ISSN No:-2456-2165

Comparison of the Effectiveness of Hyperbaric Bupivacaine and Isobaric Levobupivacaine for Spinal Anesthesia for Abdominal and Lower Extremity Surgery

[1]Farilsah Hakim, [2]Achsanuddin Hanafie, [3]Dadik Wahyu Wijaya
Department of Anesthesiology and Intensive Care, Medical Faculty, North Sumatera University,
Haji Adam Malik General Central Hospital, Medan, Indonesia

Abstract:- Bupivacaine has often been used in spinal anesthesia because of its relatively fast onset, long working hours and good sensory and motor block effects. Levobupivacaine is also reported to have more minimal side effects compared to bupivacaine. This study aims to compare the effectiveness between the use of hyperbaric bupivacaine with isobaric levobupivacaine for spinal anesthesia of abdominal surgery and lower extremity. Effectiveness was assessed based on the onset, working duration, and side effects of hyperbaric bupivacaine 0.5% 15 mg compared with isobaric levobupivacaine 0.5% 15 mg. The study involved by 62 patients who underwent abdominal and lower limb surgery. Patients were divided into two groups, each consisting of 31 people. The first group (A) received hyperbaric bupivacaine 15 mg 0.5% and the second group (B) received isobaric levobupivacaine 15 mg 0.5%. From the results of this study it was found that the average sensory action of hyperbaric bupivacaine 15 mg 0.5% (Marcain) was slightly faster than levobupivacaine 15 mg 0.5% (Levica), which was 172.39 seconds compared to 249.03 seconds to reach the sensorial block of Th6 for the administration of spinal anesthesia, with a p-value <0.05 (p = 0.008). As for the average duration of analgesia it was found that isobaric levobupivacaine 15 mg 0.5% took longer than hyperbaric bupivacaine 15 mg 0.5%, which was 334.56 minutes for levobupivacaine and 221 minutes for bupivacaine, with p-value <0.05 (p = 0.001). The side effects of isobaric levobupivacaine 0.5% 15 mg was less than hyperbaric bupivacaine 0.5% 15 mg for spinal anesthesia.

Keywords:- *Bupivacaine, Levobupivacaine, Spinal Anesthesia.*

I. INTRODUCTION

Bupivacaine has been used for spinal anesthesia for many years because it has a relatively quick onset, which is 5-8 minutes, and has a long working duration, which is 90-150 minutes. It also provides good sensory and motor block effects. However, its use tends to cause toxicity to the heart and central nervous system when it suddenly enters the blood vessels. (Stoelting 4th ed, 2006; Miller 6th ed, 2011)

Rachel H. Foster and Anthony Markam in a review of article stated that based on in vitro, in vivo and pharmacodynamic studies of nerve blocks, it was found that levobupivacaine has potential similar to bupivacaine. But in animal trials, levobupivacaine has a lower risk of heart and central nervous system toxicity than bupivacaine. In human trials, levobupivacaine has a lower negative inotropic effect at an intravenous dose> 75 mg and results in a lower elongated QT interval than bupivacaine. Changes in depiction of central nervous system depression by EEG are also less in the use of levobupivacaine. Levobupivacaine belongs to the long acting anesthetic group with dose-dependent duration. The start of the procedure takes 15 minutes in a variety of anesthetic techniques. In studies on adult people, levobupivacaine can produce sensory blocks for up to 9 hours after epidural administration ≤ 202.5 mg, 6.5 hours after intrathecal administration of 15 mg, and 17 hours after block in brachial plexus at a dose of 2 mg/kg (Foster RH, 2000).

A study conducted by Pane MH in 2015 examined the comparison of the Onset and Working Duration of 12.5 Mg of Hyperbaric and 12.5 Mg of Hyperbaric Bupivacaine + 25 µg Fentanyl in Spinal Anesthesia for Extremity Operations. Patients were divided into two groups, each consisting of 20 people. The first group (A) received hyperbaric levobupivacaine 12.5 mg and the second group (B) received hyperbaric bupivacaine 12.5 mg + Fentanyl 25 µg. From this study, it was found that there were no significant differences in the average of the onset of the drug (p = 0.116) and the duration of surgery between the two study groups (p = 0.833). The onset of the drug and the working duration in group B had a slightly higher average than group A. The average onset of the drug in group B was 1.55 minutes while in group A was 1.22 minutes. The duration of surgery in group B was 1.37 hours and in group A was 1.35 hours. Results of the analysis using the Chi Square test showed no significant differences for VAS from observations of the 1st to 18th hours (p value> 0.05). At 24 hours a significant difference was found for VAS with a significant p value (0.014). The mean regression time of 2 segments of group B was much shorter (an average of 174.25 minutes) than the time of regression of 2 segments of group A (an average of 198.75 minutes) with p value =

0.0001. In conclusion, hyperbaric levobupivacaine 12.5 mg has the same onset time as hyperbaric bupivacaine 12.5 mg + fentanyl 25 µg and has a longer working duration (average difference of 24.5 minutes). Hyperbaric Levobupivacaine 12.5 mg had better analgesia (VAS) at 24 hours compared to hyperbaric bupivacaine 12.5 mg + fentanyl 25 µg. (Pane MH, 2015).

The author tried to conduct a study comparing the effectiveness of spinal anesthesia in lower abdominal and lower limb surgery using 0.5% hyperbaric bupivacaine and 0.5% isobaric levobupivacaine, based on the onset, working duration, and side effects of these two local anesthetics.

II. RESEARCH METHODS

➢ *Research Design*

The design of this study used a double blind randomized controlled clinical trial to assess the comparison of the effectiveness of hyperbaric bupivacaine and isobaric levobupivacaine in lower abdominal and lower extremity surgery.

➢ *Place and Time of Research*

This research was conducted at the Haji Adam Malik General Hospital, Medan and other network hospitals. The study was conducted and began after ethical clearance was published and the number of samples was met.

➢ *Population and Samples*

Population were all patients undergoing lower abdomen and lower extremity surgery with spinal anesthesia. The samples were taken from patients who would undergo lower abdomen and lower extremity surgery with spinal anesthesia techniques that had met the inclusion and exclusion criteria.

➢ *Inclusion and Exclusion Criteria and Dropout*

The inclusion criteria of this study were patients who were willing to take part in the study, aged 18-50 years, and had the status of PS ASA I-II. While the exclusion criteria were patients who were allergic to the studied medication and had contraindications to spinal anesthesia. Patients would be considered dropouts if they did not experience motor or sensory block after the first injection, or the surgery was is extended so that additional general anesthesia was needed, or there was a life-threatening emergency on airway, heart, lung, and brain.

➢ *Procedure*

a. Once the patient arrives in the surgery waiting room, she/he is re-examined by the researcher for identification (name, age, sex, weight, height), diagnosis, anesthesia action plan, infusion access (make sure the infusion is with 18G abocath, threeway and smooth infusion flow).
b. Volunteer II prepares the drug given by volunteer I who does randomization. First the local anesthetic is prepared in a 5 ml syringe. Group A: 20 mg Bupivacaine 0.5% hyperbaric (4 ml). Group B: 20 mg Levobupivacaine 0.5% hyperbaric (4 ml).
c. Before the patient enters the surgery room, an anesthesia machine is connected to the oxygen source. Also prepare the sets of endo tracheal intubation devices (ETT) and injection emergency medicine such as epinephrine, atropine sulfas, ephedrine and dexamethasone.
d. After entering the surgery room, the patient is told to lie on their back and an ECG monitor, tensimeter, and oxygen saturation are attached to the patient's body.
e. The recording of the initial data is carried out, including blood pressure, pulse frequency and breath frequency.
f. Both groups of patients are given 10 ml/kg of Ringer Lactate preloading fluid for 15 minutes before spinal anesthesia.
g. The patient is seated and the head is inflated for spinal anesthesia.
h. Aseptic and antiseptic actions with 70% betadine and alcohol are used in the injection site.
i. Lumbar puncture is performed using a 25 G Spinocan (quincke type) needle on the lumbar vertebrae as high as the Tuffier imaginary line or as high as 3-4 lumbar vertebrae in a parallel bevel position with a sagittal plane to prevent larger dura tears. Then the local anesthetic is injected in a position towards the cephalad with a 5 cc syringe, a total of 15 mg or a volume of 3 ml.
j. The tip of the needle in the subarachnoid space has cerebrospinal fluid coming out of the lumen of the spinal needle.
k. Local anesthetics are then injected at a speed of 0.2 cc/sec.
l. Then the syringe was released from the spinal needle and cerebrospinal fluid appeared to flow to ensure the position of the tip of the spinal needle remains in the subarachnoid space. Local anesthetic drugs are put into the subarachnoid space and the needle is removed.
m. As soon as the anesthesia is finished, the patient is returned to the horizontal supine position. With the head propped up by a pillow, they are given 3 L/min oxygen via the nasal canule, and the block is set at Th6 level.
n. Monitoring and recording of vital signs (blood pressure, pulse frequency, respiratory rate) are carried out at minute 0.
o. Vital signs (pulse rate, blood pressure, breath frequency, oxygen saturation) are monitored, from the anesthesia to the completion of surgery, for blood pressure measured every 3 minutes.
p. To assess onset of analgesia, the time from which the drug is injected (T0) to when it reaches a Th 6 level of sensory resistance using a pinprick test was recorded.
q. To assess the duration of analgesia, the duration of sensory work from the start of the injection is recorded every 10 minutes until there is a decrease in 2 sensory level segments (two segment regression time), which is marked by Hollmens 2 degrees. It is done using pin-prick tests until the patient begins to feel pain. They are then given the analgesia drug of ketorolac 30 mg iv.
r. The occurring side effects are noted, including hypotension, bradycardia, nausea, vomiting, headaches and respiratory depression.
s. If hypotension - a decrease in systolic blood pressure to less than 90 mmHg – occurs, then an administration of crystalloid fluid, intravenous ephedrine 5 -10 mg

orepinephrine 1:200000, is needed. The administration of ephedrine can be repeated every 60 seconds until systolic blood pressure> 90 mmHg.

t. If nausea and vomiting occurs, make sure that the hemodynamic is stable first and the intravascular volume is sufficient. They can be treated with 4-8 mg of intravascular ondansetron.

u. If the patient experiences respiratory depression, management is done with supplemental oxygen, and if necessary, positive pressure ventilation is performed.

v. Evaluation of side effects must be carried out during surgery and at hour 1 (T1), hour 2 (T2), hour 4 (T3), hour 8 (T4), hour 16 (T5), and hour 24 (T6) post-surgery.

➢ *Statistical Analysis*

Data were analyzed descriptively to see the frequency distribution of the variables examined. If the data is normally distributed, then the Fischer Exact Test correlation test will be performed with a significance of p <0.05. If the data is not normally distributed, a Sperman correlation test will be performed with a significance of p <0.05.

III. RESEARCH RESULTS

➢ *Sample Characteristics*

Characteristics	**Group A**	**Group B**	***p-value***
Gender, n (%)			
Male	19 (61.3)	26 (83.9)	0.046[a]
Female	12 (38.7)	5 (16.1)	
Age, average (SD), years	36.23 (12.48)	31.35 (11.37)	0.069[b]
Ethnicity, n (%)			
Batak	18 (58.1%)	17 (54.8%)	
Javanese	12 (38.7%)	10 (32.3%)	
Karo	1 (3.2%)	0 (0%)	0.434[c]
Madura	0 (0%)	2 (6.5%)	
Nias	0 (0%)	1 (3.2%)	
Malay	0 (0%)	1 (3.2%)	
Weight, average (SD), kg	62.61 (11.39)	64.03 (10.38)	0.413[d]
Type of Surgery, n (%)			
General Surgery	14 (45.2)	13 (41.9)	
Orthopedic Surgery	9 (29.0)	11 (35.5)	0.896[c]
Urological Surgery	6 (19.4)	4 (12.9)	
Obgyn	2 (6.5)	3 (9.7)	
PS-ASA, n (%)			
PS-ASA I	16 (51.6 %)	22 (71.0%)	0.118[a]
PS-ASA II	15 (48.4 %)	9(29.0%)	
Total	31	31	

Table 1:- Demographic Characteristics
(*[a] = Chi square, [b] = T-test Independent, [c] =* ANOVA; [d] = *Mann Whitney)*

In this study, the most research samples were male, which was 19 people (61.3%) in Group A, and 26 people (83.9%) in Group B. The average age of the study sample in Group A was 36.23 years and Group B 31.35 years. In general, the sample in this study came from the Batak tribe, 18 people or (58.1%) in Group A and 17 people, (54.8%) in Group B. The average weight of the study sample in Group A was 62.61 kg and Group B was 64.03 kg. Most of the samples in the study in both groups underwent general surgery. Based on the PS-ASA, the sample in Group A that was in ASA I was 16 people (51.6%) and in ASA II was 15 people (48.4%). Meanwhile in Group B, 22 people (71%) were of ASA I and 9 people (29.0%) were of ASA II.

Statistically, there were significant differences between the two groups by sex, with a p-value <0.05. While based on age, ethnicity, weight, type of surgery, and PS-ASA, no significant difference was found with p-value> 0.05.

➢ *Average of Sensory and Motor Initial Work*

Onset of Anesthesia	**Group A (n = 31)**	**Group B (n = 31)**	***p-value***
Onset time of sensory blockade, average (SD), second	172.39 (69.17)	249.03 (122.54)	0.008
Onset time of motor blockade, average (SD), second	135.16 (43.94)	175.39 (109.79)	0.222

Table 2:- Average of onset time of sensory and motor blockade (p-value was obtained through a Mann Whitney test)

Based on Table 2, it was found that the average value of sensory work of drugs in Group A was 172.39 seconds and in Group B was 249.03 seconds. Meanwhile, the average value of the onset time of motor blockade of the drug in Group A was 135.16 seconds and in Group B was 175.39 seconds.

From the results of the analysis using the Mann Whitney test, a statistically significant difference was obtained for the onset time of sensory blockade of the drugs in Group A and Group B, with a p-value of 0.008. Meanwhile, there was no statistically significant difference in the average onset time of motor blockade of drugs in Group A and Group B, with a p-value of 0.222.

- *Average Duration of Analgesia*

Work Duration of Anesthesia	Group A (n = 31)	Group B (n = 31)	*p-value*
Duration of analgesia, mean (SD), minutes	221.00 (62.51)	334.58 (60.68)	0.001

Table 3:- Average duration of analgesia
(p-value was obtained through a Mann Whitney test)

Based on Table 3 above, the analgesia duration of the drugs in Group A was 221.00 minutes and Group B was 334.58 minutes. From the results of the analysis using the Mann Whitney test, statistically significant differences were obtained for the average duration of Group A and Group B drug analgesia, with a p-value of 0.001.

- *Maximum Block Height*

Maximum Block Height	Group A (n = 31)	Group B (n = 31)	*p-value*
Thorakal 4	3 (9.7%)	7 (22.6%)	
Thorakal 5	17 (54.8%)	21 (67.7%)	0.001
Thorakal 6	11(35.5%)	3 (9.7%)	

Table 4:- Maximum Block Height

Based on Table 4 above, the maximum block heights of drugs in Group A were: thorakal 4 in 3 people (9.7%), thorakal 5 in 17 people (54.8%), and thorakal 6 in 11 people (35.5%). While the maximum block height of drugs in Group B were: thorakal 4 in 7 people (22.6%), thorakal 5 in 21 people (67.7%), and thorakal 6 in 3 people (9.7%). Statistically, a significant difference was obtained for the maximum block height of Group A and Group B drugs, with a p-value of 0.001.

- *Segment Decrease in 1 Hour*

Segment Decrease	Group A (n = 31)	Group B (n = 31)
1 Segment, n (%)	11 (35.5%)	19 (61.3%)
2 Segment, n (%)	14 (45.2%)	9 (29%)
> 2 Segment, n (%)	6 (19.3%)	3 (9.7%)

Table 5:- Segment Decrease in 1 Hour

Based on Table 5 above, in Group A, 1 segment decrease happened in 11 people (35.5%), 2 segment decrease in 14 people (45.2%), and > 2 segment decrease in 6 people (19.3 %). Whereas in Group B 1 segment decrease happened in 19 people (61.3%), 2 segment decrease in 9 people (29%), and > 2 segment decrease in 3 people (9.7%).

- *Post-Spinal Anesthesia Side Effects*

The post-spinal anesthesia side effects that appeared in patients of lower extremity and lower limb surgery in Group A using 0.5% hyperbaric bupivacaine and Group B with 0.5% isobaric levobupivacaine are shown in the table below.

Based on Table 6 above, in Group A, 11 people suffered from a side effect of hypotension, 7 people had bradycardia, 13 people had nausea, 1 person suffered from vomiting, 1 person had shortness of breath, 4 people had headaches, and 5 people had shivers. No research samples experienced side effects of back pain and itching in Group A. Meanwhile, in Group B, 4 people had hypotension, 1 person had bradycardia, 4 people had nausea, 2 people had back pain, and 3 people had shivers. In Group B, no research samples experienced side effects of vomiting, shortness of breath, headaches, and itching. Overall, it can be concluded that post-spinal anesthesia side effects were more common in Group A.

ISSN No:-2456-2165

Side Effect	Group A (n = 31)	Group B (n = 31)	*p-value*
Hypotension	11	4	0.038
Bradycardia	7	1	0.023
Nausea	13	4	0.010
Vomiting	1	0	0.313
Shortness of breath	1	0	0.313
Headache	4	0	0.039
Back pain	0	2	0.151
Itching	0	0	-
Shivers	5	3	0.449

Table 6:- Post-Spinal Anesthesia Side Effects
(p-value was obtained through a Chi Square test)

Statistically, the Chi Square test revealed a significant difference in the side effects of hypotension, bradycardia, nausea and headaches due to drugs in Group A and Group B, with a p-value <0.05. However, there were no significant differences in the side effects of vomiting, shortness of breath, back pain and shivers due to drugs in Group A and Group B, with p-values> 0.05.

IV. DISCUSSION

This study was conducted on 62 patients who were undergoing abdominal and lower extremity surgery with spinal anesthesia. Patients were divided into two groups, each consisting of 31 people. The first group or Group A received hyperbaric bupivacaine 15 mg and the second group or B received isobaric 15 mg levobupivacaine. This study used two local anesthetics which pharmacologically have the same characteristics, both of which are in the amide group even though they have different lines.

From the results of this study, it was found that the average of sensory action of hyperbaric bupivacaine 15 mg (Marcain) was slightly faster than levobupivacaine 15 mg (Levica), which was 172.39 seconds faster than 249.03 seconds, with a p-value <0, 05 (p = 0.008) to reach the height of the Th 6 sensory block on spinal anesthesia. Meanwhile, the on-set motor work of the two drugs showed no significant difference - an average of 135.16 seconds for the bupivacaine group and 175.39 seconds for the levobupivacaine group. This is in line with the results of research conducted by Sivakumar et al (2014), which compared the administration of 0.5% 12.5 mg of isobaric levobupivacaine, isobaric levobupivacaine 0.5% 10 mg + fentanyl 25 mcg, and hyperbaric bupivacaine 0.5% 12.5 mg in patients undergoing surgery for isobaric 0.5% 10 mg + fentanyl 25 mcg, and hyperbaric bupivacaine 0.5% 12.5 mg in patients undergoing infraumbilical surgery. The results showed that the onset time of sensory blockade of hyperbaric bupivacaine drugs was faster than levobupivacaine and levobupivacaine + fentanyl, with 3.38 ± 1.69 minutes for hyperbaric bupivacaine, 6 ± 1.17 minutes for levobupivacaine isobaric, and 13 ± 2.51 minutes for levobupivacaine + fentanyl 4 to reach sensory blocks as high as Th 10 in infraumbilical surgery. Similar results were also found in the study of Souza et al (2013), which compared the administration of 0.5% hyperbaric bupivacaine, 0.5% isobaric levobupivacaine, and 0.75% ropivacaine isobaric 0.75% in lower abdomen surgery. In this study, the onset time of sensory blockade of hyperbaric bupivacaine 0.5% 15mg (3cc) was also faster than the onset time of sensory blockade of isobaric levobupivacaine 0.5% 15mg (3cc) and ropivacaine isobaric 0.75% 22.5mg (3cc). From the research of D'souza et al it was also found that there were no significant differences between the onset time of motor blockade of the hyperbaric bupivacaine group and the onset time of motor blockade of isobaric levobupivacaine group.

The results of this study indicate that the average duration of analgesia of isobaric levobupivacaine 0.5% 15 mg is longer than the average duration of analgesia of hyperbaric bupivacaine 0.5% 15 mg, i.e. 334.56 minutes for levobupivacaine and 221 minutes for bupivacaine. This is also consistent with the study conducted by D'zaza et al., which resulted in a comparison of sensory duration of levobupivacaine, which was a median value of 4.5 hours, and sensory duration of hyperbaric bupivacaine, which was a median value of 3.5 hours, for lower abdominal surgery with spinal anesthesia. Research conducted by Sivakumar et al concluded that administration of isobaric levobupivacaine 0.5% 12.5 mg resulted in an increase in the time of sensory segment regression compared with hyperbaric bupivacaine or levobupivacaine + fentanyl. The results obtained in this study were also the same as the results of research conducted by Aygen et al. in 2012, which compared the clinical effectiveness of levobupivacaine + fentanyl and bupivacaine + fentanyl.

The research conducted by J.F. Luck, P.D.W. Fettes and J.A.W. Wildsmith in 2008, which compared the clinical effects of hyperbaric bupivacaine, hyperbaric levobupivacaine, and hyperbaric ropivacaine, found that the onset of drug action showed no significant differences, with (p <0.0167). This result was also supported by other studies such as Opas Vanna MD., Lamai Chumsang Bsc, and Sarinra Thongmee Med in 2006. This study compared the effectiveness and clinical safety between isobaric levobupivacaine and hyperbaric bupivacaine. The results showed that the onset of the two drugs was almost the same. A study conducted by Pane MH in 2015, which also examined the comparison of the onset and working duration of Hyperbaric Levobupivacaine 12.5 mg and Hyperbaric Bupivacaine 12.5 Mg + Fentanyl 25 µg under spinal

anesthesia for limb surgery, concluded that hyperbaric levobupivacaine 12.5 mg had the same onset time as hyperbaric bupivacaine 12.5 mg + fentanyl 25 µg but a longer working duration (average difference of 24.5 minutes). The average onset time of the drugs in levobupivacaine group was 1.55 minutes, while in the bupivacaine group was 1.22 minutes. The duration of anesthesia was compared by assessing two-segment regression. From the results of the research conducted, it was found that levobupivacaine had a longer two-segment regression (198.75 minutes) compared to the bupivacaine group (174.25 minutes).

From the results of this study, it was found that side effects after spinal anesthesia such as hypotension, bradycardia, nausea, and headaches were more common in the hyperbaric bupivacaine group compared to the isobaric levobupivacaine group. This is also consistent with research conducted by Gulen G et al (2012) which compared the clinical effectiveness of levobupivacaine and hyperbaric bupivacaine for spinal anesthesia (both administered fentanyl 15mcg adjuvant) in the caesarian section. The results of that study showed that the incidence of hypotension, bradycardia, and nausea were less common in the isobaric levobupivacaine group, and the need for ephedrine supplementation was higher in the hyperbaric bupivacaine group. D'souza et al also reported that side effects such as nausea, bradycardia, and hypotension were more common in the hyperbaric bupivacaine group than isobaric levobupivacaine and isobaric levobupivacaine + fentanyl. From a review article by A Macleod in 2001, it is known that the toxicity of levobupivacaine is lower than the toxicity of bupivacaine.

V. CONCLUSION

- The onset of 0.5% 15 mg isobaric levobupivacaine is not much different from the onset of hyperbaric 0.5% 15 mg bupivacaine.
- The working duration of isobaric levobupivacaine analgesia 0.5% 15 mg is longer than the working duration of hyperbaric bupivacaine 0.5% 15 mg, with an average time difference of 110 minutes.
- The side effects of 0.5% 15 mg isobaric levobupivacaine are less than the side effects of 0.5% 15 mg hyperbaric bupivacaine in spinal anesthesia administration.

REFERENCES

[1]. Arias MG. Levobupivacaine: A long acting local anaesthetic, with less cardiac and neurotoxicity. Update.anesthesiologists.org. 2007:1-3
[2]. Atkinson RS, Rushman GB, Lee JA. Spinal Analgesia. A Synopsis Of Anesthesia. 10th ed. Singapore : P.G. Publishing Pte Ltd, 1987 : 662-713, 694-706.
[3]. Bajwa SJS, Kaur J, Clinical profile of levobupivacaine in regional anesthesia: A systematic review. Journal of Anesthesiology Clinical Pharmacology. 2013; 29(4):1-10. Cohen PS. Dragovich A. Intratechal Analgesia. Anethesiology Clin 2007; 2 : 862-3.
[4]. Covino BG, Scott DB, Lambert DH. Handbook of Spinal Anaesthesia and Analgesia, Mediglobe, Fribourg: 1994; 71-104. Critchley L, Conway F. Hypotension during subarachnoid anaesthesia : Haemodynamic effects of colloid and metamirol. British Journal of Anaesthesia 1996 ; 76 : 734-736.
[5]. Drasner K, Chapter 11: Local Anesthetics. Miller MD eds. Basic of Anesthesia, 6th ed, Philadelphia, Elsevier . 2011. p.130-142. D'Souza AD, Saldanha NM, Monteiro AD et. al. Comparison of Intrathecal hyperbaric 0.5% Bupivacaine, isobaric 0.5% Levobupivacaine and isobaric 0.75% Ropivacaine for lower abdominal surgeries. Int J Health Sci Res. 2014;4(1):22-29.
[6]. Foster RH, Markam A. Levobupivacaine, a review of its pharmacology and use as a local anaersthetic. Drugs 2000:59(3);551-79. Glaser, et al. Levobupivacaine Versus Racemic Bupivacaine for Spinal Anesthesia. Anestha Analg 2002;94:194–8
[7]. Gulen G, et al. A comparison of spinal anesthesia with levobupivacaine and hyperbaric bupivacaine for cesarean section: a randomized trial. Open Journal of Anesthesiology 2012;2:84-9.
[8]. Hall PA, Bennet A, Wilkees MP. Spinal Anaesthesia for Caesarian Section : Comparison of infusion of Phenileprine and Ephedrine. BJA 1994 ; 73 : 471-4.
[9]. Kleinman W, Mikhail M. Spinal, epidural and caudal blocks. Morgan GE, Mikhail MS, eds. Clinical Anesthesiology. 5th edition. New York: Mc Graw Hill Lange Medical Books: 2013, 937-76.
[10]. Lee YY, et al. Levobupivacaine Versus Racemic Bupivacaine in Spinal Anaesthesia for Urological Surgery. Anaesth Intensive Care 2003; 31: 637-641
[11]. Leone S, et al. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. ACTA BIOMED 2008; 79: 92-105
[12]. Levica. Package insert. PT Dexa Medica.2017. McLeod GA, Burke D. Review article levobupivacaine. Anaesthesia. 2001;56:331-41.
[13]. Miller R, Pardo MC. Basic of Anesthesia. 6th Ed. Philadelphia. Elseiver. 2007:111- 4
[14]. Morgan GE, Mikhail MS, Murray MJ. Local Anesthetics. Clinical Anesthesiology. 5th edition. New York: Mc Graw Hill Lange Medical Books: 2013, 263-76.
[15]. Pane MH. Perbandingan Mula Dan Durasi Kerja Levobupivacaine Hiperbarik 12,5 Mg Dan Bupivacaine Hiperbarik 12,5 Mg + Fentanyl 25 µg Pada
[16]. Anestesi Spinal Untuk Operasi Ekstremitas Bawah Di RSUP. H. Adam Malik Medan. http://repository.usu.ac.id/handle/123456789/44606
[17]. Panni M, Segal S. New local anesthetics are they worth the cost? Anesthesiology Clinics of North America 2003;21:19-38.

[18]. Rushman GB, Danvies NJH, Cashman Lee. Synopsis of Anaesthesia. 12th ed. Oxford : Butterworth Heineman, 1999 : 152-73.
[19]. Sanansil V. et al. Clinical Characteristic of Spinal Levobupivacaine: Hyperbaric Compared with Isobaric Solution. The Scientific World Journal. 2012;1-7
[20]. Sivakumar S, Manickam A, Krishna B. 0.5 % Isobaric Levobupivacaine, 0.5 % Isobaric Levobupivacaine With Fentanyl And 0.5 % Hyperbaric Bupivacaine -Comparative Study In Infraumbilical Surgeries. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 12 Ver. IX (December. 2016), PP 79-85
[21]. Snow JC. Spinal Anestesia. Manual of Anestesia. Tokyo : Igaku Shoin Ltd, 1980 : 167-91. Stoelting RK, Hiller SC. Pharmacology & Physiology in Anesthetic Practice. Fourth Edition, Lippincott Williams & Wilkin, Philadelphia: 2006; 1 40-154.
[22]. Tarkkila P. (2007) Complications Associated with Spinal Anesthesia. In: Finucane B.T. (eds) Complications of Regional Anesthesia. Springer, New York, NY.
[23]. Wibowo B. Uji Klinis Perbandingan Mula Serta Durasi kerja Antara Bupivacaine 0,5% 12,5 mg Hiperbarik dan Isobarik Pada Anestesi Spinal, UNDIP, 2008:1-101
[24]. Wildsmith JAW, Whitesdie JW. Developments in Local Anesthetics Drugs. BJA. 2001;87(1):27-35