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Research

Comparison of The Effectiveness of Remifentanyl versus Fentanyl in Pediatric Undergoing Methotrexate Therapy

Purwoko[1)], Bambang Novianto Putro[1)], Ferdy Pamungkas[1)]
Febby Gunawan Siswanto[2)]

[1)]Anesthesiology Department, Moewardi General Hospital, Surakarta, Indonesia
[2)]Medical Faculty Universitas Sebelas Maret, Moewardi General Hospital, Surakarta, Indonesia

ABSTRACT

Background: Anesthesia procedure is routinely performed for some painful pediatric oncologic procedures such as lumbar puncture (LP) and bone marrow examination (BME). Several studies mentioned that fentanyl and remifentanyl are often used as anesthetic agent of this procedure, but none of them compare the recovery time of both agent. This study aims to compare the recovery time of fentanyl and remifentanyl in pediatric patients undergoing methoterexate therapy.
Subjects and Method: This was a double-blind randomized controlled trial on 36 patients who underwent intratechal methotrexate chemoterapy under general anesthesia anesthesia in pediatric intervention room of Moewardi General Hospital Surakarta that met inclusion criteria. The dependent variable was recovery time and the independent variable were fentanyl and remifentanyl. The samples were divided into 2, Fentanyl (F) and Remifentanyl (R) group. Recovery time was recorded after the procedure until the subject reached Pediatric Glasgow Comma Scale (PGCS) of 15. Statistical analysis was Mann Whitney U Test using SPSS 25 for Windows.
Results: The mean recovery time of F group was 373.39 ± 29.48 seconds, while R group was 124.67±11.55 seconds. There was a significant difference in recovery time between patients in the Fentanyl group and the Remifentanyl group (p= 0.000).
Conclusion: Remifentanyl recovery time was significantly faster than with fentanyl in pediatric patients undergoing intrathecal methotrexate chemotherapy.

Keywords: Fentanyl, Methotrexate, Outpatient anesthesia, Recovery time, Remifentanyl

Correspondence:
Ferdy Pamungkas. Anesthesiology Department, Moewardi General Hospital, Surakarta. Jalan Kolonel Sutarto 132 Jebres, Kecamatan Jebres, Surakarta City 57126. Central Java, Indonesia. dr.ferdypamungkas@gmail.com. +6281230269501.

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BACKGROUND

Outpatient anesthesia is the specialty of anesthesiology that deals with the preoperative, intraoperative, and postoperative anesthetic care of patients undergoing elective surgical procedures, on the same day, both inside and outside the operating room. Patients undergoing outpatient surgery rarely require admission to the hospital and are reasonably fit to be discharged from the surgical facility after the procedure (Butterwoth et al., 2018a)

Several intervention methods can be performed for ambulatory patients, considering any possibilities of problems and complications compared to patients undergoing surgical procedure. Procedural techniques of anesthesia are done by giving seda-

tive or dissociative agents with or without analgesics to induce the patient that allows them tolerating the unpleasant procedure, but keeping them in an adequate cardio-respiratory function (Butterwoth et al., 2018b; Butterwoth et al., 2018a).

In pediatric oncology practice, this anesthesia procedure is routinely performed for painful procedures such as lumbar puncture (LP) and bone marrow examination (Chayapathi et al., 2018). There is no such different patient standard care for anesthesia inside and outside the operating room. Basic standards such as appropriate equipment and monitoring must be ensured without compromising safety. Depending on the characteristics of the patient and the treatment procedure, either general anesthesia or light sedation may be applied. In the majority of cases, childhood cancer requires several short, painful, and repeated interventional procedures such as bone marrow aspiration (BMP), bone marrow biopsy (BMB), and lumbar puncture (LP) (Omara et al., 2019).

The anesthesiologist can use techniques that can restore quickly after the procedure. There are several studies conducted with different anesthetic agents, used for sedation or anesthesia during hemato-oncological interventions in pediatric patients. Some studies are done and agreed that propofol is more beneficial in providing amnesia and patient comfortness during elective oncological procedures (Bajwa et al., 2017). Sedation can be given in the form of pure propofol or in combination with fentanyl. It was found that in the combination of fentanyl and propofol, the amount of propofol in total dose and side effects experienced a significant reduction (Nazemroaya et al., 2018).

A study was done by Gorji et al., (2016) in patient with acute leukemia who underwent lumbar puncture. Most patients (or families) prefer that Propofol - Fentanyl combination due to its lower side effects and faster recovery from anesthesia (Duffy et al., 2019).

Another study also investigated anesthetic techniques to find rapid recovery during short painful oncological procedures, combination of sevoflurane propofol - N_2O compared to propofol remifentanil (PR). Recovery time was found to be significantly shorter in the PR group rather than in the other groups and the parents mostly chose the PR combination. Sedation with remifentanil and midazolam was also applied to children during painful procedures, and it was concluded that administration of remifentanil with midazolam would provide adequate analgesia and sedation. It was reported that this drug combination was effective but was reported to cause respiratory depression at a subtherapeutic level. Administration of propofol alone or in combination with remifentanil during BMP was observed during the procedure and caused a decrease in the total dose of propofol but increased the risk of respiratory depression (Omara et al., 2019). Until now, there's lack evidence that comparing the effectiveness of fentanyl and ramifentanyl as the anesthesia agent in non-operating room.

This study aims to compare the recovery time of fentanyl and remifentanyl in pediatric patients undergoing methoterexate therapy.

SUBJECTS AND METHOD

1. Study Design

This was a double-blind randomized control trial. The research was conducted at the Dr Moewardi Hospital Surakarta in March 2021.

2. Population and Sample

The included 36 patients scheduled for elective intratechal methotrate chemotherpy procedure under general anesthesia in

pediatric intervention room of Moewardi General Hospital Surakarta. The inclusion criterias were pediatric patient ageing 3-18 years old with physical state of ASA II who can communicate verbally and whom family giving the consent to participate in the study.

Meanwhile, the exclusion criterias were patient who has contraindication to anesthesia procedure, patient who has difficult airway, airway problem, or circulatory problem, patient with chronic pain under the intervention of pain management team, patient who was under opioid therapy or benzodiazepine therapy more than 3 months, patient with allergic history of the anesthesia agent and egg, and patient who was under psychoactive drugs therapy. Patient who was in an emergency of cardiopulmonary, patient who was in hypersensitivity to propofol, fentanyl, and/or remifetanyl, and patient who underwent any complication during the procedure were dropped out from the study.

3. Study Variables

The dependent variable was recovery time of pediatric patient who underwent the intratechal methotrexate chemoterapy procedure in numeric scale. Meanwhile, the independent variable were fentanyl and remifentanyl with nominal scale.

4. Operational Definition of Variables

Recovery time of pediatric patient who underwent the intratechal methotrexate chemoterapy procedure. The time it takes for the patient to reach full awareness of the elimination of the anesthetic agent from the brain and to be easily aroused and aware of his environment and identity. A volunteer recorded the time needed for the patient to recover fully (Pediatric Glasgow Comma Scale 15) after the intratechal methotrxate chemoterapy procedure.

Fentanyl is a synthetic lipophilic fenofpiperidine opioid agonist with analgesic and anesthetic properties. In this study, fentanyl was given 1µg/kgBW bolus slowly diluted by NaCl 0.9%.

Remifentanil is a fentanyl derivative, a pure -opioid receptor agonist metabolized by nonspecific esterases with a pharmacodynamic profile typical of opioid analgesic agents, intravenous anesthetics and sedatives. In this study, remifentanil was given using syringe pump in 0.1 g/kgBW/min.

5. Study Instruments

Fentanyl was given bolus intravenously and remifentanyl was given using syringe pump with body-weight based dose. Recovery time was recorded based on the time needed by the patient to get PGCS 15.

This study was assisted by two volunteers. The first volunteer helped in administering the drugs. The second volunteer assessed the subject's consciousness with PGCS and recorded the study subject's recovery time after the completion of intrathecal methotrexate therapy. Both of them were not knowing the drug that had been given to the subject.

6. Data analysis

Data analysis was performed using SPSS version 25 for Windows. The research hypothesis was tested using the Independent T Test if the data was normally distributed and the Mann Whitney U Test if the data were not normally distributed. The limit of significance set was $p < 0.05$ with a 95% confidence interval. If $p < 0.05$ then the results are considered statistically significant.

7. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Research Ethics Committee at Dr. Moewardi Hospital, Surakarta, Indonesia, Number: 569/IV/HREC/2021.

RESULTS

1. Sample Characteristics

There were 36 subjects involved in this study and no subjects that were included in the drop out criteria. In this study, they were divided into 2 groups; 18 subjects for fentanyl group (F) and 18 subjects for remifentanyl group (R). The F group received a bolus injection of fentanyl 1µg/kgBW. The R group received a continuous syringe pump drug with remifentanil 0.1µg/kgBW/m. Both of them recieved propofol induction of 1-2mg/kgBW.

Based on the data from the characteristics of the research subjects, data on the age and weight of the entire sample were obtained. Table 1 shows the sample characteristics of the subjects.

Table 1. Sample characteristics

Characteristic	F group	R group	p
Sex			
Male	13 (72.23%)	13 (72.23%)	1.000
Female	5 (27.77%)	5 (27.77%)	
Age	7.44+1.00	5.67+0.57	0.229
ASA			-
I	0 (0.0%)	0 (0.0%)	
II	18 (100.0%)	18 (100.0%)	
BMI			-
Underweight	0 (0.0%)	0 (0.0%)	
Normal	18 (100.0%)	18 (100.0%)	
Overweight	0 (0.0%)	0 (0.0%)	

Based on the table 1, there's no significantly difference between F and R group in sex, age, ASA physical status, and BMI. It can be concluded that the study sample is homogeneous.

1. Bivariate analysis

Normality test was done using Shapiro Wilk test due to the small group sample. The result of normality test.

Table 2. Normality Test

Variable	p
Remifentanyl (R)	0.008

Based on Table 2, both p value of F group (p=0.048) and R group (p=0.008) are lower than 0.05. It can be concluded that the data were unnormaly distributed.

Table 3. The Difference of Recovery Time of the subject

Variable	Recovery time (minute)		p
	Mean	SD	
Fentanyl (F)	373.39	29.48	<0.001
Remifentanyl (R)	124.67	11.55	

Based on table 3, it is known that 18 subjects in F group mean recovery time of 373.39 (Mean= 373.39; SD= 29.48) seconds, while 18 subjects in R group with mean recovery time of 124.67+11.55 seconds. The results of the statistical test obtained a p<0.001. There is a significant difference in recovery time between patients in the Fentanyl group and the Remifentanyl group.

Based on the description above, it can be concluded that the recovery time for remifentanil is faster than fentanyl in

pediatric patients undergoing intrathecal methotrexate oncology therapy.

DISCUSSION

The equipotency dose of remifentanil versus fentanyl is difficult to calculate, because remifentanil has a more rapid onset and elimination time than fentanyl. In a study of the dose of fentanyl vs. remifentanil in adults, Sung et al., (2020) found a corrrelation of 3:1 during induction, but 1:8-10 during maintenance for 30 minutes. According to the statment, there is a difference in the time of administering propofol in this study. We bolused the propofol right after the administration of remifentanil or fentanyl had reached its onset according to the reference. Meanwhile, Sung et al administered propofol as a bolus after 3 minutes of continuous syringe pump remifentanyl and 5 minutes after the bolus of fentanyl intravenously (Sung et al., 2020).

Gulec (2015) conducted a study comparing remifentanil-propofol with fentanyl-propofol in pediatric circumcision surgery. They found that the recovery time in patients receiving remifentanil-propofol was 4.2 (Mean= 4.2; SD= 2.8) minutes and fentanyl-propofol was 4.2 (Mean= 4.2; SD= 2.8) minutes and fentanyl-propofol was 9.4 (Mean= 9.4; SD= 3.2) minutes with a significant difference ($P<0.05$). It can be concluded that remifentanil has faster recovery time than fentanyl. According to this study, statistically remifentanil has a faster recovery time than fentanyl.

Vittinghoff et al., (2018) concluded that pediatric patients who received remifentanil had a faster recovery time such as eye opening, spontaneous breathing, extubation to verbalization than fentanyl. The discharge time for patients receiving remifentanil was also shorter than fentanyl. However, fentanyl provides a better analgesic effect than patients receiving remifentanil. In our study, remifentanil provided a better recovery effect from sedation than fentanyl, regardless of the analgesic effect in this study (Vittinghoff et al., 2018).

The same result was also found from a study conducted by Wang et al., (2016) by comparing remifentanil with fentanyl in pediatric patients. In this study, the recovery in the group of patients given remifentanil was 50 (Mean= 50; SD= 27) minutes while in the group of patients given fentanyl it was 63 (Mean= 63; SD= 27) minutes. Therefore, the study also found that when pediatric patients were given ice cream, the time required by the subject to eat the ice cream in the remifentanil group was 91 (Mean= 91; SD= 37) minutes while in the fentanyl group it was 119 (Mean= 119; SD= 42) minutes with a significant difference ($p< 0.05$). From this study, it can be concluded that the recovery time in remifentanil group was faster and patients were able to carry out their usual activities as tested in this study, which was given ice cream compared to the group of patients who were given fentanyl (Wang et al., 2019).

Remifentanil has several advantages over other opioids (fentanyl, alfentanyl, sufentanyl) during general anesthesia, including hemodynamic stability. For example, Soontrakom et al., (2018) conducted a study to the hemodynamic profile of remifentanil in 34 children of various ages, undergoing elective surgery and receiving a single dose of 5 mcg/kg, administered slowly during anesthesia with a mixture of nitrate and isoflurane. They found that 17% of cases spread across all age ranges had clinically significant hypotension following administration of this large dose. They also noted that, although <40% of children received atropine or a vagolytic muscle relaxant, there was no significant change in heart rate.

Fentanyl is often used as analgesia in pediatric patients because of its relatively

short duration, so fentanyl is usually only used for surgical anesthesia and is not recommended postoperatively. When combined, it can be with benzodiazepines or inhalation anesthetics with low doses (Soontrakom et al., 2018).

In a retrospective study by Chollat et al., (2019), they observed that continuous administration of remifentanil after a bolus of atropine led to favorable intubation conditions for 87% of neonatal patients, although side effects included chest wall stiffness (11%), breathing problems (9%) , and laryngospasm (2%). occurred in 22% of procedures. In addition, 23% of the procedures were complicated by severe bradycardia and 37% by severe desaturation. Given the favorable conditions of intubation and the high incidence of adverse events, the exclusive use of high-dose remifentanil and the benefits of premedication before intubation may require careful evaluation. Indeed, it does not seem appropriate to consider achieving general anesthetic levels with opioids alone. When combined with midazolam or propofol, 1 mcg/kg remifentanil appears to be sufficient for quality sedation without side effects (Chollat et al., 2019).

Omara et al., (2019), in their study said that the potential side effects of remifentanil cannot occur with proper use. Slow administration and prevention of repeated dosing may prevent the development of bradycardia, hypotension, and chest wall rigidity. This is in accordance with this study, there were no side effects in the form of hemodynamic and respiratory abnormalities in the group of subjects receiving remifentanil.

This study is limited due to the small amount of subject. Further study needs to be done in larger population and multicenter study. Besides, various dose of remifentanyl can be used to know the effective dose of remifentanyl in pediatric patient. From this study, we can conlude that remifentanyl recovery time was significantly faster than with fentanyl in pediatric patients undergoing intrathecal methotrexate chemotherapy.

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Nil.

CONFLICT OF INTEREST

There is no conflict of intereset in this research.

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