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Research Article

Comparison of Pain Scale, Hemodynamics, and Side Effects of Percutaneous and Intravenous Fentanyl in Post Sectio Caesaria Patients at Bunda Hospital

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Abstract

This is novel research about comparison pain scale, hemodynamics, and side effects of percutaneous and intravenous fentanyl in post sectio cesarean patients. Sectio cesarean is a method of delivering a fetus through an incision in the abdominal wall (laparotomy) and the uterus wall. This method induces pain in the incision, so patients feel complicated or afraid to mobilize. Fentanyl is one of the opioid analgesics, which is the main choice in section caesarian surgery because safe for breastfeeding, is more potent than morphine, and acts as balanced anesthesia—comparing the use of percutaneous fentanyl with intravenous fentanyl with pain scale parameters, hemodynamics, and side effects in sectio caesarian patients at Bunda Mother and Child Hospital Jakarta. Before conducting this research, an observational study first makes an ethical approval. Data were taken prospectively and collected simultaneously to compare percutaneous and intravenous fentanyl performed on post sectio cesarean patients with the physical status of the American Society of Anesthesiologists (ASA) I–II at Bunda Mother and Child Hospital Jakarta from September to November 2020. Comparative data observed were pain scale parameters, hemodynamics, and side effects after percutaneous fentanyl therapy or intravenous fentanyl therapy. Data were processed using SPSS 22 version and Microsoft Excell 2016. In conclusion, intravenous fentanyl is more effective in reducing pain scale and has more minor side effects than percutaneous fentanyl. There is no significant difference in hemodynamic parameters (p-value >0.05).

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INTRODUCTION

Cesarean delivery is one method of delivering the fetus through an incision in the abdominal wall (laparotomy) and the uterus wall. Delivery by cesarean section impacts the mother because of the pain that appears in the incision after cesarean section so that the patient is difficult or afraid to mobilize[1]. Based on the results of *Riset Kesehatan Dasar* (Basic Health Research) 2018 of the Republic of Indonesia, there was an increase in the percentage of cesarean section delivery by 7.8%; in 2013, it was 9.8%, and in 2018 it was 17.6%[2].

Postoperative pain is a complex physiological reaction to tissue damage or a response to illness that the patient perceives as an unpleasant sensory and emotional experience and is still a significant problem faced by anesthetists. Inadequate pain management will cause physiological side effects, increasing morbidity and hindering the healing process[3]. Opioids are the analgesic of choice for moderate to severe pain. Opioid analgesics are drugs that act on opioid receptors in the central

nervous system (CNS). This drug is given to treat moderate to severe pain according to the strength of the pain that is felt and the strength of the drug[4]. This drug acts on the CNS selectively to affect consciousness and cause dependence if taken in the long term. The mechanism of this drug is to activate opioid receptors in the CNS to reduce pain. Activation of the drug is mediated by mu (μ) receptors which can produce analgesic effects in the CNS and peripheries[5]. Opioids are given to surgical patients, such as morphine, codeine, fentanyl, and pethidine[6]. Fentanyl is used in this study and is the main choice of an opioid analgesic in the cesarean section, consisting of[7,8]:

1. For consideration of the level of safety for breastfeeding mothers because fentanyl is not distributed in breast milk.
2. Fentanyl is 75 -125 times more potent than morphine due to its good analgesic properties with a fast onset of action, fewer cardiovascular depressants, and does not cause histamine release, which can trigger bradycardia.
3. Fentanyl as part of balanced anesthesia can help achieve good hemodynamic stability during anesthesia, both in response to surgery and reduced the need for inhalation anesthetics or other anesthetic drugs.

There are two fentanyl preparations given percutaneously and intravenously using the Patient Controlled Analgesia (PCA) method. Each form of fentanyl has several advantages and disadvantages. Intravenous fentanyl is lipophilic, so it quickly reaches μ receptors in the central nervous system so that fentanyl is suitable for labor analgesia[9]. Based on the research of Purnomo *et al.*[10], intravenous fentanyl given by PCA has a volume distribution of 4.0 L/kg, a clearance of 13.0 mL/min/kg, and an elimination half-life of 3.5 hours.

Fentanyl transdermal patch is an analgesic that has been approved for use in the United States and Europe for the management of moderate to severe postoperative acute pain approved by the Food and Drug Administration (FDA) which is easy to administer, designed for acute and chronic pain management, and can help postoperative analgesics for adult patients[11]. Apart from having advantages, intravenous and percutaneous fentanyl also has disadvantages. Percutaneous fentanyl has a slow effect that occurs only after 12 hours. This is due to the formation of fentanyl depots in the skin layer before the drug enters the systemic circulation. Percutaneous fentanyl distribution is characterized by a slow drug absorption rate and a sustained serum concentration after patch removal, making it unsuitable for acute pain management[12]. Patients with acute pain syndrome are not suitable candidates for percutaneous fentanyl. Time-limited acute pain syndromes are not compatible with the pharmacokinetics of the percutaneous fentanyl device. The FDA states that percutaneous fentanyl is contraindicated for postoperative pain control. However, some clinicians recommend percutaneous fentanyl for postoperative pain control but with caution and close clinical monitoring[13,14].

During the Covid-19 pandemic, delivery of sectio caesaria was still carried out at several hospitals in Jakarta, including at the Bunda Mother and Child Hospital Jakarta. Based on data from the Bunda Mother and Child Hospital Jakarta drug inventory, the average monthly use of percutaneous fentanyl was 78 patches; intravenous fentanyl was 228 ampoules; morphine 21 ampoules; and pethidine 13 ampoules. From these data, the use of fentanyl is 80% of other types of opioids that anesthetists have used in analgesic therapy for post-sectio caesaria patients. Based on the description above, there is no published data regarding the effectiveness of fentanyl in post sectio caesaria. So it is necessary to conduct a study to compare the effectiveness of two fentanyl forms at Bunda Mother and Child Hospital Jakarta in post sectio caesaria patients from September to November 2020.

MATERIALS AND METHODS

Materials

The materials and software used in this study include medical records, post sectio caesaria patient registration lists, informed consent, data collection forms, patient diaries, clinical pharmaceutical drug therapy monitoring sheets, clinical pharmacy checklists, SPSS 22 programs, and Microsoft Excel 2016.

Methods

Before conducting the research, the authors made ethical approval and dealt with patients using informed consent. Subject patients (inclusions) must be patient sectio caesaria with physical status ASA I-II, age more than 20, and used anesthesia medicines such as midazolam, lidocaine, and propofol with the same dosage. The patient who could not be subject (exclusions) is a patient with fentanyl allergy, using fentanyl for more than three months, or using inflammatory and steroid medicine within 24 hours before sectio caesaria. Data were taken prospectively, and data was collected at once to compare percutaneous and intravenous fentanyl use in post sectio caesaria patients from September to November 2020 at Bunda Mother and Child Hospital Jakarta. Comparative data observed were pain scale parameters, hemodynamics, and side effects after percutaneous fentanyl therapy or intravenous fentanyl therapy. The research scheme is presented in **Figure 1**.

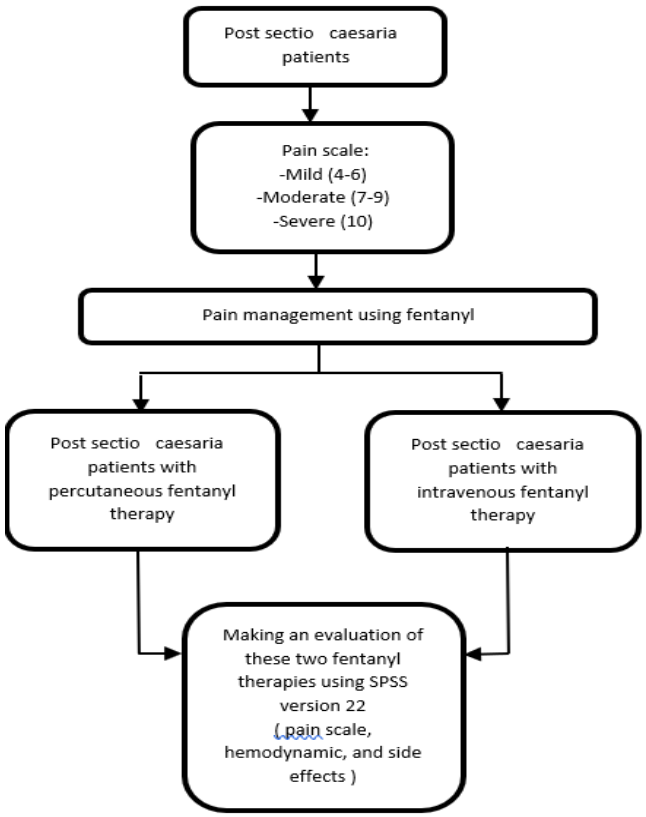


Figure 1. Research scheme

Research data were obtained from medical records, patient diaries, data collection forms, clinical pharmacy checklists, and drug therapy monitoring. The number of test subjects was 304 and divided into two test groups. The first group consisted of 152 patients receiving percutaneous fentanyl therapy and 152 patients receiving intravenous fentanyl therapy. The dose of percutaneous fentanyl was 25 µg/hour using transdermal preparations, and intravenous fentanyl was 25 µg/hour using PCA. The doses were recorded on the date and time of administration, and the progression of pain scale reduction, hemodynamics, and side effects was observed after three hours of administration.

Data were collected directly to the location of the study sample (the operating room) to determine the scale or degree of pain after surgery (post sectio caesaria). The doctor recorded the degree of pain in the patient's medical record or recorded by the nurse in the patient's diary. For observation of pain scale after intravenous or percutaneous administration of fentanyl after three hours of administration, it was carried out in an adult inpatient room. Drug therapy monitoring was carried out by identifying Drug Related Problems (DRP) and assessing the pain scale by interviewing post sectio caesaria patients and recording them on a clinical pharmacy checklist. The data obtained were carried out by statistical tests using SPSS 22.

RESULTS AND DISCUSSION

Data distribution tests were carried out to check the homogeneity of the research variables using the Levene test. After the homogeneity test was carried out for all research variables, the following results were obtained and presented in **Tables I** and **II**.

Table I. Homogeneity test of the characteristics of research subjects using the Levene test

No.	Characteristics of research subjects	N	Percutaneous fentanyl	Fentanyl intravenous	p-value
1.	Age (Years)	152	31 ± 3.38	30 ± 2.85	0.055
2.	Weight (Kg)	152	73 ± 5.28	70 ± 3.37	0.001
3.	Gestational age (GPAH)	152	37.8 ± 1.08	37.6 ± 1.29	0.294

Table II. Homogeneity test of the research variable parameters using the Levene test

No.	Parameter		N	Percutaneous fentanyl	Fentanyl intravenous	p-value
1.	Pain scale after drug administration		152	3.8 ± 0.68 n (2) = 4 n (3) = 37 n (4) = 90 n (5) = 21	3.3 ± 0.57 n (2) = 3 n (3) = 92 n (4) = 55 n (5) = 1 n (6) = 1	0.978
2.	Hemodynamics					
	a.	Temperature (°C)	152	36.3 ± 0.27	36.4 ± 0.23	0.054
	b.	Pulse (x/minute)	152	82.45 ± 3.89	82.35 ± 3.63	0.198
	c.	Systole (mmHg)	152	119.93 ± 8.79	114.9 ± 17.97	0.063
	d.	Diastole (mmHg)	152	77.38 ± 5.78	75.26 ± 5.58	0.309
	e.	Saturation (%)	152	98.9 ± 0.012	98.3 ± 0.0129	0.483
3.	Side effects					0.000
	a.	Nausea	152	0.532 ± 0.5 n (1) = 81	0.072 ± 0.25 n (1) = 11	
	b.	Throw up	152	0.335 ± 0.47 n (1) = 51	0.066 ± 0.081 n (1) = 1	
	c.	Headache	152	0.309 ± 0.46 n (1) = 47	0.065 ± 0.24 n (1) = 10	
	d.	Sleepy	152	0.914 ± 0.28 n (1) = 139	0.953 ± 0.21 n (1) = 145	

Identification of Research Subjects

The number of research subjects after going through the inclusion criteria was 304 patients. The subjects selected were patients with post-sectio caesaria physical status of ASA I-II at Bunda Mother and Child Hospital Jakarta from September to November 2020. Subjects were divided into two groups: the group that received percutaneous fentanyl therapy and intravenous fentanyl therapy. The characteristics of the research sample were presented in **Table III**. Data on general characteristics of research subjects showed that there was no significant difference ($p > 0.05$) on variables, age, weight, ASA physical status and pregnancy diagnosis. These results indicate that the samples taken for the research are homogeneous so that they are comparable.

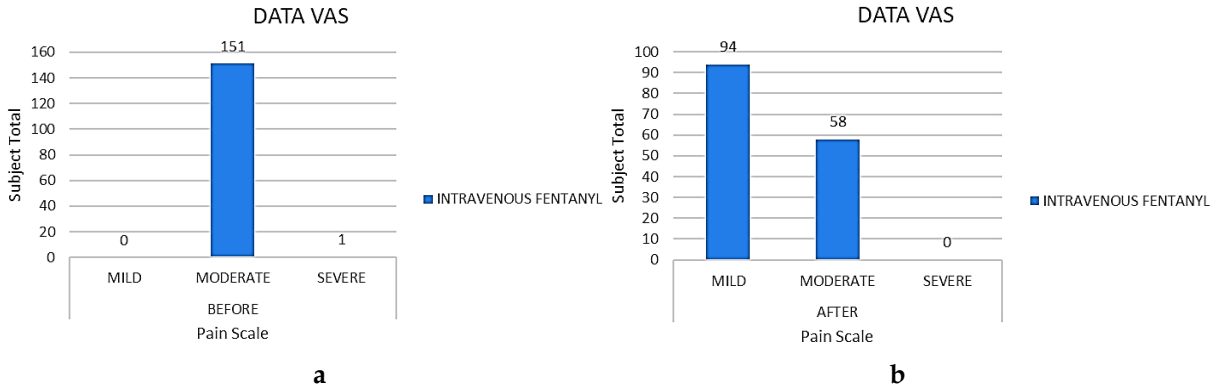
Table III. Characteristics of the research sample

Variable	Percutaneous fentanyl	Intravenous fentanyl	p-value
Age (years)	31.00 ± 3.39	30.56 ± 2.86	0.385
Weight (Kg)	73.04 ± 5.28	70.79 ± 3.38	0.001
Gestational age	37.79 ± 1.07	37.68 ± 1.30	0.966

Pain Effectiveness Analysis

To determine the effectiveness of pain, first a normality test was performed on the variable parameters of the pain scale on intravenous fentanyl and percutaneous fentanyl using the Saphiro-Wilk statistical method. From the results of the normality test of the pain scale parameter using the Shapiro-Wilk shows the p-value of the test is 0.000. The Sig value (p-value) of the two tests is above <0.05, which means that the data is not normally distributed. Then the test for the homogeneity of the variables was carried out using the Levene test obtained p value of 0.976. The Levene's test value is indicated by p-value

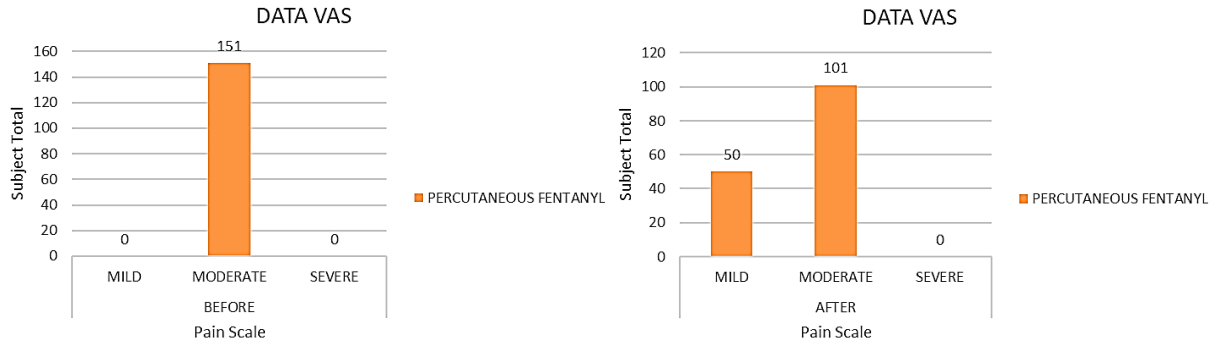
0.976 > 0.05, which means that the variance of the two groups is the same or what is called homogeneous. Thus, we will test different hypotheses using the Mann-Whitney test. To determine the effectiveness of pain in test subjects before and after intravenous and percutaneous administration of fentanyl, it can be seen from the **Figures 2** and **3**.



a **b**

Figure 2. Intravenous fentanyl VAS data before (**a**) and after (**b**) treatment

Based on the **Figure 2**, for the group of test subjects given intravenous fentanyl for three months on the basis of Lejus *et al.*[15], in the treatment before the administration of intravenous fentanyl, the visual analogue scale (VAS) results were 99.34% medium scale and 0.66% heavy scale. Observation of pain scale reduction was carried out after three hours of intravenous fentanyl administration, obtained a decrease in the VAS results from a severe pain scale to a moderate pain scale by 100% and a decrease in VAS from a moderate scale to a mild pain scale of 62.25%. However, there were still test subjects who experienced moderate pain of 38.16% after three hours of intravenous fentanyl administration.



a **b**

Figure 3. Percutaneous fentanyl VAS data before (**a**) and after (**b**) treatment

Based on the **Figure 3**, in the treatment before giving percutaneous fentanyl which was carried out for three months, 100% moderate-scale VAS results were obtained. Observation of pain scale reduction was carried out after three hours of percutaneous fentanyl administration, obtained a decrease in the VAS results from moderate pain scale to moderate to mild pain scale by 33.11%. But there were still test subjects who experienced moderate pain at 66.89% after three hours of percutaneous fentanyl administration.

In this study, anesthetists considered on the basis of giving fentanyl starting in the moderate category to prevent increased stress, anxiety and persistent chronic pain. This is in accordance with the basis for giving fentanyl according to WHO Three Analgesic Ladder on the assessment of the degree of pain based on the category of moderate (scale 4-6), severe (scale 7-9) and very painful (scale 10)[16]. To determine the effectiveness of pain in the two groups, different tests and hypotheses were carried out using the Mann Whitney test, as presented in **Table IV**.

Table IV. Mann Whitney test results on the effectiveness of intravenous and percutaneous fentanyl

Types of preparations	N	p-value
Intravenous fentanyl	152	0.005
Percutaneous fentanyl	152	

From the results of statistical tests for the effectiveness of pain, it was found that p-value <0.05, there was a significant difference between the two groups. Thus it can be said that there is a significant difference in the effect of the use of the two pain medications based on the observation of differences in the VAS, from the three hours VAS shows a significant difference in the three hours after analgesic administration (p-value <0.05). The distribution of fentanyl by the transdermal patch is characterized by a slow drug absorption rate and a sustained serum concentration after patch removal, making it unsuitable for acute pain management. Exogenous and endogenous factors such as the amount of subcutaneous fat, skin integrity, hair follicle structure and composition, possibly a dermal depot, body core temperature, skin thickness, first-pass skin biotransformation and environmental temperature cause strong differences in absorption of fentanyl into the bloodstream, this is a factor that influence change or decreas in pain scale when using percutaneous or transdermal fentanyl[17,18].

Percutaneous fentanyl has a slow effect, occurs only after 12 hours. This is due to the formation of fentanyl depots in the skin layer before the drug enters the systemic circulation. Patients with acute pain syndrome are not suitable candidates for percutaneous fentanyl. Time-limited acute pain syndromes are not compatible with the pharmacokinetics of the percutaneous fentanyl device. The FDA states that percutaneous fentanyl is contraindicated for postoperative pain control. However, some clinicians recommend percutaneous fentanyl for postoperative pain control but with caution and close clinical monitoring[12,13].

Intravenous administration of fentanyl does not use skin media for a longer period of time in the process of releasing and distributing fentanyl to its receptors, so this causes a reduction in acute pain, especially in post-cesarean patients, it is better at reducing the severe pain scale and moderate to mild pain scale[19]. Rayburn *et al*.[20] compared women who received intravenous fentanyl for labor pain with women who didn't receive analgesics or anesthetics during labor and determined that at low doses of intravenous fentanyl in women who delivered experience temporary analgesia and sedation without an immediate risk to mother and baby. When intravenous fentanyl was compared with intravenous meperidine for labor pain relief in a randomized, non-blind trial (N = 105 women with uncomplicated pregnancies during active labor), both fentanyl and meperidine produced similar reductions in pain scores; However, fentanyl was associated with less sedation, nausea, and vomiting and fewer newborns requiring naloxone therapy (1/49 vs 7/56, respectively; p <0.05). There was no difference in the rate of reduction in fetal heart rate variability, Apgar score, and neonatal neurologic and adaptive ability scores. Because fentanyl has fewer side effects in mothers and newborns, the investigators suggest that fentanyl may be preferred over meperidine for labor analgesia[21].

Hemodynamic Analysis

Opioids are drugs that act as receptor binding agonists μ. This drug has the effect of reducing pain and so is widely used as a regimen of postoperative analgesia[22]. Fentanyl is an opioid drug most widely used as a regimen for post sectio caesaria analgesia at Bunda Mother and Child Hospital Jakarta. The study was conducted on 304 patients who gave birth using the cesarean section method. These patients were divided into two test groups. The first group was given intravenous fentanyl therapy, and the second group was given percutaneous fentanyl therapy. Then, after three hours of intravenous administration of fentanyl and percutaneous fentanyl, the observed hemodynamic factors were tested, including temperature, blood pressure, pulse, and saturation. After the observations were made, the data obtained were subjected to statistical testing. The T-test results for hemodynamic parameters are presented in **Table V**.

The statistical test found that the administration of intravenous fentanyl and percutaneous fentanyl did not have a significant difference in the hemodynamic factors of temperature, pulse, blood pressure, and saturation. Intravenous fentanyl administration has a faster onset of action and a shorter duration of action because fentanyl is lipophilic. This reflects the large solubility of fentanyl in fat and can also cross the blood-brain barrier more quickly. The redistribution process of

fentanyl to inactive tissues such as fat and skeletal muscle is also accelerated. Administration of fentanyl by continuous infusion causes an increase in the saturation of the drug in the inactive tissue. As a result, the concentration of fentanyl in plasma does not drop rapidly, and respiratory depression can be prolonged. However, there was no change in saturation between the test group receiving intravenous and percutaneous fentanyl therapy[23].

Table V. Results of the T-test on intravenous and percutaneous administration of fentanyl

Variable	Percutaneous fentanyl	Intravenous fentanyl	p-value
Temperature (°C)	36.3 ± 0.27	36.4 ± 0.23	0.054
Pulse (x/minute)	82.45 ± 3.89	82.35 ± 3.63	0.198
Systole (mmHg)	119.93 ± 8.79	114.9 ± 17.97	0.063
Diastole (mmHg)	77.38 ± 5.78	75.26 ± 5.58	0.309
Saturation (%)	0.989 ± 0.012	0.983 ± 0.0129	0.483

The second hemodynamic factor to be monitored was blood pressure. Normal blood pressure is 120/80 mmHg, and blood pressure is declared high if the systolic pressure reaches more than 140 mmHg and diastolic blood pressure is more than 90 mmHg when sitting down[24]. From the study results, there were no significant differences in both systolic and diastolic blood pressure in patients who were given intravenous and percutaneous fentanyl. A drop in blood pressure can occur rapidly after anesthesia because of its vasodilating effect. A decrease in blood pressure is associated with decreased cardiac output, systemic vessel resistance, inhibition of the baroreceptor mechanism, depression of myocardial contractility, decreased sympathetic activity, and ionotropic effects[25]. The administration of fentanyl does not lead to depression of myocardial contractibility so that the decrease in blood pressure is not too large[26]. Myocardial depression and vasodilation effects occur depending on the dose of fentanyl given. Vasodilation occurs due to decreased sympathetic activity and the direct effect of calcium mobilization on intercellular smooth muscle[27]. Research conducted by Wickham *et al*.[28] said that giving fentanyl to induction of anesthesia with propofol can maintain hemodynamic stability of patients with a decrease in the mean arterial pressure (MAP) value <20% during induction of anesthesia. This occurs because fentanyl does not directly suppress sympathetic reflexes but maintains the patient's blood pressure. In this study, there was no hypotension because the administration of fentanyl served as hemodynamic stability. According to research conducted by Klamt *et al*.[29], the combination of fentanyl-midazolam assisted by isoflurane is effective and safe to provide long analgesic and hypnotic effects in pediatric patients undergoing cardiac surgery. Besides that, fentanyl also functions as hemodynamic stability, maintaining blood pressure and pulse within normal limits in pediatric heart surgery patients.

Laksono and Isngadi[30] said that shivers could occur after anesthesia. One way that is thought to be pharmacologically effective is to give fentanyl. The addition of intrathecal fentanyl can reduce the risk of shivering with minimal side effects of nausea and vomiting[28]. In patients with cesarean section, the incidence of shivering is more significant than in patients with other surgical methods. Because the method of spinal anesthesia performed on patients with sectio caesaria has more influence on temperature regulation. The effect of peripheral vasodilation on spinal anesthesia causes heat transfer from the central compartment to the peripheral compartment, causing hypothermia[30]. In addition, Techanivate *et al*.[31] concluded that adding 2 µg of fentanyl in 2.2 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of morphine 0.2 mg intrathecally could reduce the incidence and the severity of intraoperative and postoperative shivering after spinal anesthesia in patients undergoing cesarean section without increasing the incidence of side effects. This study resulted in no significant change in the body temperature of the test sample. It is thought that the administration of fentanyl keeps the body temperature in normal condition or maintains thermoregulation to prevent hypothermia.

Fentanyl lowers the patient's shivering threshold so that even though there is hypothermia, it does not pass the shivering threshold that falls[30]. Another study conducted by Nugroho *et al*.[32] said that the labor process is a physical process that is thermogenic or causes heat due to increased oxygen consumption due to uterine and skeletal muscle contraction. The hypothalamus then triggers vasodilation, sweating, and hyperventilation to increase heat loss. Epidural analgesia is said to cause an imbalance between heat production and heat loss mechanisms. Generally, epidural analgesia causes a decrease in core temperature due to the redistribution of body heat from the core to the periphery, increasing heat dissipation by the

body. This effect is then offset by epidural analgesia, which lowers the threshold for shivering thermoregulation by blocking the intake of cold afferents from the anesthetic agent of the body. As a result, the patient will shiver to increase heat production[31]. Gleeson *et al*.[33] found that fever was twice as common in women who shivered than those who did not come after epidural insertion. Sweating is one of the body's responses to lower body temperature. Sympathectomy of epidural analgesia will prevent this from occurring. The epidural block alters the thermoregulatory response to heat generation by increasing the sweating threshold. In this case, the epidural is said to block sweat in the body segment that gets the epidural so that body temperature increases. Patients who do not receive analgesia during labor are also more likely to hyperventilate. This, together with the expulsion of sweating, will reduce the patient's body temperature. Providing adequate analgesia, such as epidural analgesia, reduces the degree of hyperventilation and heat loss, and body temperature will increase.

For pulse hemodynamic factors in this study, there were no significant differences in patients given intravenous or percutaneous fentanyl. Administration of fentanyl can cause bradycardia due to increased central vagal tone and depression of the SA and AV nodes. In hypovolemic patients, fentanyl causes a decrease in stroke volume, a decrease in heart rate, and cardiac output, causing the heart rate to decrease, but the heart rhythm does not change[34]. According to research conducted by Klamt *et al*.[29], infusion of a combination of midazolam and fentanyl can provide analgesic and hypnotic effects by maintaining hemodynamic stability such as heart rate in children undergoing heart surgery. Giving fentanyl is the right thing to do during surgery to maintain hemodynamic factors to remain stable, especially the pulse. Fentanyl is a suitable opioid that is suitable for use. Besides maintaining hemodynamic factors, it also has a fast onset and makes minimal hemodynamic changes even though it is given in large quantities.

Side Effects Analysis

From the results of statistical tests for the side effects of intravenous and percutaneous fentanyl administration (**Table VI**), it was found that the p-value critical limit was <0.05, so there was a significant difference between the two groups. Thus, there is a significant difference in the effect of using two pain medications from the side effect parameters. If you look at the mean value, where the intravenous fentanyl pain medication has a smaller mean, the resulting side effects are smaller. Thus, it can be concluded that intravenous fentanyl has more minor side effects than percutaneous fentanyl.

Fentanyl is an opioid with a μ agonist active against the μ receptor, where the μ receptor mediates analgesia, sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, decreased gastrointestinal motility, and urinary retention[35]. In transdermal preparations, fentanyl is sufficiently soluble in the lipid and water compartments of the skin to allow penetration. In its alkaloid (alkaline) form, fentanyl readily enters the stratum corneum keratin. This epidermal layer provides the most significant barrier for water movement both into and out of the body[17]. Only substances with sufficient fat solubility can dissolve and diffuse through this dermal layer's ceramides and other wax lipids. Subsequent drug movement from the lipid layer into the dermal water is required to allow systemic absorption. So the chemical must be lipid and water-soluble to be effectively internalized once it passes through the skin. The relationship between the lipid and water solubility of a chemical is indicated numerically by the octanol-water partition coefficient. It is expressed as the ratio of the concentration of a chemical in octanol and water when it is in equilibrium at a specific temperature. Fentanyl bases have an octanol-water partition coefficient of 860 (fentanyl citrate is 717 at pH 7.4), so they pass through the lipid portions of the epidermis with relative ease. Although fentanyl base and salt (citrate) are bioavailable, systemic base absorption appears to be slightly faster. In comparison, morphine is less lipophilic and has an octanol partition coefficient of 0.7, and predictably shows poor epidermal permeability. This is what chooses fentanyl in transdermal form compared to morphine.

Table VI. Mann-Whitney test results of side effects of intravenous fentanyl with percutaneous

Factor	N	Intravenous fentanyl	Percutaneous fentanyl	p-value
Nausea	81	0.072 ± 0.25	0.532 ± 0.5	0.000
Throw up	51	0.066 ± 0.081	0.335 ± 0.47	
Headache	47	0.065 ± 0.24	0.309 ± 0.46	
Sleepy	139	0.953 ± 0.21	0.914 ± 0.28	

The uptake of fentanyl in patch preparations depends on the transdermal site's exogenous and endogenous factors. The thickness and temperature of the skin can alter transdermal fentanyl bioavailability and blood flow to and from the patch site. Applying the patch to the damaged skin can cause an increase in blood fentanyl concentration, and an increase in skin temperature will also increase fentanyl absorption. The chest area is a site that can accept transdermal attachment and blood flow, and this is due to the minimal effect on systemic drug absorption under normal physiological conditions.

Pharmacokinetically, fentanyl patch (percutaneous) is detectable in serum 1-2 hours with onset for six hours after fentanyl action. Serum fentanyl concentration increased gradually at 12 hours and remained constant for 72 hours. This causes nausea, vomiting, and headache side effects found in this study because after the patch is removed from the skin media, fentanyl remains constant in the blood. The patient complained of being switched to TFP with other analgesics that did not cause the side effects of nausea, vomiting, and headaches.

The ideal general anesthesia can provide rapid and quiet induction, predictable loss of consciousness, stable intraoperative state, minimal side effects, rapid and smooth restoration of protective reflexes, and psychomotor function. In addition, the ideal physical and pharmacological properties of intravenous anesthetics should be soluble and stable in water, painless during injection, not releasing histamine or hypersensitivity reactions, rapid and gentle onset of hypnosis without causing excitatory activity, metabolism, rapid inactivation of drug metabolites, is related Steep dose and response to increase titration effectiveness and minimize tissue drug accumulation, minimal respiratory and cardiac depression, decrease cerebral metabolism and intracranial pressure, recovery of consciousness and cognition that is fast and gentle, and does not cause postoperative nausea and vomiting (PONV), amnesia, psychomimetic reactions, dizziness, headaches and prolonged sedation time (hangover effect)[36]. One of the disadvantages of fentanyl as a single anesthetic is that it requires a large initial dose with a large dose range ranging from 50-150 μg/kg BW or fentanyl concentration in plasma ranges from 20-30 μg/mL[37].

CONCLUSION

Based on the results, it can be concluded that intravenous fentanyl is more effective in reducing the pain scale in post sectio caesaria patients than percutaneous fentanyl. In hemodynamic parameters, p-value >0.05 showed no significant difference in hemodynamic factors (temperature, pulse, blood pressure, and oxygen saturation) in the administration of intravenous percutaneous fentanyl. Intravenous fentanyl has fewer side effects (nausea, vomiting, headache, and drowsiness) than percutaneous fentanyl.

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AUTHORS' CONTRIBUTION

Annisa``a Nurillah Moesthafa: conceptualization, funding acquisition, project administration, investigation, data curation, formal analysis, software, visualization, and writing - original draft. **Achmad Riviq Said**: conceptualization, resources, investigation, data curation, and validation. **Ros Sumarny**: resources, methodology, supervision, validation, and writing - review & editing. **Yati Sumiyati**: project administration, methodology, formal analysis, supervision, validation, visualization, and writing -review & editing.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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