et al.* (2002) 'Incidence and Prognosis of Syncope', *New England Journal of Medicine*. Massachusetts Medical Society, 347(12), pp. 878–885. doi: 10.1056/NEJMoa012407.
[19]. Terkawi, A. S. *et al.* (2015) 'Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: A double-blind, placebo-controlled randomized trial', *Pain Physician*, 18(2), pp. E139–E146.
[20]. Woolf, C. J., American College of Physicians and American Physiological Society (2004) 'Pain: moving from symptom control toward mechanism-specific pharmacologic management.', *Annals of internal medicine*, 140(6), pp. 441–51. doi: 10.7326/0003-4819-140-8-200404200-00010.
[21]. Yücel, M. A. *et al.* (2015) 'Specificity of Hemodynamic Brain Responses to Painful Stimuli: A functional near-infrared spectroscopy study', *Scientific Reports*, 5(1), p. 9469. doi: 10.1038/srep09469.