RESEARCH

Comparison of The Effectiveness Between Fentanyl and Ketamine as Adjuvant Epidural Analgesia with Ropivacaine In Post Operation of The Lower Extremity

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ABSTRACT

Background: One typical side effect that frequently follows surgery is pain. Lower limb surgery procedures can cause tissue and nerve damage. When compared to systemic opioids, epidural analgesia provides better postoperative analgesia. Adjuvants extend and intensify sensory blockage, which increases the effectiveness of local anesthesia. They also cause the dose of local anesthetic drugs to be reduced.

Objective: To determine the comparative effectiveness of adjuvant fentanyl compared with ketamine and ropivacaine as adjuvant epidural analgesia in post-lower extremity surgery patients.

Methods: The purpose of this randomized controlled experiment is to compare the efficacy of ketamine and fentanyl as adjuvant epidural analgesia in postoperative lower extremities when combined with ropivacaine. In this study, two groups of patients were given epidural anesthesia: the first group received ropivacaine 0.25% with 125 mcg of fentanyl adjuvant, while the second group received ropivacaine with 0.25% with ketamine 10 mg. The double-blind technique was used to select a total sample of 29 individuals from each group based on inclusion and exclusion criteria. The assessment of pain scores, hemodynamics, treatment-related side effects, and bromage scores was used to test both groups.

Result: The T5 assessment showed a substantial difference in the pain scores at rest. With a total of 14 side effects, blood pressure and pulse rate fluctuations were the most common, accounting for 20% of the side effects. Despite this, patients in the ropivacaine + ketamine adjuvant group continued to experience hemodynamic stability and comfort. There were two side effects in the fentanyl combination group, with nausea being the most common. Between the therapy groups, there was no difference in the recovery of the bromage score ($p>0.05$).

Conclusion: Ropivacaine-ketamine has favorable effectiveness as an analgesia adjuvant compared to ropivacaine-fentanyl.

Keywords: adjuvant; epidural analgesia; fentanyl; ketamine; postoperative

INTRODUCTION

Pain is an unpleasant sensory and emotional experience resulting from actual or potential tissue damage or the appearance of tissue damage.[1,2] Pain is a common complication following surgery. Although clinicians have significantly increased their knowledge of pain mechanisms and have made improvements in analgesic techniques, postoperative pain remains poorly managed. Uncontrolled postoperative pain can result in short- and long-term consequences, including increased morbidity, decreased quality of life, delayed recovery time, prolonged duration of opioid use, higher healthcare costs, and a higher incidence of chronic pain after surgery.[3] A prospective study of 1,490 surgical in patients who received standardized postoperative pain treatment according to acute pain protocols showed that 41% of patients reported moderate or severe pain in the recovery room, 30% on the first postoperative day, and 19% on day 2.

These recent years have seen a widespread increase in the use of epidural techniques, which is the administration of drugs from injections or infusions of drugs into the fatty tissue around the dura. This technique is used not only during surgery to provide anesthesia and analgesia, but also for obstetrics and trauma as well as for acute, chronic and cancer pain conditions. There is sufficient evidence to suggest that epidural analgesia offers superior postoperative analgesia compared to systemic opioids, including controlled analgesia in patients intravenously. A variety of drugs are used to provide epidural analgesia, including local anesthetics, opioids, α-2 agonists, and ketamine. Ropivacaine is a drug approved by the Food and Drug Administration (FDA) for surgical anesthesia and acute pain management. Ropivacaine has a better safety profile than bupivacaine.[4] Clinical data has shown that epidural ropivacaine 0.2% is almost identical to bupivacaine 0.2% in terms of onset, quality and duration of sensory blockade for initiation and maintenance of labor analgesia. Without the addition of opioids, epidural ropivacaine 0.2% by infusion is considered the most effective concentration for postoperative analgesia.[5] The addition of adjuvants not only increases the effectiveness of local anesthesia by prolonging and intensifying sensory blockade but also leads to a reduction in the dose of the local anesthetic agent. Many adjuvants can be used to prolong sensory blockade, e.g. epinephrine, opioids, ketamine, fentanyl, neostigmine.

Fentanyl is a highly selective synthetic opioid agonist that acts primarily on mu-opioid receptors but also on delta and kappa receptors. Epidural fentanyl has been widely used as an analgesic adjuvant. In the study of Cohen et al showed that the required analgesic dose was significantly reduced when combined with fentanyl and epinephrine.[6] While in the study of Batul et al in children undergoing infraumbilical surgery, the use of fentanyl 0.5 mcg/kg as an adjuvant to ropivacaine 0.2% dose of 0.5ml/kg for caudal block increased analgesic effectiveness and prolonged the duration of postoperative analgesia. In another study using ropivacaine 0.25% dose of 1 mg/kg combined with adjuvant fentanyl 1 mcg/kg can also extend the duration of analgesia after single injection caudal epidural anesthesia. However, the use of adjuvant fentanyl in the study caused unwanted side effects such as respiratory depression, vomiting and bradycardia.[7,8] Ketamine is a derivative of

phencyclidine with a chemical structure similar to bupivacaine and has a local anesthetic effect that works in the spinal cord and functions as an NMDA receptor antagonist. Intravenous ketamine at subanesthetic doses has been successfully used to treat pain after surgery and reduce the incidence of opioid-induced side effects. According to the study, the addition of adjuvant ketamine 0.5 mg/kg to ropivacaine 0.2% at a dose of 0.75 mg/kg administered caudally prolonged the duration of postoperative analgesia and maintained hemodynamic stability without major complications. Other studies using ropivacaine 0.2% combined with adjuvant ketamine at a dose of 0.3 ml/kg and 0.5 ml/kg can improve pain outcomes after elective surgery of the lower abdomen and lower extremities without systemic side effects.[9,10] Based on these phenomena, this study was conducted to evaluate the comparison of the administration of ropivacaine with adjuvant fentanyl and ketamine in epidural analgesia, especially in postoperative lower extremities, so as to reduce the incidence of postoperative chronic pain.

METHOD

This study was a randomized control trial using the double-blind method. This study was conducted at the Haji Adam Malik General Hospital Medan, Haji Hospital Medan, and Dr. Pirngadi Hospital Medan during January - March 2024. This study has obtained permission from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara with Ethical Clearance number RM.2.11 / IC. Spenelitian / 2024. The population in the study consisted of all patients who underwent lower extremity surgery. The sample in the study were patients undergoing epidural anesthesia who met the inclusion and exclusion criteria. The inclusion criteria of the study subjects were patients aged 18-65 years, patients who agreed to take part in the study (informed consent), patients undergoing lower extremity surgery with epidural anesthesia and hemodynamically stable in the duration of surgery and patients with physical status (PS) American Society of Anesthesiologists (ASA) 1-2. While the exclusion criteria were patients or families refusing, pregnant women, patients with cardiac abnormalities, hematological abnormalities and patients with neurological disorders or uncooperative. Based on the sample size calculation, the minimum sample required is 29 samples in each group with a total sample requirement of 64 samples. This sampling technique was carried out using the consecutive sampling method. This study will be divided into two treatment groups. Treatment group I (RF) received epidural anesthesia medication with 0.25% ropivacaine (9.75 ml) plus the adjuvant fentanyl 25 mcg (0.25 ml) in a 10 ml syringe, administered every 12 hours via epidural route. Treatment group II (RK) received epidural anesthesia medication with 0.25% ropivacaine (9 ml) plus the adjuvant ketamine 10 mg (1 ml) in a 10 ml syringe, administered every 12 hours via epidural route. Randomization was carried out in 2 groups, namely the RF group and the RK group. Then a hemodynamic assessment and epidural assessment are carried out before the drug is administered (T0). Patients were monitored again at the first 2 hours (T1), 6 hours (T2), 8 hours (T3), 12 hours (T4), and 24 hours (T5). After that, the patient was assessed and recorded the pain score (NRS), hemodynamic parameters, bromage score side effects. Then data tabulation is carried out.

After the necessary data was collected, the data was analyzed using SPSS software. Descriptive analysis was conducted to see the characteristics and frequency distribution of the subjects. After the Shappiro Wilk normality test was performed. Numerical data were displayed as mean ± SD (standard deviation) and median (minimum-maximum). While categorical data is displayed in number (percentage). Furthermore, to analyze differences in pain scores, hemodynamic parameters, duration of analgesia using an unpaired T test. The 95% confidence interval with a value of $p<0.05$ was considered significant. To analyze differences in side effects and complications using the Chi-square Test.

RESULTS

This study was conducted on 64 samples who met the inclusion and exclusion criteria. The data collected consisted of demographic data and characteristics, hemodynamic difference test between groups, pain score difference test between groups, rescue and side effects between groups and bromage score difference test between groups.

The baseline characteristics reported in this study consisted of age, height, weight, body mass index (BMI), duration of surgery, PS-ASA, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, and Pre-operative SpO2. Table 1 shows that the age of the RF group has a mean ± SD value of 42.94± 17.89 years and the RK group has a mean ± SD value of 46.63 ± 15.21 years. Male gender distribution was 20 people in the RF group and 18 people in the RK group, female gender was 12 people in the RF group and 14 people in the RK group. The height distribution of the RF group had a mean + SD value of 164.13 ± 8.79 cm and the RK group had a mean ± SD value of 161 ± 9.25 cm. The weight distribution of the RF group had a mean ± SD value of 68.69 + 12.43 kg and the RK group had a mean ± SD value of 69.19 ± 14.87 kg. The BMI distribution of the RF group had a mean ± SD value of 25.48 ± 4.29kg/m2 and the RK group had a mean ± SD value of 26.59 ± 4.6 kg/m2. The distribution of the duration of surgery in the RF group had a mean ± SD value of 2.7 ± 0.86 hours and the RK group had a mean + SD value of 2.73 ± 0.72 hours. The distribution of PS-ASA in the RF group with score 1 was 15 people and score 2 was 13 people, then the RK group with score 1 was 13 people and score 2 was 19 people.

Hemodynamic differences between RF and RK groups were analyzed. The difference was analyzed using T-test on normally distributed data and Mann-Whitney if not normally distributed (Table 2). Differences in pain scores between RF and RK groups were analyzed. The analysis used the Mann-Whitney test because all data were not normally distributed.

Based on Table 3, it is known that there is a significant difference in pain scores at rest at measurement T5 ($p=0.008$) between the RF and RK groups, but in other measurements no significant differences were found. Then there was no significant difference in pain scores during movement at all measurement times ($p>0.05$).

Descriptive analysis of the use of rescue morphine and the incidence of side effects between the RF group and the RK group was carried out using the Crosstab test followed by presentation of data in tabular form. It was found that in both groups there was no use of rescue morphine in all patients.

Based on Table 4, it is known that side effects were found more in the fentanyl combination group, there were 2 side effects with the highest incidence of nausea.

Based on Table 5, it is known that drug effects are found more in the RK group with a total of 14 drug effects with the highest incidence of drug effects of changes in blood pressure and changes in pulse rate around 20%, but this condition is still within normal limits and does not interfere with hemodynamics.

Differences in bromage scores between RF and RK groups were analyzed. The difference analysis used the Mann-Whitney test because all data were known to be not normally distributed.

Based on Table 6, it is known that there is no difference in bromage score recovery at all measurement times between the RF group and the RK group ($p>0.05$). All patients could move their lower extremities again after 2 hours and monitoring up to 24 hours post-operatively.

Table 1. Demographic data and characteristics

Characteristics	RF Group (N= 32)	RK Group (N=32)	P-value
Age (year)			
- Mean±SD	42.94±17.89	46.63±15.21	
- Median	45	52	0.514[b]
- Min-Maxs	18-65	18-65	
Gender			
- Male	20 (31.3)	18 (28.1)	0.611[c]
- Female	12 (18.8)	14 (21.9)	
Height (cm)			
- Mean±SD	164.13±8.79	161±9.25	
- Median	166	161	0.253[b]
- Min-Maxs	145-179	145-175	
Weight (cm)			
- Mean±SD	68.69±12.43	69.19±14.87	
- Median	68	69	0.884[a]
- Min-Maxs	44-95	48-96	
Body Mass Index (kg/m^2)			
- Mean±SD	25.48±4,29	26.59±4,69	
- Median	25.35	27.33	0.326[a]
- Min-Maxs	17.63-39.54	18.75-36.58	
Duration of operation (hour)			
- Mean±SD	2.7±0.86	2.73±0.72	
- Median	2.5	2.5	0.761[b]
- Min-Maxs	1-5	1.5-4.5	
PS-ASA			
- 1	15 (23.4)	13 (20.3)	0.614[c]
- 2	17 (26.6)	19 (29.7)	

[a]T-test
[b]Mann-Whitney Test
[c]Chi-Square Test

Table 2. Results of hemodynamic difference test analysis

Variable	RF	RK	P-value
SBPT0	116.4±9.99	116.09±13.43	0.697[b]
SBPT1	114.38±9.12	125.41±8.51	P<0.001[b]
SBPT2	115.69±9.93	125.59±7.11	P<0.001[b]
SBPT3	123.18±8.99	122.84±7.49	0.667[b]
SBPT4	119.84±8.27	130.06±7.16	P<0.001[a]
SBPT5	119.19±7.43	124.63±8.42	0.008[a]
DBPT0	72.34±7.07	77.84±11.11	0.130[b]
DBPT1	73.19±5.19	83.44±9.07	P<0.001[b]
DBPT2	74.28±4.67	84.94+7.11	P<0.001[a]
DBPT3	78.13±4.75	82.19±6.23	0.013[b]
DBPT4	76.75±4.06	88.56±7.88	P<0.001[b]
DBPT5	74.75±3.94	81.94±7.92	P<0.001[a]
MAPT0	87.02±6.15	90.59±11.63	0.528[b]
MAPT1	88.16±4.61	98.49±6.73	P<0.001[b]
MAPT2	88.16±4.61	98.49±6.73	P<0.001[b]
MAPT3	93.19±4.39	95.74±6.24	0.063[a]
MAPT4	91.09±3.73	102.39±7.14	P<0.001[b]
MAPT5	89.53±3.41	96.17±7.73	P<0.001[b]
HRT0	68.03±6.27	73.03±5.53	0.005[b]
HRT1	6.94±4.01	77.91±5.66	P<0.001[a]
HRT2	69.91±4.13	76.94±4.45	P<0.001[a]
HRT3	73.44±4.79	78.81±3.72	P<0.001[a]
HRT4	74.5±5.4	81±3.66	P<0.001[a]
HRT5	73.16±4.61	78.53±3.59	P<0.001[a]

[a]T-test
[b]Mann-Whitney Test

Table 3. Results of differential test of pain score data between groups

NRS Break						
	T0	T1	T2	T3	T4	T5
RF	0	0	0	1.56	2.5	2.38
RK	0	0	0	1.34	2.22	2.09
P-value[b]	1.000	1.000	1.000	0.140	0.062	0.008
NRS Move						
RF	0	0	2.84	3.41	3.69	3.19
RK	0	0	2.63	3.19	3.66	3.06
P-value[b]	1.000	1.000	0.269	0.276	0.709	0.374

[b]Mann-Whitney Test

Table 4. Results of side effect analysis test between groups

Side Effects	RF Group (N = 32)	RK Group (N = 32)
Nausea	2	0
Hypotension	0	0
Shivering	0	0
Breath depression	0	0
Seizures	0	0
Decreased conscousness	0	0
PDPH	0	0
Total	2	0

Table 5. Test results of intergroup drug effect analysis

Side Effects	RF Group (N = 32)	RK Group (N = 32)
Changes in blood pressure more than 20%	0	9
Changes in heart rate more than 20%	0	5

Table 6. Results of intergroup bromage score difference test

	Bromage Score 3-0					
	T0	T1	T2	T3	T4	T5
RF	2.5	1	0	0	0	0
RK	2.48	0.89	0	0	0	0
P-value	0.899	0.496	1.000	1.000	1.000	1.000

DISCUSSION

In this study, the mean age, gender, height, weight, BMI, duration of surgery, PS-ASA, pre-operative systolic and DBP, pre-operative heart rate, and pre-operative peripheral oxygen saturation did not show any significant differences in the two treatment groups, so it was concluded that the distribution of demographic characteristics and pre-operative data of the two groups was homogeneous and could reduce selection bias. The impact of aging on pain intensity should be considered based on several factors. Aging is associated with anatomical and neurochemical changes that affect pain perception. Aging is associated with increased pain threshold and reflects reduced pain sensitivity. It has been reported that pain intensity in chronic pain does not vary with age. However, acute pain can be caused by damage, such as surgical procedures, and is associated with skeletal muscle spasm and activation of the sympathetic nervous system.[11] In elderly patients, there is a decrease in myelin fibers in the dorsal and ventral radix, resulting in increased sensitivity to local anesthetics, reduced epidural fat, and increased permeability, may cause epidural anesthesia to be more potent and powerful in older patients than in younger patients. However, elderly patients showed a higher incidence of sedation and hypotension compared to younger patients in previous studies. Although anesthesiologists reduced the dose of fentanyl administered to elderly patients, a greater proportion of elderly patients (1.4% vs 0.2%) were sedated compared to the younger group.[12]

In this study, there was a significant difference in the systolic blood pressure variable between the groups given fentanyl compared to ketamine, where at T1, T2, T4, and T5, the systolic blood pressure of the fentanyl group was significantly lower than the group given ketamine. Similarly, with diastolic blood pressure, there was a significant difference between the fentanyl and ketamine groups where those given fentanyl had significantly lower blood pressure compared to ketamine at observation times T1, T2, T3, T4, and T5. In this study, the fentanyl group also showed lower systole, diastole, and mean arterial pressure (MAP) blood pressure than ketamine, but there was no decrease in blood pressure >25% from baseline so it can be said that fentanyl provides good hemodynamic stability. Of all the research subjects, there were also no side effects in the form of hypotension. This is because ketamine can stimulate sympathetic and inhibit catecholamine re-uptake by central and peripheral mechanisms. The mechanism of ketamine on blood vessels is very complex. This drug also stimulates the release of adrenergic norepinephrine which will increase the concentration of venous blood, thus increasing blood pressure and pulse rate. Therefore, this research study conducted there are differences from blood pressure systole, diastole, pulse rate, and MAP with changes ranging from 20% from baseline on adjuvant use. However, it still provides hemodynamic stability and comfort to the patient. For pulse rate variables, there was a significant difference in pulse rate where the fentanyl group had a significantly lower mean pulse rate. This lower rate did not lead to bradycardia. For the pulse rate variable, there was a significant difference in pulse rate where the fentanyl group had a significantly lower mean pulse rate. This lower rate did not lead to bradycardia.[13,14]

In this study, there was no significant difference between pain scales in the fentanyl and ketamine groups. Resting numeric rating scale (NRS) scores began to increase at T3, T4, and T5 in both groups, with the highest average pain score at T4 which was 2.5 for the fentanyl group and 2.22 for the ketamine group. Likewise with the moving NRS score, the highest pain score was obtained at T4, namely 3.69 for the fentanyl group and 3.66 for the ketamine group, and at T5 an average of 3.19 for the fentanyl and 3.06 for the ketamine group. This shows that ketamine is better as an analgesia adjuvant than fentanyl as seen from the difference in the average value of NRS.

Table 4 shows that in the fentanyl combination group, there were 2 adverse events with the most common adverse event being nausea. There were no other side effects such as hypotension, chills, respiratory depression, seizures, decreased consciousness, and PDPH. Previous studies evaluating the efficacy of ropivacaine fentanyl in major lower extremity surgery showed that patients given fentanyl and ropivacaine were more hemodynamically stable. In that study, only 3.3% of patients experienced hypotension after being given ropivacaine-fentanyl.[15] In table 5, drug effects were found more in the ketamine group with the highest incidence of drug effects, namely changes in blood pressure and changes in pulse rate around 20%.

In this study, there was no significant difference in bromage score recovery between fentanyl and ketamine administration. All patients were able to re-mobilize their lower extremities after

2 hours and monitoring up to 24 hours post-operatively. This shows that fentanyl-ropivacaine and ketamine-ropivacaine in the use of epidural analgesia are equally effective in not producing motor blockade after drug administration.

This study also showed that the administration of ketamine-ropivacaine has good effectiveness as an analgesia adjuvant compared to fentanyl-ropivacaine, which can be seen from the lower average NRS value. There was a difference in blood pressure and pulse rate of around 20% in the use of ketamine-ropivacaine, but these changes were still within normal limits that did not interfere with patient comfort and safety. This study also has several limitations, namely the results of this study may only apply to certain patient populations with specific health conditions such as in lower extremity surgical procedures and cannot be directly applied to a wider population. It is also difficult to fully control external factors that may affect analgesia effectiveness, such as patient anxiety levels, comorbidities or different surgical techniques. The measurement methods used to evaluate analgesia effectiveness may have limitations, such as subjectivity in patient pain assessment or the inability to measure long-term effects, limited observation time postoperatively may preclude studies to evaluate the long-term effects of using fentanyl and ketamine as adjuvant epidural analgesia.

CONCLUSION

Ropivacaine-ketamine has good effectiveness as an analgesia adjuvant compared to ropivacaine-fentanyl which can be seen from the lower average numeric rating scale (NRS) scores in postoperative lower extremity patients. There were also differences in systolic blood pressure (SBP) and MAP at T1, T2, T4, and T5, diastolic blood pressure (DBP) and pulse rate at all measurement times between the fentanyl group compared to ketamine as an epidural analgesia adjuvant with ropivacaine in lower extremity postoperative patients. In addition, in the ropivacaine-ketamine group, there were 14 blood pressure changes and pulse rate changes within 20% of baseline, which still provided hemodynamic stability and comfort to patients. In the ropivacaine-fentanyl group, there were two adverse events such as nausea and no other adverse events. This study also concluded that there was no difference in bromage scores at all observation times between the ropivacaine-fentanyl and ropivacaine-ketamine groups, indicating the absence of motor blockade after drug administration.

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