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Spinal Anesthesia Ambulation Time of Cervical Cancer Brachytherapy Outpatient Clinic: Comparison of 5 mg Hyperbaric Bupivacaine Fentanyl with 2,5 mg Hyperbaric Bupivacaine and 25 mcg Fentanyl

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A B S T R A C T

Introduction: Regional anesthetic techniques and local anesthesia have proven to be more effective than general anesthesia in the practice of ambulatory anesthesia. Spinal anesthesia is the technique of choice for ambulatory anesthesia in cervical cancer brachytherapy patients. Low-dose local anesthetics can speed up the ambulation time. This study aims to compare the ambulation time of low-dose spinal anesthesia with conventional doses. Fast ambulation time can speed up recovery time for patients, thereby reducing the patient's length of stay. **Methods:** This study was a double-blind, randomized controlled trial conducted in August – September 2022 at the Radiotherapy Installation of Dr. Mohammad Hoesin General Hospital (RSMH) Palembang. All cervical cancer patients undergoing brachytherapy in adults with ASA I-II physical status were included in the study sample. Samples will be randomized into two groups, namely a combination of hyperbaric bupivacaine 5 mg and fentanyl 25 mcg and a group of bupivacaine 2.5 mg and fentanyl 25 mcg. Patients with allergies, impaired motor function, spinal failure, block level not achieved, shock, apnea, respiratory depression, and experiencing pain during the procedure were excluded from the study. **Results:** Ambulation time in the hyperbaric bupivacaine 5 mg and 25 mcg fentanyl group was longer than the hyperbaric bupivacaine 2.5 mg and 25 mcg fentanyl (155.22 + 10.68 minutes versus 98.69 + 7.13 minutes) with a significance level of $p<0.001$. Spinal anesthetic drugs work in a dose-dependent manner. Increasing the dose will increase the duration of action of the spinal anesthetic. The only side effects found were hypotension and pruritus. **Conclusion:** Spinal anesthesia with hyperbaric bupivacaine 2.5 mg and fentanyl 25 mcg can accelerate the ambulation time of cervical cancer patients undergoing brachytherapy.

1. Introduction

Outpatient/ambulatory anesthesia is a subspecialty in patients undergoing surgery without hospitalization. The goal of outpatient anesthesia is to reduce costs and increase patient comfort. There are several anesthetic techniques that can be performed under ambulatory anesthesia. Regional anesthetic techniques and local anesthesia have proven to be more effective than general anesthesia in the practice of ambulatory anesthesia.[1] Cervical cancer is the leading cause of cancer death in women worldwide.[2] Annual incidence is 370,000 cases, with 160,000 deaths.[2] The standard treatment for cervical cancer is radical hysterectomy with pelvic lymph node

dissection for the early stages, plus radiation and chemotherapy. In women with advanced cervical cancer, standard care may be external beam radiation therapy (EBRT) alone, EBRT and brachytherapy, or combining EBRT and brachytherapy with current chemotherapy. EBRT management includes the management of pelvic lymph nodes, parametrium, and the primary tumor to adequately control the microscopic disease. Meanwhile, brachytherapy is a treatment for large tumors and improves disease control and survival. [3] Brachytherapy is defined as the treatment of cancer by placing radioactive isotopes on the lesion or near the lesion being treated. Brachytherapy is usually used to treat prostate, breast, brain, and cervical cancers.[4] Based on the speed of dosing, brachytherapy can be divided into two techniques, namely high-dose-rate (HDR) and low-dose-rate (LDR).[4,5] Spinal anesthesia techniques are generally suitable for surgical procedures involving the lower abdomen, perineum, and lower extremities.[6-8] A local anesthetic solution injected into the intrathecal space prevents the conduction of impulses along motor, sensory, and autonomic nerves. Optimal anesthesia will provide satisfactory operating conditions, fast recovery, early discharge from treatment, no postoperative side effects, and high patient satisfaction, apart from the high quality and low cost of anesthetic services.[9] Bupivacaine is a local anesthetic with a long duration of action in sensory and motor blockade. This makes bupivacaine the drug of choice in spinal anesthesia techniques [10,11]

Postoperative pain control is a major problem of spinal anesthesia.[9] One of the disadvantages of spinal anesthesia using pure local anesthetics is that the duration of action is relatively short, so the effect on postoperative analgesia is shorter and thus requires analgesic intervention in the postoperative period.[12,13] A number of adjuvants, such as clonidine and midazolam, have been studied to prolong the effects of spinal anesthesia.[14] These adjuvants include a variety of opioid and nonopioid drugs.[15] Fentanyl is a synthetic lipophilic opioid with a rapid onset of action, and in contrast to morphine, this drug has a faster onset of action.[16] Fentanyl will bind to mu receptors and inhibit presynaptic and postsynaptic release responses to excitatory neurotransmitters released by nociceptive neurons. This suggests that the addition of fentanyl improves the quality of intraoperative analgesics, reduces the intrathecal dose of local anesthetic drugs, and is associated with fewer side effects and better postoperative analgesia.[11] In addition to pain control and postoperative side effects, a consideration in selecting drugs used in spinal anesthesia is recovery time. Recovery time, as measured by an adequate Bromage score until the patient is able to get treatment at home, is an important consideration. This can have an impact on patient satisfaction, as well as on the financial burden on patients and hospitals.[17] A study of patients undergoing cesarean section showed a faster recovery time for bupivacaine and fentanyl than in those receiving bupivacaine alone.[18] Administration of high doses of bupivacaine can cause prolonged sensory and motor block and the risk of hypotension leading to a prolonged hospital stay. The use of local anesthetics in low doses can facilitate ambulatory anesthesia. The addition of fentanyl to low-dose bupivacaine may deepen the sensory block and prolong its duration without increasing the intensity of the motor block or recovery time. A prospective study comparing standard doses of hyperbaric bupivacaine (9 mg) and lower doses of bupivacaine (5 mg) in combination with 15 mcg fentanyl for spinal anesthesia for cervical carcinoma brachytherapy showed that doses of hyperbaric bupivacaine 5 mg and fentanyl 15 mcg would result in recovery time a faster rate.[17] Fast ambulation time can speed up recovery time for patients, thereby reducing the patient's length of stay. [19]

2. Methods

This study is a randomized controlled trial in a double-blind method. The study was conducted at the Radiotherapy Installation of Dr. Mohammad Hoesin General Hospital (RSMH) Palembang August-September 2022. The study population was all cervical cancer patients who underwent brachytherapy procedures with spinal anesthesia. The inclusion criteria in this study were patients who underwent brachytherapy procedures with spinal anesthesia at

Dr. Mohammad Hoesin General Hospital, Palembang, with physical status ASA I-II, and adult patients aged 18-65 years. Meanwhile, the exclusion criteria for patients were patients with allergies to bupivacaine and fentanyl and had impaired motor function so that Bromage scores could not be measured and patients with hypotension prior to spinal anesthesia. Samples were collected using the block randomization method, namely computer randomization, by entering the sequences on the website https://www.random.org/lists/. The treatment group was divided into two groups, namely group 1 and group 2. Group 1 was the group that received a combination of bupivacaine 5 mg hyperbaric and fentanyl 25 mcg, while group 2 was a group that received a combination of bupivacaine 2.5 mg hyperbaric and fentanyl 25 mcg. minimum sample size (36) is met.

Data taken from medical records included identity (name, age, gender), ambulation time, duration of brachytherapy, weight, height, and body mass index. The patient will be given spinal anesthesia at an altitude of L3-L4 with drugs according to the treatment group, and the patient will be monitored for up to 24 hours after the brachytherapy procedure. The collected data is processed with the SPSS ver 22.0 tool. Ambulation time data and treatment group will be analyzed using an independent T-test, and confounding variables in the categorical form will be analyzed using the Chi-square test or Fisher's exact test.

3. Results and Discussion

There were 36 samples eligible for research, which were divided into 2 groups: 18 samples in the 5 mg bupivacaine and 25 mcg fentanyl groups and 18 samples in the 2.5 mg and 25 mcg bupivacaine and fentanyl groups. There is one sample that includes dropout criteria in the hyperbaric 2.5 mg bupivacaine and 25 mcg fentanyl group because the block height was not achieved, so the sample in this group became 17 samples. Based on the data of the two groups, there was no significant difference ($p > 0.05$) in the characteristics of age, weight, body mass index, duration of brachytherapy, and physical status, so a comparative study was needed. There was no difference in ASA physical status in the two groups where there were significant patients with ASA 1 and ASA 2 physical status.

Table 1. Baseline characteristic.

Variable	Groups		p
	Bupivacaine 2,5 mg hyperbaric and fentanyl 25 mcg	Bupivacaine 5 mg hyperbaric and fentanyl 25 mcg	
Age (year), mean ± SD*	49,76 ± 11,51	47,11 ± 11,59	0,502
Weight (kg), mean ± SD*	52,71 ± 4,01	52,50 ± 3,63	0,874
Height (cm), mean ± SD*	163,18 ± 2,76	162,89 ± 3,19	0,778
Body mass index, n(%)**			
Underweight	4 (23,5%)	4 (22,2%)	1,000
Normoweight	13 (76,5%)	14 (77,8%)	
Overweight	0 (0%)	0 (0%)	
Obesity	0 (0%)	0 (0%)	
Obesity II	0 (0%)	0 (0%)	
Brachytherapy duration (min), mean ± SD*	94,82 ± 6,50	98,22 ± 8,01	0,179
ASA physical status***			
ASA 1, n (%)	11 (64,7%)	9 (50%)	0,380
ASA 2, n (%)	6 (35,3%)	9 (50%)	

*Independent T Test, p > 0,05 = not significant.
** Fisher's Exact Test, p > 0,05 = not significant.
*** Chi Square, p > 0,05 = not significant.

The onset of sensory block is related to the amount of local anesthetic. The lower the dose of local anesthetic given, the longer the onset of the drug will be achieved. Bupivacaine has an anesthetic onset of 5-8 minutes. 20 There are no studies on the onset of sensory block using bupivacaine 2.5 mg and fentanyl 25 mcg. The onset of sensory block in the hyperbaric 5 mg bupivacaine and 25 mcg fentanyl group was faster than the hyperbaric bupivacaine 2.5 mg and 25 mcg fentanyl (5.388 ± 0.60 versus 10.47 ± 2.06 minutes) and significantly different. (Independent T-Test; $p < 0.001$). The height of the block in the two groups was significantly different (Independent T-Test; $p < 0.001$), where the height of the sensory block of hyperbaric bupivacaine 5 mg and fentanyl 25 mcg could reach T8 in 13 samples (72.2%) while all samples in the bupivacaine group 2.5 mg hyperbaric and 25 mcg fentanyl achieves only T10 block height. The dose of local anesthetic affects the height of the sensory block. The higher the dose, the higher the height of the sensory block obtained, while the smaller the dose of local anesthetic, the less cephalad spread. 20 In this study, there was no difference in patient position, injection speed, volume, and drug concentration, so these factors did not play a role in block height.

Table 2. Sensoric block.

Variable	**Groups**		**p**
	Bupivacaine 5 mg hyperbaric and fentanyl 25 mcg	**Bupivacaine 2,5 mg hyperbaric and fentanyl 25 mcg**	
Sensoric block onset (min), mean ± SD*	5,388 ± 0,60	10,470 ± 2,06	<0,001
Block height, median (min-max)	T8 (T8-T10)	T10 (T10-T10)	<0,001
Thoracal 8, n (%)	13 (72,2%)	0 (0%)	
Thoracal 10, n (%)	5 (27,8%)	17 (100%)	

*Independent T Test, $p < 0,05$ = significantly different.

The hemodynamics of the patients assessed included systolic blood pressure before and after the procedure, diastolic blood pressure before and after the procedure, and heart rate before and after spinal anesthesia for bupivacaine 5 mg hyperbaric and fentanyl 25 mcg with bupivacaine 2.5 mg hyperbaric and fentanyl 25 mcg (Table 3). After analysis, there was no statistically significant difference in systolic blood pressure and diastolic blood pressure before and after spinal anesthesia in the hyperbaric 5 mg bupivacaine and 25 mcg fentanyl group with 2.5 mg hyperbaric bupivacaine and 25 mcg fentanyl (Paired T-Test, $p > 0.05$). From the results of the Independent T-Test analysis, there was a significant difference between the two groups with a significance level of $p < 0.001$. The ambulation time in the hyperbaric 2.5 mg bupivacaine and 25 mcg fentanyl group was shorter than the hyperbaric bupivacaine 5 mg and 25 mcg fentanyl and was significantly different (Independent T-Test; $p < 0.001$). The ambulation time in the hyperbaric bupivacaine 2.5 mg and fentanyl 25 mcg group was 98.53 $\pm$ 6.93 minutes, while the ambulation time in the hyperbaric 5 mg bupivacaine and 25 mcg fentanyl group was 155.11 $\pm$ 10.4 minutes (Table 4).

Table 3. Hemodynamic profile before and after spinal anesthesia.

Variable	Groups		p
	Bupivacaine 5 mg hyperbaric and fentanyl 25 mcg	Bupivacaine 2,5 mg hyperbaric and fentanyl 25 mcg	
Systolic Blood Pressure Before Spinal (mmHg), mean ± SD*	121,11 ± 8,32	127,35 ± 18,29	0,281
Systolic Blood Pressure After Spinal (mmHg), mean ± SD*	115,27 ± 8,98	120,29 ± 14,83	0,092
Diastolic Blood Pressure Before Spinal (mmHg), mean ± SD*	73,33 ± 6,18	76,17 ± 8,93	0,468
Diastolic Blood Pressure After Spinal (mmHg), mean ± SD*	68,88 ± 6,76	69,70 ± 6,95	0,870
Heart Rate Before Spinal, mean ± SD*	78,55 ± 10,26	77,05 ± 8,89	0,098
Heart Rate After Spinal, mean ± SD*	79,83 ± 10,83	79,70 ± 7,98	0,295

*Paired T Test, p < 0,05 = significantly different.

This study applies the principle of low-dose local anesthesia with the aim of early ambulation. The effect of spinal anesthesia is needed in the brachytherapy of cervical cancer patients from the beginning of the applicator installation to the release of the applicator after the patient has brachytherapy. After brachytherapy, the patient was observed in the recovery room until the motor block effect of the spinal anesthetic drug disappeared. The time the patient reaches a bromage score of 0 is the ambulation time. This ambulation time is influenced by the type and dose of local anesthetic used.[19]

Table 4. Ambulation time.

Variable	Groups		Variable
	Bupivacaine 5 mg hyperbaric and fentanyl 25 mcg	Bupivacaine 2,5 mg hyperbaric and fentanyl 25 mcg	
Ambulation Time (minute), mean ± SD*	155,22 ± 10,68	98,53 ± 6,93	<0,001

*Independent T Test, p < 0,05 = significantly different.

There was no significant difference in side effects of spinal anesthesia in the two groups (Fisher's Exact Test; p = 0.512). In this study, the side effects of spinal anesthesia were assessed, including hypotension, pruritus, bradycardia, shivering, nausea and vomiting, PDPH, and urinary retention. Descriptively, one sample (5.6%) experienced hypotension in the 5 mg bupivacaine and 25 mcg fentanyl groups, while in the 2.5 mg hyperbaric bupivacaine group and fentanyl 25 mcg found no side effects at all. The side effects of spinal anesthesia depend on the dose of local anesthetic. Low doses of bupivacaine can reduce the side effects of spinal anesthesia. Administration of low-dose local anesthetics can maintain blood pressure by reducing sympathetic blockade and minimizing the effect of decreasing systemic vascular resistance.[27] Another side effect obtained was pruritus where there were 2 samples (11.8%) experienced pruritus in the 2.5 mg bupivacaine and 25 mcg fentanyl groups, and 1 sample (5.6%) experienced pruritus in the 5 mg bupivacaine and 25 mcg fentanyl groups. Both groups experienced a side effect of pruritus because this effect was due to the use of intrathecal opioids, and both groups took 25 mcg of fentanyl.[22] The pruritic effect of neuraxial opioids was found to be greater with spinal anesthesia than with

epidurals.[20] Pain and pruritus are transmitted on the sensory nerve type. In the dorsal horn of the spinal cord, there are 5-hydroxytryptamine subtype 3 (5-HT3) receptors and receptors. Intrathecal opioids can trigger the itch system in the central nervous system, activation of the medullary dorsal horn, and modulation of serotonergic pathways that trigger pruritus. Activation of -opioid receptors can trigger pruritus due to spinal anesthesia.[30] The opioid used in both groups of this study was fentanyl, which stimulated -opioid receptors, thus enabling pruritus after spinal anesthesia in both groups. Management of patients with pruritus is carried out by administering diphenhydramine 25 mg IV. [22,30–32]

Table 5. Spinal anesthesia side effects.

Variable	Groups		p
	Bupivacaine 5 mg hyperbaric and fentanyl 25 mcg	Bupivacaine 2,5 mg hyperbaric and fentanyl 25 mcg	
Hypotension, n (%)	1 (5,6%)	0 (0%)	0,512
Pruritus, n (%)	1 (5,6%)	2 (11,8%)	
Bradycardia, n (%)	0 (0%)	0 (0%)	
Shivering, n (%)	0 (0%)	0 (0%)	
Nausea vomiting, n (%)	0 (0%)	0 (0%)	
PDPH, n (%)	0 (0%)	0 (0%)	
Urinary retention, n (%)	0 (0%)	0 (0%)	

*Fisher's Exact Test, p > 0,05 = not significant.

After analyzing the confounding variables (Table 6), such as age, weight, height, body mass index, brachytherapy duration, and ASA physical status, it was found that only spinal anesthetic dose had a relationship with ambulation time (p < 0.01). So only the drug dose group can predict ambulation time if the patient uses hyperbaric bupivacaine 5 mg and fentanyl 25 mcg will prolong the ambulation time by 56,693 minutes compared to the use of hyperbaric bupivacaine 2.5 mg and fentanyl 25 mcg without being influenced by other variables. Other confounding variables and side effects of spinal anesthesia did not have a significant relationship with ambulation time.

Table 6. Multivariate analysis.

Variable	B	Confidence interval 95%		p
		Lower	Upper	
Treatment group	56,693	50,45	62,92	<0,01

*Linear Regression Test , p < 0,05 = significant.

A study comparing age to sensory and motor blockade in geriatric patients compared to adults using bupivacaine found that there was no difference in block height, sensory block, and motor block because the sensitivity of bupivacaine was not affected by age.[33] A study on spinal anesthesia in obese patients found that the recovery time for a motor block in obese patients after spinal anesthesia was longer than in non-obese patients. In this study, there were no samples with obesity characteristics.[34] Therefore, only the drug dose group affected ambulation time in this study. The limitation of this study is that the study was conducted outside the operating room with limited facilities and patient monitoring tools.

4. Conclusion

Spinal anesthesia with hyperbaric bupivacaine 2.5 mg and fentanyl 25 mcg can accelerate the ambulation time of cervical cancer patients undergoing brachytherapy.

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