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COMPARISON OF POST OPERATIVE EPIDURAL ANALGESIA EFFECT USING CONTINUOUS 0.125% BUPIVACAINE WITH BOLUS 3 MG MORPHINE ON INSULIN LEVELS IN PATIENT UNDERGOING LOWER LIMB SURGERY

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ABSTRACT

The procedure for lower limb surgery is one of the major and long-standing operations. Surgical trauma stimulates the stress response of surgery. The surgical stress response will interfere with stress hormones including insulin. Insulin is an anabolic hormone that is important in the body and has a role in the process of wound healing. Previous studies have shown insulin levels to correlate with increased surgical stress and the type of anesthesia given. This study analyzed differences insulin levels in bupivacaine 0,125% with morphine 3 mg and to compare the analgesia effect of continuous bupivacaine 0,125% with 3 mg morphine epidural in postoperative lower extremity assessed from insulin levels. A retrospective cohort study taken from secondary data from previous studies and their medical records at RSUP Dr. Mohammad Hoesin Palembang. Statistical analysis used STATA 15th edition. Wilcoxon showed that there was a significant difference in 0,125% bupivacaine group on insulin leves after 12th hours postoperative ($p<0.05$). Man-Whitney showed that there was no significant difference between the 0,125% bupivacaine with 3 mg morphine on insulin levels postoperative lower extremity after 6th hours, 6th and 12th hours and after 12th hours ($p>0.05$). In this study, there was no significant difference between the 0,125% bupivacaine with 3 mg morphine on insulin levels

Keywords: Bupivacaine 0,125%, Morphine 3 mg, Insulin, Epidural Analgesia

1. INTRODUCTION

Surgical intervention puts high stress on the human body which can cause inflammation and insulin resistance. Insulin resistance can occur several hours after surgery.[1] Surgical procedures and their metabolic effects can cause stress that results in perioperative hyper-glycemia called stress hyper-glycemia. According to the American Diabetes Association, stress hyper-glycemia is defined as transient hyper-glycemia in non-diabetic patients, who are acute illnesses or undergo an invasive procedure. This is characterized as an increase in blood sugar levels> 180 mg / L or 10 mmol / L) and return to normal (<126 mg / L or 7 mmol / L) after the stress disappears.[2]

The severity of hyper-glycemia stress depends on the type of surgery, the aggressiveness of the surgical procedure and the length of surgery. This occurs in 30% to 80% of patients depending on the type of surgery. Some other risk factors include catecholamine infusion, corticosteroid use, obesity, age, hypothermia, hypoxia, cirrhosis, trauma, extensive burns and sepsis.[2]

Insulin is the main anabolic hormone in the human body.[3] This hormone plays an important role in the regulation of glucose homeostasis by facilitating glucose transport and suppressing endogenous

glucose production. Insulin also plays an important role in fat storage and protein synthesis, lipolysis inhibition and protein breakdown. Insulin is also thought to have non-metabolic effects such as vasodilators, anti-inflammatory, antioxidant, antifibrinolytic and positive inotropes.[3] Pain management can help maintain glucose metabolism. Greisen et al found that acute pain can interfere with or reduce insulin sensitivity depending on the degree of pain experienced. This is likely caused by nonoxidative glucose metabolism due to hormonal contraceptive responses.[5] Pain management can be overcome by pharmacological and non-pharmacological. One technique used is epidural analgesia. Epidural analgesia is a safe procedure to reduce pain compared with systemic opioids, reducing the risk of side effects due to opioid administration. The drugs used are local anesthetics and can also use opioids, one of which is morphine. [6,7,8]

Li et al found that morphine can amplify signals from insulin receptors by interfering with the interaction between insulin substrate-1 (IRS-1) but inhibiting signals from Extracellular Signal Regulated Kinase (ERK) by disrupting the complex of insulin receptors.[9] Research from Salarinasab et al obtained biosynthesis from insulin, insulin like growth factor (IGF) and insulin receptors are reduced after exposure to morphine concentrations with a concentration of 100 μM for 24, 48 and 72 hours. This is presumably because morphine and other opioids can reduce the rate of cell development and the health status of neural stem cells. In addition, long-term opioid administration can cause hormonal disorders by reducing IGF1 and IGF2 secretion by inhibiting hypothalamic-pituitary function.[10] In this study, the dose of bupivacaine used was 0.125% which is the most appropriate dose for epidural analgesia because it is the lowest risk.[11] For morphine doses used 3 mg because it has lower complications. Morphine at doses> 4 mg have more complications such as respiratory depression, pruritus, severe urinary retention, and nausea, vomiting.[12]

Increased blood sugar and insulin resistance can inhibit the healing process of surgery, postoperative infections renal disorders, cardiovascular, muscle weakness.[13] Impaired insulin during this surgery process causes an increase in release of free fatty acids, which can adversely affect myocardium, and interfere with protein metabolism so that increase protein catabolism and slow the healing process.[2]

2. METHOD

This was a retrospective cohort observational analytic study conducted at Rumah Sakit Mohammad Hoesin (RSMH), Palembang, Indonesia. This study was approved by the Health Research Review Committee of the Mohammad Hoesin Central Hospital and the Faculty of Medicine, Sriwijaya University, Palembang Indonesia (No. 55 / kepkrsmhfkunsri / 2020).

The sample of this study was all patients who underwent lower limb surgery at RSMH Palembang and performed epidural anesthesia with postoperative analgesia through an epidural catheter in the form of 0.125% continuous bupivacaine or morphine 3 mg bolus. Data taken is secondary data from medical records based on previous study conducted in December 2015 to March 2016 in patients given continuous 0.125% bupivacaine and 3 mg bolus morphine per epidural and insulin levels were examined using the DRG® Insulin Enzyme Immunoassay reagent. The sampling technique in this study used total sampling technique, which is taking all

medical record data during the specified time period.

Inclusion criteria were patients aged between 17 to 65 years, ASA I / II physical status, body mass index between 17 kg / m2 to 30 kg / m2, lower limb surgery performed epidural anesthesia with postoperative analgesia through epidural catheters in the form of continuous 0.125% bupivacaine or morphine 3 mg bolus. Incomplete data is excluded from study.

Data were divided into 2 groups of patient samples according to treatment. Group I was the group that had been given 0.125% continuous bupivacaine as postoperative epidural analgesia and group II was the group that had been given morphine 3 mg bolus on the epidural catheter as postoperative analgesia.

The study data was collected in a prepared form, then the data was processed statistically using the STATA program version 15.1, with paired T-Tests if the data were normally distributed, Wilcoxon if the data were not normally distributed for continuous variables and Chi Square Test for dichotomous variables. Significance was determined if p value <0.05. Quantitative data with normal distribution are reported in the form of mean and standard deviations, while abnormal data are reported in the form of median with minimum and maximum values. Qualitative data analysis categorized was done by Chi-Square test and with a significance limit set p <0.05.

3. RESULT

The general characteristics of the patients in the two groups were not significantly different (Table 1).

Table 1. Sample Characteristic

Variable	Anesthesia drugs		p
	Bupivacaine (N=20)	Morphine(N=20)	
Age (Years)	38,2±16,31	36,5 ±13,99	0,725**
≤25	4(44,4%)	5(55,6%)	0,298
26-35	8(57,1%)	6(42,9%)	
36-45	0(0%)	3(100%)	
≥46	8(57,1%)	6(42,9%)	
Height(cm)	1,59±0,07	1,62±0,05	0,598**
Weigh (kg)	55,65±6,12	58,45±8,43	0,435**
BMI (kg/m^2)	21,76±1,79	22,09±3,05	0,684**
BMI			0,591
Underweight	0(0%)	1(100%)	
Normal	10(50%)	10(50%)	
Overweight	10(52,6%)	9(47,4%)	
Sex			
Male	11(40,7%)	16(59,3%)	0,091*
Female	9(62,2%)	4(30,8%)	
Study Degree			0,731*
Elementary	2(50%)	2(50%)	
Junior high	2 (40%)	3(60%)	
High school	11 (52,3%)	10(47,7%)	
D3	0 (0%)	1 (100%)	
≥S1	5(55,5%)	4(45,5%)	
ASA Score			0,358*
I	14(46,7%)	16(53,3%)	
II	6(60%)	4(40%)	
Operation length (hours)	127±49,93	124±63,56	0,204**

*uji *chi square* ** T-Test

There were 40 participant samples enrolled in this study. Subjects were divided into 2 groups where each group consisted of 20 participants. Group 1 received 0.125% bupivacaine continuously for postoperative analgesia while group 2 received morphine 3 mg bolus per epidural for postoperative analgesia.

Examination of postoperative plasma insulin levels was carried out 3 times, namely 0 hours (To), 6 hours (T6) and 12 hours (T12) postoperatively (Figure 1). There was an increase in plasma insulin levels in both groups, namely to 18.68 in the 0.125% bupivacaine group and 19.63 in the 3 mg morphine group. In the morphine group there was only a slight increase in 0 and 6 hours postoperatively. 12 hours postoperatively, there was an increase in plasma insulin levels in both groups, namely 32.17 in the 0.125% bupivacaine group and 21.7 in the 3 mg morphine group.

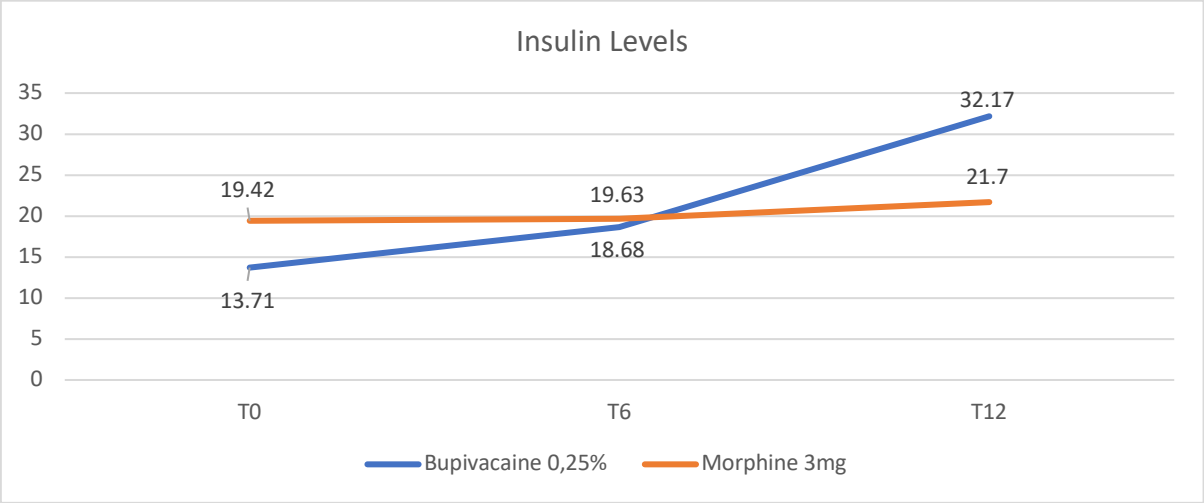

Figure 1. Insulin plasma levels between Bupivacaine 0,125% and Morphine 3 mg group

At 6 hours postoperatively, insulin levels increased from 13.71 ± 13.20 to 18.68 ± 16.36 in the bupivacaine group and slightly increased from 19.42 ± 24.38 to 19.63 ± 14.71 in the morphine group (Table 2). Wilcoxon test results showed no significant differences in the two groups (p> 0.05).

Table 2. Comparison of Insulin plasma level 6 hours postoperative

Variable	Bupivacaine 0,125%		p	Morphine 3 mg)		p
	0 Hours	6 Hours		0 Hours	6 Hours	
Insulin	13,71±13,20	18,68±16,36	0,156	19,42±24,38	19,63±14,71	0,370

**Wilcoxon Test*

At 12 hours postoperatively, insulin levels increased in both groups. In the bupivacaine group, insulin levels increased from 13.71 ± 13.20 to 32.17 ± 59.25 and in the morphine group increased from 19.42 ± 24.38 to 21.70 ± 18.90 (Table 3). Wilcoxon test results showed there were significant differences in the bupivacaine group (p <0.05) and there were no significant differences in the morphine group (p> 0.05).

Table 3. Comparison of Insulin plasma level 12 hours postoperative

Variable	**Bupivacaine 0,125%**		**p**	**Morphine 3 mg**		**p**
	0 Hours	12 Hours		0 Hours	12 Hours	
Insulin	13,71±13,20	32,17±59,25	0,04	19,42±24,38	21,70±18,90	0,601

**Wilcoxon Test*

After being analyzed by the Mann Whitney test, differences in insulin levels at 0-6 hours, 6-12 hours and 0-12 hours did not have a significant difference (p>0.05) in the two groups (Table 4).

Table 4. Comparison of insulin levels between bupivacaine 0,125% and morphine 3 mg

	Insulin Levels					
	0 – 6 Hours	p	6 – 12 Hours	P	0 – 12 Hours	P
(Bupivacaine 0,125%)	-4,97±14,34	0,807	-13,48±61,04	0,645	-18,46±59,69	0,432
(Morphine 3 mg)	-0,22±21,29		-2,07±17,13		-2,28±26,19	

* *Mann Whitney test*

The most common side effect in bupivacaine group were hypotension (20%) and nausea (20%). Pruritus (35%) and nausea (30%) were the most common side effect in morphine group. There was no life-threatening side effect such as respiratory depression in both groups (Table 5).

Table 5. Side effect of Bupivacaine 0,125% and morphine 3 mg

Efek samping	**Anesthesia drug**	
	Bupivacaine 0,125%	**Morphine 3 mg**
Hypotension		
Yes	4(20%)	3(15%)
No	16(80%)	17(85%)
Bradycardia		
Yes	1(5%)	0(0%)
No	19(95%)	20(100%)
Nausea		
Yes	4(20%)	6(30%)
No	16(80%)	14(70%)
Throw up		
Yes	0(0%)	1(5%)
No	20(100%)	19(95%)
Respiratory depression		
Yes	0(0%)	0(0%)
No	20(50%)	20(50%)
Shivering		
Yes	1(5%)	1(5%)
No	19(95%)	19(95%)
Pruritus		
Yes	0(0%)	7(35%)
No	20(100%)	13(56%)

4. DISCUSSION

Trauma or injury caused by surgery can induce metabolic and hormonal changes, better known as the stress response. This response is a systemic reactin involving endocrine, immunological and hematological changes. The stress response to surgery is characterized by increased pituitary hormone secretion and activation of sympathetic nervous system. The neuroendocrine stress responses arise when surgery is characterized by increased stress hormones that persist for several days after surgery. The clinical consequences of a stress response include hypertension, tachycardia, arrhythmias and possible myocardial ischemia, protein catabolism, suppression of the immune system and impaired renal function. Changes in pituitary hormone secretion cause secondary effect on target organ hormone secretion. [14]

Surgical interventions induce high stress level to human body which can cause inflammation and insulin resistance. Insulin resistance can occur several hours after surgery. [1,14] This also supported by Greisen et al. study which found that acute pain can interfere with or decrease insulin sensitivity depending on the pain degree. [15]

Morphine is an μu receptor agonist and an kappa opioid. Opioid act as agonists in the pre and post synaptics of the central and peripheral nervous system. Opioid

receptors are distributed along the central nervous system in the nucleus of the solitary tract, the peri-aquaductal gray area (PAG), cerebral cortex, thalamus and in the gelatinous substance of spinal cord. Opioid receptors are also found in peripheral afferent nerves and some organs. Morphine reduce neural cell excitation which results in reduced transmission of nociceptive impulses so that it is effective in pain management and reduces inflammation. Surgical stress activates the hypothalamus pituitary axis, which increases blood sugar due to insulin resistance. Endogenous opioids play a role in reducing the stress response that arises. This is in line with this study, in the 3 mg Morphine group, insulin levels increased slightly from 0 hours, 6 hours and 12 hours. In another study, Babae et al (2019) from a statistical analysis concluded there was no significant difference between insulin levels in morphine administration but found insulin levels that increased postoperatively 6 hours to 12 hours. [16,17] Study from Salarinasab et al also found postoperative insulin levels increase to 12 hours postoperatively, but after statistically analyzed there was no significant difference between insulin at 12, 24. 48 and 72 hours with morphine administration. This is presumably because morphine and other opioids can reduce the rate of cell development and the health status of neural stem cells. In addition, long-term opioid administration can cause hormonal disorders by reducing IGF1 and IGF2 secretion by inhibiting hypothalamic-pituitary function. [10,18]

Study by Hout et al found that 4 hours and 24 hours postoperatively since the incision began, there was a stress response in the form of a high increase in cytokines, systemic inflammation and suppress the immune system. This study found a combination of general anesthesia with epidural can reduce levels of cytokines and stress hormones including cortisol at 4 hours and 24 hours postoperatively. The decrease in cortisol and the release of cytokines such as IL1 and TNF due to inflammation can increase insulin sensitivity so that the combination of general anesthesia with epidural can increase insulin sensitivity. Insulin levels are usually normal or decrease with peripheral insulin resistance. Activation of alpha receptors in the pancreas can reduce insulin secretion. In this study there was a significant increase in insulin 0-12 hours in the group given bupivacaine so that it can be concluded giving bupivacaine can improve insulin resistance. [19]

In another study, it was found that bupivacaine can affect postoperative insulin levels in the blood. Piskin et al (2018) found no difference between administration of 0.125% bupivacaine with postoperative insulin levels but there was differences in insulin levels in bupivacaine at 0.5% and 0.75%.[20] In line with study above, Fettiplace et al (2016) also found that low doses of bupivacaine did not affect insulin levels ($p>0.05$) but the administration of local anesthetics bupivacaine and lidocaine at a dose of 0.5% and 0.75% can clear the adverse effects because insulin can reverse peripheral nerves that are inhibited by bupivacaine or lidocaine which also affects postoperative insulin levels. [21] Ma et al (2019) also found differences in insulin levels after 1 hour and 12 hours of postoperative bariatric. [22]

In table 5. The side effects of 0.125% bupivacaine are hypotension, nausea, bradycardia and shivering. Based on study conducted by Yu et al (2018), the found postoperative bupivacaine side effects in total hip arthroplasty were nausea, vomiting, bradycardia, respiratory depression and hypotension. [23] In line with this study and Yu et al, Karduman et al (2017) found side effects of bupivacaine were respiratory depression, bradycardia, hypotension, urinary retention, nausea and vomiting. [24] In this study respiratory depression side effect was not occur. In this study the side effects of 3 mg morphine were nausea, hypotension, vomiting, shivering and pruritus. Karduman et al

(2017) found side effects in morphine administration were respiratory depression, nausea, vomiting and pruritus. [24] In this study only respiratory depression was not found. Atisook et al (2018) also found 34.7% of respondents given morphine 2 mg and 3 mg had pruritus and another 34.5% experienced vomiting. [25] Miyamoto (2018) also found that the most dominant side effect of morphine administration was vomiting, there are also nausea, shivering and allergic reactions. [26] The incidence of nausea and vomiting is higher in the morphine group. This is because morphine directly stimulates the emetic chemoreceptor trigger zone (CTZ) in the medulla oblongata, not stimulated by the emetic center itself and is strengthened by vestibular stimulation. In this study, pruritus did not occur in the bupivacaine group but occurred in the morphine group (35%), this was due to the histamine release in morphine. The limitation of this study is that this research is a study conducted at one hospital. Future studies can experiment with more varied doses of bupivacaine and morphine or multimodal analgesia that can be more varied than morphine and bupivacaine.

5. CONCLUSION

There were significant differences in insulin levels in the bupivacaine group after 12 hours postoperatively. Insulin levels in the bupivacaine group tend to increase from 0 hours, 6 hours to 12 hours postoperatively. However, this study found no significant difference between insulin levels in the administration of 0.125% bupivacaine and morphine 3 mg postoperatively in the lower extremities after 6 hours, 6-12 hours and 12 hours postoperatively.

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