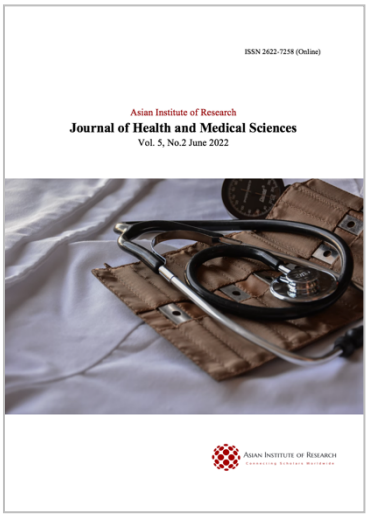

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Comparison of Intravenous Fentanyl and Intravenous Remifentanil on Emergence Time and Discharge Time in Patients Undergoing Odontectomy: An Observational Analytical Review

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Abstract
Background: Recovery time and fast patient discharge after surgery are goals of fast-track surgery that uses the concept of ERAS (Enhanced Recovery After Surgery) to minimize pain, speed up recovery, and reduce pain and complications. Fast-track surgeries such as odontectomy require drugs with a fast onset of action and short duration hence the patient can recover from the drugs as soon as possible. The use and types of opioids have been developed for optimal fast-track surgery. One of the most widely used opioids is remifentanil. Purpose: This study aims to compare the administration of fentanyl and remifentanil to the emergence and discharge time of post-odontectomy patients with general anesthesia. Methods: Patients were divided into two groups, the fentanyl group (group F, n=21) and the remifentanil group (group R, n=21). This study used a retrospective cohort analysis of the medical records of 42 patients with elective odontectomy surgery for the period December 2020 to June 2021 at RSUP dr. Hasan Sadikin Bandung. Emergence time was assessed using the OAA/S score and discharge time was considered using the modified Aldrete score. Results: This study showed a significant difference between the emergence time in group R (168+47.98 seconds) and group F (368+58.16 seconds) with a p-value = 0.0001. There was a significant difference between the discharge time in group R (20.00+7.24 minutes) and group F (58.57+12.46 minutes) with a p-value = 0.001. Conclusion: Recovery time and discharge time for patients receiving remifentanil were faster than for patients receiving fentanyl for odontectomy.

Keywords: Discharge Time, Fentanyl, Odontectomy, Recovery Time, Remifentanil

1. Introduction

Emergence from general anesthesia can be defined as a condition where neuromuscular conduction, protective reflexes, airway, and consciousness have returned after discontinuation of anesthetic drugs and completion of surgery (Permatasari et al., 2017).

Emergence from anesthesia is a process that can cause high physiological stress levels. Emergence from anesthesia should be smooth and controlled. The time required can vary depending on the patient's condition, types of anesthesia given, and duration of the surgery. In waking up from anesthesia, one can face airway obstruction, chills, agitation, delirium, pain, nausea, and vomiting. After general anesthesia, the patient should be able to regain consciousness within 30–60 minutes. The leading cause of delayed emergence is the effects of the anesthetic drugs still present. Impaired healing of consciousness can occur because of the potentiation of the effects of anesthetics with preoperative medications (Permatasari et al., 2017).

A study in India in 2016 reported factors that affect emergence time into 4 groups, namely the patient, drug, procedure, and metabolic factors. Patient factors were age, gender, genetic variation, Body Mass Index (BMI), comorbid smoking history, and duration of fasting before surgery. Drug factors are influenced by drug pharmacokinetics in absorption, distribution, metabolism and excretion, dose, duration of use, previous drug use, drug interactions, and selection of anesthetic drugs. Surgical factors that affect emergence time are duration of surgery, type of surgery, and use of instruments such as nasogastric tubes and catheters. Meanwhile, metabolic factors influence blood glucose status, electrolyte balance disorders, and temperature (Misal et al., 2016).

Discharge time for odontectomy patient is determined by several factors, namely pre-existing medical conditions and the location of the infection that can prolong up to 1-1.8 days (Katznelson & Fisher, 2015). The concept of fast-track surgery, which aligns with the idea of ERAS (enhanced recovery after surgery), has been mentioned in the surgical literature for the last two decades. The ERAS protocol provides a transformative plan to minimize pain, reduce opioid administration, accelerate patient recovery, and reduce perioperative complications and length of hospital stay (McLean House et al., 2016).

Anesthesia with rapid onset, minimal post-operative pain, good patient satisfaction, and low cost without complications such as nausea, vomiting, and delirium is the main goal in outpatient or fast-track surgery, one of which is performed on patients undergoing odontectomy. Since most dental surgeries are performed on One Day Surgery (ODS) patients, an anesthetic technique that allows for rapid recovery is preferred. Low lipid-solubility volatile with short-acting opioids such as Remifentanil, sufentanil, and fentanyl, or a targeted propofol infusion remifentanil are preferred for anesthesia maintenance in order to ensure rapid recovery (Permatasari et al., 2017; Twersky et al., 2001)

Currently, fentanyl is the opioid of choice for induction and analgesia in surgery. Fentanyl is the first generation of the fentanyl group, with its derivative opioids such as fentanyl, alfentanil, and Remifentanil. Fentanyl is a synthetic opioid in the form of a solution that binds to citrate and has good analgesic properties. Fentanyl has rapid onset, short duration, and slight effect on depressing the cardiovascular, and do not cause histamine release (Gül et al., 2013). Analgesia effect occurs 1-2 minutes after intravenous (IV) administration. The duration of action lasts for 2–4 hours after IV administration. The plasma concentration of fentanyl required is about 1–2 ng/ml to achieve an analgesic effect, which can achieve by administering 2–8 µg/kg. Maximum plasma concentration is reached within the first 5 minutes. Therefore, fentanyl is the agent of choice in general anesthesia. Fentanyl is a mu (µ) receptor agonist, and its analgesic properties are 100 times more potent than morphine. Fentanyl is generally given intravenously, although it can also be given intramuscularly, intrathecally, and epidurally (Awad & Chung, 2006; Twersky et al., 2001).

In addition, other opioid drugs are currently being developed; namely, Remifentanil which is an opioid that acts on mu (µ) receptor agonists, has an ester group chemical structure, has a concise action with a fast onset, a very short half-life of 3-10 minutes, while the peak effect of the drug is around 3-5 minutes. Remifentanil is rapidly metabolized by the blood by non-specific esterification in blood plasma to produce inactive carboxylic acids. The clinical effect wears off in 2 to 5 minutes. Therefore, Remifentanil can provide controlled levels of sedation and analgesia with minimal or unsustainable side effects (DG et al., 2021; Pavlin et al., 1998). This study aims to compare the administration of fentanyl and remifentanil to the recovery time and discharge time of post-odontectomy patients with general anesthesia.

2. Materials and Methods

This research is an analytic observational study with a retrospective cohort design. The research subjects were medical records of patients who underwent odontectomy surgery under general anesthesia at the Central Operating Theater (COT) at Hasan Sadikin General Hospital until June 2021 who met the inclusion and exclusion criteria. The research sample was taken by consecutive sampling. The study was conducted after obtaining approval from the Research Ethics Committee with the number LB.02.01/X.6.5/274/2021 and authorized by the Director of Hasan Sadikin Hospital Bandung with the number LB.02.01/X.2.2.1/22170/2021.

The inclusion criteria in this study were: 1. Patients aged 18 to 64 years who underwent elective odontectomy surgery; 2. Patients with normal BMI range; 3. Patients with physical status in categories I-II (WHO) according to the American Society of Anesthesiologists (ASA); 4. Patients who received remifentanil 1 µg/kgBW bolus for induction followed by maintenance remifentanil at a dose of 0.1µg/kg BW/min, without any additional opioid drugs; 5. Patients who received induction drug fentanyl 2 µg/kgBW for induction without additional opioid medications; and 6. Odontectomy patients who received propofol 2 mg/kgBW and atracurium 0.5 mg/kgBW as induction agents; 7. Patients who received maintenance anesthesia with sevoflurane with O2:N2O, FiO2 50%; 8. Patients who received analgesic paracetamol 20 mg/kgBW intravenously during the surgery; and 9. Patients with complete data regarding emergence time and discharge time in the PACU. While the exclusion criteria in this study were: 1. Patients who received additional opioids before emergence time could be assessed; 2. Odontectomy patients surgery duration more than two hours; 3. Patients who received opioids other than remifentanil and fentanyl; 4. Patients who were induced with drugs other than propofol and atracurium, and 5. Patients who received premedications of sedative and tranquilizers drugs in the ward.

Numerical scale data such as patient age are presented with mean, standard deviation, median, and range. Characteristic data in the form of categorical data such as the gender of the patient, coding is given and presented as a distribution of frequency and percentage. Normality test using Shapiro-Wilk test. The significance test to compare the characteristics of the two research groups used an unpaired t-test. The Chi-square test was used for categorical data. The data obtained were recorded in a particular form and then processed through the SPSS version 24.0 for the Windows program.

3. Results

3.1. Characteristics of patients

The study was conducted to 42 patients who had undergone odontectomy surgery. The research subjects were divided into two groups: the group that received fentanyl 2 µg/kgBW as a single bolus and the group remifentanil 1 µg/kg BW given during induction followed by maintenance at 0.1 µg/kg BW/min during intraoperatively with 21 samples in each group.

The data on the characteristics of the research subjects can be seen in Table 1 based on age, gender, Body Mass Index (BMI), ASA physical status, and duration of surgery. The fentanyl group had a mean patient age of 24.95 ± 5,861 years and consisted of 10 (47.6%) male patients and 11 (52.4%) female patients. BMI has an average of 21.59±1,836 kg/m^2. Most of the patients were ASA 1 (90.5%). The length of operation has an average of 96.19±12,339 minutes.

Table 1: Comparison of Research Subject Characteristics in the two groups

Variable	Groups		p-value
	Fentanyl N=21	Remifentanil N=21	
Age (year)			**0.112**
Mean±Std	24.95±5.861	27.10±5.674	
Median	24.00	27.00	

Range (min-max)	18.0-40.00	19.00-40.00	
Gender			**0.758**
Male	10(47.6%)	11(52.4%)	
Female	11(52.4%)	10(47.6%)	
IMT (kg/m^2)			**0.918**
Mean±Std	21.59±1.836	21.54±1.345	
Median	21.63	21.91	
Range (min-max)	18.67-24.24	19.15-24.49	
ASA			**1.000**
1	19(90.5%)	20(95.2%)	
2	2(9.5%)	1(4.8%)	
Duration of surgery (minutes)			**0.230**
Mean±Std	96.19±12.339	100.00±12.145	
Median	95.00	100.00	
Range (min-max)	80.00-120.00	80.00-120.00	

The * sign indicates the $p < 0.05$ and the ** sign indicates the $p < 0.01$ value, which means that it is statistically significant or significant.

The remifentanil group had an average patient age of 27.10 ± 5,674 years and consisted of 11 (52.4%) male patients and 10 (47.6%) female patients. The mean BMI was 21.54±1.345 kg/m^2. Most of the patients were ASA 1 (95.2%). The duration of operation has an average of 100.00±12.145 minutes. From the comparative analysis of the characteristics of the two groups above, it can be concluded that there were no differences in characteristics at the beginning of the examination. This shows that the two groups are the same or homogeneous.

3.2. Comparison of Emergence Time and OAA/S Score in Fentanyl and Remifentanil groups

Comparison of emergence time and OAA/S scores in the two groups can be seen in Table 2. The fentanyl group had an average emergence time of 368.57±58.162 seconds and an average OAA/S score of 2.86±0.478. The remifentanil group had an average emergence time of 168.57±47.988 seconds and an average OAA/S score of 3.33±0.577.

Table 2: Comparison between Emergence Time and OAA/S Score in Both Groups

Variable	**Groups**		**p-value**
	Fentanyl N=21	**Remifentanil N=21**	
Emergence time (seconds)			**0.0001****
Mean±Std	368.57±58.162	168.57±47.988	
Median	360.00	160.00	
Range (min-max)	260.00-460.00	80.00-300.00	
OAA/S			**0.007***
Mean±Std	2.86±0.478	3.33±0.577	
Median	3.00	3.00	
Range (min-max)	2.00-4.00	2.00-4.00	

OAA/S = Observer Assessment of Alertness/ Sedation.. The * sign indicates the p value <0.05 and the ** sign indicates the p value < 0.01 which means statistically significant or significant.

The results of statistical tests in both research groups obtained information on the P-value of the emergence time of 0.0001 and OAA/S score of 0.007, which is smaller than 0.05 ($p < 0.05$). Therefore, it can be concluded that there is a statistically significant difference in the average emergence time and OAA/S score between the fentanyl and remifentanil groups.

3.3. Comparison of discharge time in the Fentanyl and Remifentanil groups

Table 3 compares discharge time in the fentanyl and remifentanil groups. In the fentanyl group, the average discharge time was 58.57±12,464 minutes, while in the remifentanil group, the average discharge time was 20.00±7,246 minutes. Based on the Mann-Whitney test's analysis results, the p-value was less than 0.05. Therefore, there was a statistically significant difference in discharge time between the fentanyl and remifentanil groups.

Table 3: Comparison of discharge time in the Fentanyl and Remifentanil groups

Variable	Groups		p-value
	Fentanyl N=21	Remifentanil N=21	
Discharge time (second)			**0.0001****
Mean±Std	58.57±12.464	20.00±7.246	
Median	60.00	15.00	
Range (min-max)	45.00-75.00	15.00-30.00	

The * sign indicates the $p < 0.05$ and the ** sign indicates the $p < 0.01$ value, which means that it is statistically significant or significant.

4. Discussion

Characteristics of study subjects are based on gender, age, BMI, ASA status, and duration of surgery, as described in Table 1. Previous study has shown that women recover more quickly from anesthesia than men. This is due to the high concentrations of the hormones estrogen and progesterone in women, which affect the excitability of the central nervous system so that it affects the receptor modulation of sedative drugs and makes women less sensitive to the hypnotic effects of anesthetics than men (Buchanan et al., 2011).

Body Mass Index can affect recovery time and discharge time in patients undergoing general anesthesia. This is because patients with higher BMI tend to have more adipose tissues. Anesthetic agents are mostly lipophilic, so they are distributed to adipose tissue. This causes changes in the volume of distribution and lengthens drug clearance time. As a result, the duration of action of anesthetic drugs is longer and can affect emergence and discharge time of the patient (Katznelson & Fisher, 2015).

ASA physical status is based on patient's morbidity and its effect on functional limitations, thereby helping anesthesiologists to predict perioperative risk. High ASA physical status indicates the presence of morbidities, including diabetes mellitus, morbid obesity, alcohol dependence, kidney failure, and others that may alter the effect of anesthetic drugs on the patient's emergence and discharge time. The duration of surgery is related to the patient's exposure to anesthetic agents. The longer the surgery, the longer it will take for the patient to regain consciousness. Previous studies have shown that surgery duration of more than 2 hours increases recovery time by 1.2 times (McLean House et al., 2016).

This study found that the emergence time in the remifentanil group was faster than in the fentanyl group. These results are consistent with a previous study in Japan which stated that patients receiving remifentanil showed faster emergence time characterized by faster time to follow orders, extubation, and adequate ventilation compared to other opioids, including fentanyl. This may be caused by the pharmacokinetics of remifentanil with

smaller distribution volume (30 L) compared to fentanyl (335 L). The systemic clearance of remifentanil is 4,000 ml/minute, which is faster than fentanyl which is 1,530 ml/minute. This causes the effect of remifentanil to wear off more quickly and predictable (Twersky et al., 2001).

Previous study in Turkey showed similar result which stated that the average emergence time in the remifentanil group was 10.78 + 3.32 minutes compared to the fentanyl group of 13.87 + 3.0 minutes. These results show a statistically significant difference. This may be due to the slow clearance of fentanyl, resulting in a longer duration of anesthesia. This study recommended using low-dose remifentanil for induction of anesthesia in outpatient procedures because it produces the same anesthetic qualities as fentanyl without increasing the risk of complications, especially in children (Gül et al., 2013).

This study is also supported by previous study, which stated that remifentanil showed a faster emergence time than fentanyl which is characterized by a quicker response to verbal commands and faster time to leave the operating room. Rapid clearance of remifentanil by esterase results in faster recovery however it also shows higher postoperative pain, so postoperative pain management with other strategies or agents is recommended. A survey on anesthesiologists showed that 54% anesthesiologists rated “complete” emergence in remifentanil group compared to only 19% in the fentanyl group (Twersky et al., 2001).

This study showed that remifentanil group had faster discharge time than fentanyl group, with statistically significant effects. Discharge time is influenced by various factors, both in nursing and anesthesia. In terms of anesthesia, the prevention of pain, nausea, and dizziness (drowsiness) are the most crucial factors. The selection of appropriate anesthetic techniques and drugs can reduce recovery duration and discharge time (Awad & Chung, 2006; Pavlin et al., 1998).

In this study, the remifentanil group had an average discharge time of 20.00±7,246 minutes. This is in accordance with a previous study of dental surgery patients receiving propofol and remifentanil, which showed a discharge time of about 20 minutes after surgery (DG et al., 2021). The results of this study are also in line with previous studies on short urological surgery, which stated that patients receiving remifentanil had lower Aldrete scores better than fentanyl with less sedative effects. This is because remifentanil has a short half-life of about 9 minutes. The prolonged continuous infusion did not result in tissue accumulation of remifentanil nor changes in the half-life and elimination of the drug. With many surgeries with short duration and minimum postoperative pain, remifentanil can be an alternative opioid of choice to achieve faster discharge times or fast-track surgery (Kovac & Summers, 2009; Min et al., 2008).

Another study in one day surgery patients undergoing urological surgery showed that remifentanil is an ideal short-acting opioid in achieving the balance of anesthesia in ODS surgery, especially in procedures with short duration and minimal postoperative pain where discharge time from PACU is the main focus in cost efficiency. This study showed that the group receiving remifentanil achieved an Aldrete score of 10 faster than the fentanyl group, with a significant difference. This difference might be caused by the short elimination half-time and less sedative effect of remifentanil which is shown by lower end-tidal concentration of isoflurane compared to fentanyl. The group receiving remifentanil was discharged from the PACU within 60 minutes (Kovac & Summers, 2009).

In contrast, the study on various types of surgery showed different where patients who received fentanyl and remifentanil had similar discharge time. The difference in the results of this study was because remifentanil did not provide analgesia postoperatively when the infusion was stopped. This is due to the pharmacology of remifentanil that has rapid half-life and elimination. Therefore, in surgery with moderate to severe postoperative pain, patients who received remifentanil without additional analgesia might feel disturbing pain that prolongs the patient's discharge time. In this study, all patients underwent odontectomy with mild postoperative pain therefore the remifentanil group did not feel disturbing pain that might prolonged discharge time (Syroid et al., 2010).

5. Conclusion

This study showed that patients' emergence time and discharge time on remifentanil 1 μg/kgBW at induction followed by maintenance at 0.1 μg /kgBW/min were faster than fentanyl 2 μg/kg BW single bolus undergoing odontectomy surgery.

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Declaration Of Conflicting Interest
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